Antibiotic susceptibility of asymptomatic spontaneous bacterial peritonitis in decompensated liver cirrhosis: A prospective study

Haidi K.-A. Ramadan[a], Sherif I. Kamel[a], Hebat-Allah G. Rashed[b], Antony A. Georgy[a], Asmaa O. Ahmed[b]

Departments of [a]Tropical Medicine and Gastroenterology, [b]Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Haidi K.-A. Ramadan, M.D, Lecturer of Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt
Fax: (+20) 88-2354130;
e-mail: haidikaram@aun.edu.eg

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Background and aim
Asymp to matic spontaneous bacterial peritonitis (SBP) is rare but has similar variants to symptomatic SBP. Our aim is to determine the antibiotic susceptibility in asymptomatic SBP.

Patients and methods
Patients with decompensated liver cirrhosis were included in our study. Ascitic fluid analysis for polymorphonuclear count, as well as culture was done at baseline and 48 h after antibiotic initiation if polymorphonuclear count more than or equal to 250/mm^3 and/or positive culture. Cefotaxime was used empirically, whereas in bacterascites, initial antibiotic was based on the culture.

Results
A total of 70 patients were included. Approximately 15.7% had asymptomatic SBP. Overall, 9% of patients with asymptomatic SBP were classic SBP, culture-negative neutrocytic ascites (CNNA) in 54.5%, and bacteriascites in 36.4%. Classic SBP and five cases of CNNA were cefotaxime sensitive. The resistant case in CNNA responded to meropenem. Bacterascites was cefotaxime resistant and sensitive to ciprofloxacin and piperacillin-tazobactam. The overall resistance to cefotaxime was 45.5%.

Conclusion
CNNA is predominant in asymptomatic SBP with high resistance to third-generation cephalosporin which requires antibiotic susceptibility to be identified before therapy.

Keywords:
antibiotic, ascites, bacterial infections, liver cirrhosis, peritonitis

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Introduction

Spontaneous bacterial peritonitis (SBP) definition is ascetic fluid bacterial infection of a previously sterile ascitic fluid. Exclusion of a source of infection (intraabdominal) known as secondary bacterial peritonitis is a prerequisite for the diagnosis of SBP [1]. All ascetic patients are at risk of SBP, with outpatients prevalence of SBP in cirrhotic patients ranging between 1.5 and 3.5% [2] and between in-hospitalized patients from 10 to 30% [3]. Moreover, the mortality rate of SBP is high (20–30%), and the 1-year survival is only 30–40% [4]. However, the mortality of SBP has been decreased recently owing to early management [5]. Therefore, early diagnosis of SBP could help in preventing complications like sepsis, deterioration of liver disease, hepatorenal syndrome, and hepatic encephalopathy [6].

Classic SBP variant is reported in ~40% of SBP, and it is diagnosed when absolute polymorphonuclear count (PMN) is more than 250/mm^3 with positive culture results [1]. If the culture is negative with the absolute neutrophilic count being more than 250/mm^3, it is labeled as culture-negative neutrocytic ascites (CNNA). When the ascitic fluid culture is positive for microorganism and the count of PMNs is less than 250/mm^3, the condition is called bacterascites [6].

Performing a diagnostic paracentesis for a rapid diagnosis of this life-threatening infection demands a high index of suspicion in different clinical settings because clinical presentation of infection could be subtle [7]. Nevertheless, few articles have discussed the incidence of asymptomatic SBP in cirrhotics, and the results of asymptomatic SBP prevalence were very low [8,9]. Therefore, the American Association for the Study of Liver Diseases practice guidelines recommended diagnostic paracentesis to be performed in every patient with cirrhosis and ascites admitted to the hospital [10].

Once SBP is diagnosed, empirical antibiotic therapy must be initiated [11]. For community-acquired SBP infection, third-generation cephalosporins are effective, with recovery rates of ~80%; however, the development of resistance to third-generation cephalosporins is of great concern. Failure to respond to empirical therapy can be seen in 33% -75% of cases, which is associated with reduced survival, it can be associated with reduced survival, which may be owing to treatment resistance [12].

According to the European Association for the Study of the Liver (EASL) guidelines in the treatment of SBP, a third-generation cephalosporin, cefotaxime, 2.0 g every 12 h or every 8 h for a minimum of 5 days, is recommended as an empirical antibiotic therapy. As alternatives, amoxicillin with clavulanic acid and fluoroquinolones such as ciprofloxacin or ofloxacin are recommended, but not for patients using prophylactic norfloxacin and in areas with high rates of fluoroquinolones resistance [11].

SBP-inducing pathogens vary in characteristics according to the site of acquiring the infection, which reflects the antibiotic resistance. SBP was classified into nosocomial or hospital acquired (HA), health-care associated (HCA), and community acquired (CA) [1]. In HA infections, pathogens with multidrug resistant are usually cultivated, which contribute to more resistant therapy and worse outcome [13,14]. The effectiveness of third-generation cephalosporins among patients with HA infections with liver cirrhosis was 40%, 73% in those with HCA, and 83% in those with CA [14]. The response to antibiotics was determined by the decrease of ascitic neutrophil count to less than 250/mm^3 [15]. EASL guidelines in 2010 reported that the level of ascitic PMN count should be less than 25% of the pretreatment level after 48 h of initiating antibiotic therapy, to indicate response to treatment [11].

However, the profiles of microorganisms causing asymptomatic SBP and the pattern of their antibiotic susceptibility are not well studied. Thus, our aim is to determine the profile of microorganisms causing asymptomatic SBP in patients with decompensated liver cirrhosis and their antibiotic susceptibility.

Patients and methods

This prospective study was carried out in Tropical Medicine and Gastroenterology Department, Al Rajhy University Liver Hospital, Assiut University, from June 2019 to February 2020.

Patients with decompensated liver cirrhosis were recruited. The diagnosis of decompensated liver cirrhosis was based clinically on; jaundice, edema, and ascites, biochemically on; hypoalbuminemia, hypoprothrombinemia, and hyperbilirubinemia and finely by ultrasonographic confirmation. The severity of the liver disease was assessed by the Child–Pugh and Model of End-Stage Liver Disease (MELD) scores.

We excluded patients with evidence of intraabdominal cause of infection, for example, recent abdominal surgery; patients with evident clinical manifestation of SBP; patients with hepatic encephalopathy; patients with previous episode of SBP; patients with renal impairment, or those who received antibiotic within 2 weeks before enrollment in the study either as therapy or prophylaxis for SBP and hepatocellular carcinoma (HCC).

All patients were subjected to full medical history, clinical examination, and laboratory tests including complete blood picture, liver and kidney function tests, and international normalized ratio. Under a sterile technique, ~3 ml of ascitic fluid was used in a plain tube for measurement of protein and albumin. Another 2 ml of fluid was collected in tubes containing EDTA as anticoagulant and was used for PMNL cell counts by an automated counter.

The microbiological examination was done by collecting ascitic fluid sample under aseptic condition before the start of antibiotic therapy, and directly inoculated onto a blood culture bottle of Bact/Alert instrument and transported to the Microbiology Laboratory of Clinical Pathology Department. Positive bottles were inoculated on blood agar, chocolate agar, MacConkey agar, and Sabouraud agar for isolation of the causative organisms using standard microbiological techniques [16,17]. MacConkey agar was incubated at 37°C under aerobic conditions for 18–48 h. Blood agar and chocolate agar were incubated at 37°C in 5–7% CO_2 for 18–48 h. Two plates of Sabouraud agar were incubated at 37°C and at room temperature under aerobic conditions for 48–72 h. Microscopic examination of gram stain from the growth colonies was performed. Bacterial identification and drug sensitivity were performed by using the Vitek2 compact system (bioMérieux, Marcy l'Etoile, France) through its manual instruction. The interpretation of the antibiotic susceptibility tests was performed in accordance with the recommendations of Clinical and Laboratory Standards Institute (CLSI), M100-S29 Performance Standards for Antimicrobial, 2019.

SBP diagnosis and its variants was based on the PMN count and the culture. Ascitic fluid analysis was done on two occasions in the study: on admission for all patients and after 48 h of initiation of the antibiotic for

cases diagnosed to have SBP. As the recommendations, antibiotics would be initiated once a laboratory diagnosis of SBP has been made. All patients diagnosed as SBP by PMN count initially received intravenous cefotaxime 2 g/12 h for 48 h until the results of cultures were obtained, except cases with bacterascites. The response to the therapy was assessed based on a decrease of ascitic neutrophil count to less than 250/mm^3 [15] or more than 25% of the pretreatment value and/or sterile cultures of ascitic fluid, if positive at diagnosis after 48 h of initiating the antibiotics [11].

Then patients were divided into two groups: patients without asymptomatic SBP (non-SBP) and the other group with asymptomatic SBP. The data were compared between both groups.

Patients received treatment according to SBP variants identified. In classical SBP and CNNA, the patient received empirically cefotaxime 2 g/12 h until the results of culture sensitivity were obtained, and then the antibiotic would be changed according to the results of the culture sensitivity test in the classic variant. If ascitic fluid analysis after 48 h showed a response, then patients continue to receive cefotaxime to complete 5 days of therapy. If there was failure of response, then we shifted to another antibiotic according to the culture and sensitivity result. In the CNNA variant, if no response, then we shifted to another antibiotic, for example, piperacillin-tazobactam or meropenem. Meanwhile, in the bacterascites variant; antibiotics were given for 5 days according to the results of culture sensitivity test, and the follow-up after 48 h was done also with ascitic fluid culture and sensitivity test (Fig. 1).

Ethical approval and consent to participate: this study was conducted in accordance with Declaration of Helsinki. It was approved by the Ethical Committee of Assiut University (IRB number: 17101225). Patients signed informed consent.

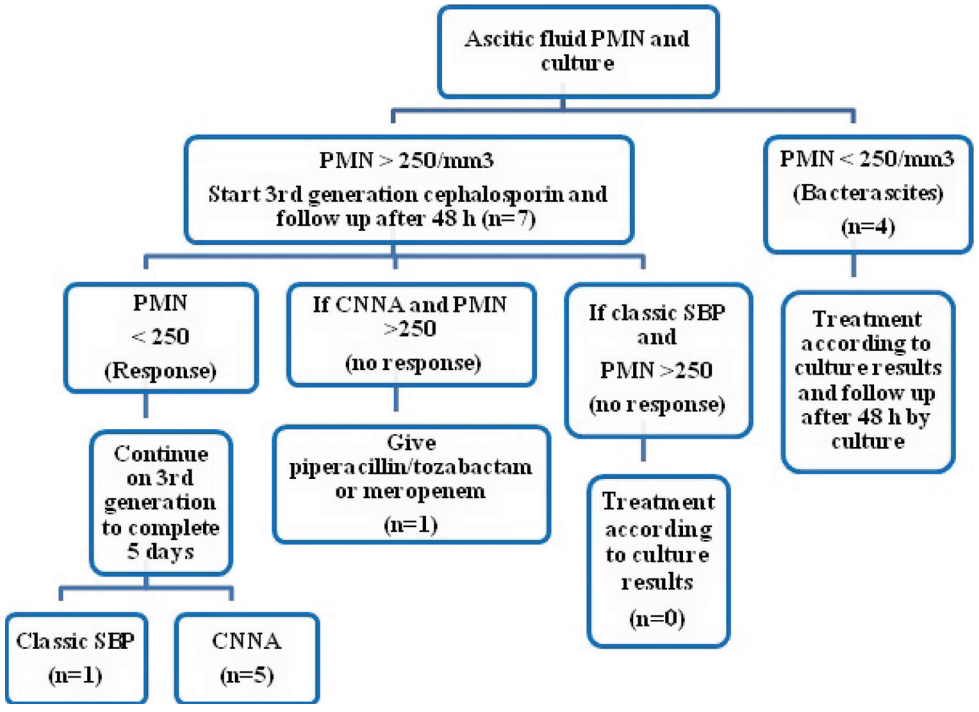
Statistical analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Science, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD if the data were normally distributed, the median and interquartile range if they were nonparametric, whereas the nominal data were expressed in the form of frequency (percentage). χ^2 test was used to compare the nominal data of two groups in the study, whereas Student *t* test was used to compare the mean of two groups if the data were normally distributed and the Mann–Whitney *U* test if the data were not normally distributed. *P* value was considered significant if less than 0.05.

Results

A total of 70 patients eligible for the inclusion criteria were recruited in the study. Demographic data showed

Figure 1



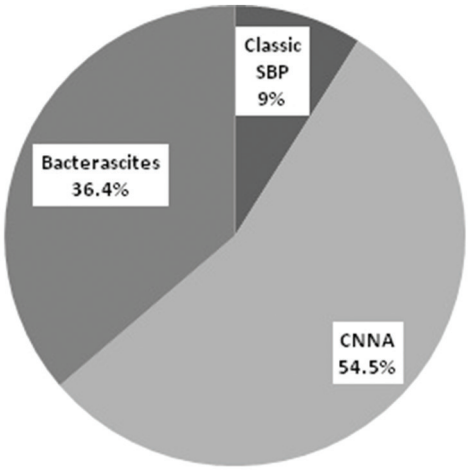
The algorithm of the treatment used in the study based on the ascitic fluid polymorphonuclear count (PMN) and culture. CNNA, culture-negative neutrocytic ascites.

that their mean age was 55.69 ± 11.97 years. There were 40 (57.1%) males and 30 (42.9%) females. Diabetes mellitus as a comorbidity was present in 41.4%. The etiology of cirrhosis was chronic hepatitis C virus in 60% of patients. Most cases were Child C (51.4%), and the median MELD score was 13 (11–17) (Table 1).

Patients with asymptomatic SBP were 11 (15.7%). One (9%) case presented with classic SBP, six (54.5%) cases had CNNA, and four (36.4%) cases had bacteriascites, as shown in Fig. 2.

There was no significant difference in comparing demographic, clinical, and laboratory data between patients without SBP and patients with asymptomatic SBP. However, 54.5% of patients with asymptomatic SBP had moderate ascites and had Child class C. MELD score was slightly higher in the group with asymptomatic SBP (16 vs 13) (Tables 1, 2).

Figure 2



The percentages of variants of asymptomatic SBP in the studied patients. SBP, spontaneous bacterial peritonitis.

The profile of identified microorganisms and their antibiotic susceptibility in patients with asymptomatic SBP showed that five (45.5%) patients with asymptomatic SBP had positive ascitic fluid culture: one with classic SBP and four with bacterascites. The identified organisms in the culture were *Staphylococcus aureus* (*n* = 3), *Escherichia coli* (*n* = 1), and Acinetobacter (*n* = 1) (Table 3).

Only one (20%) patient was cefotaxime sensitive (the only classic variant patient) (*E. coli*), and four (80%) cases with bacterascites were resistant according to culture sensitivity. They showed sensitivity and response to ciprofloxacin in three (75%) cases and piperacillin-tazobactam in one (25%) case in the form of no growth in the follow-up culture sensitivity performed after 48 h.

In CNNA, five patients showed a response to cefotaxime as an empirical treatment based on the decrease of the PMN count more than 25% in the ascitic fluid after 48 h of the initiation of antibiotic treatment. However, one case had no response to cefotaxime, and the antibiotic was shifted to meropenem, which showed a good response.

Sensitivity to other antibiotics included mainly ciprofloxacin (four cases), gentamycin (three cases), piperacillin-tazobactam (two cases), tetracycline (two cases), tigecycline (two cases), and other antibiotics. None of the patients with asymptomatic SBP developed

Table 1 Comparison of demographic features, clinical data, and liver disease severity scores between non-spontaneous bacterial peritonitis patients and patients with asymptomatic spontaneous bacterial peritonitis

Items	Total (*n*=70)	Without asymptomatic SBP (non-SBP) (*n*=59)	With asymptomatic SBP (*n*=11)	*P*
Age (years)	55.69±11.97	56.03±11.37	53.81±15.34	0.57
Sex [*n* (%)]				
Male	40 (57.1)	34 (57.6)	6 (54.5)	0.55
Female	30 (42.9)	25 (42.2)	5 (45.5)	
Diabetes mellitus [*n* (%)]	29 (41.4)	25 (42.4)	4 (36.4)	0.49
Etiology of cirrhosis [*n* (%)]				
HCV	42 (60.0)	35 (59.3)	7 (63.6)	0.18
Cryptogenic	16 (22.9)	13 (22)	3 (27.3)	
HBV	8 (11.4)	7 (11.9)	1 (9.1)	
HCV/HBV coinfection	4 (5.7)	4 (6.8)	0	
Degree of ascites [*n* (%)]				
Mild	6 (8.6)	4 (6.8)	2 (18.2)	0.09
Moderate	33 (47.1)	27 (45.8)	6 (54.5)	
Marked	31 (44.3)	28 (47.5)	3 (27.3)	
Child-Pugh class [*n* (%)]				
Child B	34 (48.6)	29 (49.2)	5 (45.5)	0.09
Child C	36 (51.4)	30 (50.8)	6 (54.5)	
MELD score (median)	13 (11-17)	13 (11-17)	16 (13-18)	0.36

HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model of End-Stage Liver Disease; SBP, spontaneous bacterial peritonitis.

Table 2 Comparison between laboratory data of non-spontaneous bacterial peritonitis patients and patients with asymptomatic spontaneous bacterial peritonitis

Items	Without asymptomatic SBP (non-SBP) (*n*=59)	With asymptomatic SBP (*n*=11)	*P*
Hemoglobin (g/dl)	10.02±2.12	9.09±2.41	0.19
Platelets (×10^9/l)	92.5 (60.8-153.3)	110 (60-170)	0.14
Leukocytes (×10^9/l)	5.02±2.09	5.40±2.12	0.58
Bilirubin (μmol/l)	41 (19.6-66.3)	45 (10.6-79)	0.57
Direct bilirubin (μmol/l)	18.3 (9.4-33)	24 (5.8-45)	0.58
AST (u/l)	37.5 (22-62)	57 (34-74)	0.14
ALT (u/l)	26.5 (20-40)	26 (15-50)	0.58
Serum albumin (g/l)	24.51±6.67	24.70±5.63	0.93
Serum total protein (g/dl)	65 (58.8-73.3)	62 (58-77)	0.45
INR	1.70±0.48	1.69±0.39	0.96
Urea (mmol/l)	8 (5.2-8)	5.9 (2.2-8)	0.35
Creatinine (mmol/l)	95 (69.5-104)	80 (57-96)	0.21
Sodium (mEq/l)	132.16±8.70	130.18±5.60	0.62
Potassium (mEq/l)	3.70±0.68	3.55±1.06	0.55

Parametric data are expressed as mean±SD and nonparametric are expressed as median (interquartile range). ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; SBP, spontaneous bacterial peritonitis.

Table 3 Results of culture and antibiotic susceptibility test in patients with asymptomatic spontaneous bacterial peritonitis (*n*=5)

Items	*n* (%)
Types of organism in culture positive	
Staphylococcus aureus	3 (60.0)
Escherichia coli	1 (20.0)
Acinetobacter	1 (20.0)
Resistance to third-generation cephalosporin	
CNNA variant	1 (9.09)
Bacterascites variant	4 (36.36)
Pattern of antibiotics sensitivity in asymptomatic SBP	
Ciprofloxacin	4 (36.36)
Gentamycin	3 (27.77)
Piperacillin-tazobactam	2 (18.18)
Meropenem	2 (18.18)
Tetracycline	2 (18.18)
Tigecycline	2 (18.18)
Levofloxacin	1 (9.09)
Nitrofurantoin	1 (9.09)
Rifampin	1 (9.09)
Vancomycin	1 (9.09)
Aztreonam	1 (9.09)
Ofloxacin	1 (9.09)
Co-trimoxazole	1 (9.09)
Cefotaxime	1 (9.09)

CNNA, culture-negative neutrocytic ascites; SBP, spontaneous bacterial peritonitis.

hepatorenal syndrome, hepatic encephalopathy, or mortality during the 5 days duration of therapy.

Discussion

SBP is identified as an intraabdominal infection of ascites without a surgically treatable cause according to the EASL new guideline [8]. Approximately 50% of the episodes of SBP are diagnosed on hospital admission, whereas the rest are acquired during hospitalization [18]. Our study showed that 15.7% had infection with asymptomatic SBP. This is similar to an Egyptian study by Elsherif *et al.* [19] that reported 13% had asymptomatic SBP. de Mattos *et al.* [6] showed the frequency of asymptomatic SBP was ~10%, whereas Mohan and Venkataraman [20] found it in seven (2.5%) outpatients during paracentesis [20].

Bacterial overgrowth in the intestine, decreased phagocytosis, low complement levels in serum and ascites, and impaired activity of the reticuloendothelial system could result in an increased number of microorganisms and failure to clear them from the blood, resulting in their translocation and proliferation within the ascitic fluid [21].

SBP affects cirrhotic patients with variable etiologies and subsequent research has not covered causal factors, such as the translocation of intestinal bacteria to the lymph nodes, making the etiology less evasive [22]. In our study, chronic hepatitis C virus was the commonest cause of liver cirrhosis in both patients with asymptomatic SBP and non-SBP, with no significant difference. As the liver disease progresses, the risk of SBP increases, presented as bilirubin more than 54.7 μmol/l and platelets lower than 98.000/ml [23]. Each additional point on the MELD score increases the risk by 11% [24].

In this study, Child C was relatively predominant either in patients with asymptomatic SBP and those non-SBP but without significant difference. The MELD score in our study also demonstrated no predictive value between the two groups (P = 0.3). Similarly, Elsherif *et al.* [19] reported that there was no significant difference regarding Child class or MELD score between cases with infection and those without. On the contrary, in the study by Kasztelan–Szczerbinska

et al. [25], it was reported that seven patients out of nine with asymptomatic SBP were Child C. Patients with asymptomatic SBP in the current study had a relatively higher MELD score than non-SBP patients. This is supported by the by study McDonald *et al*. [26] which stated that SBP-positive patients had a higher baseline MELD score. Nevertheless, they included 30% of the studied patient with cholestatic cirrhosis and 24% had HCC which could explain worse MELD score in these patients. Regarding laboratory data, there was no meaningful difference between the two groups. In concordance with these results, Mohan and Venkataraman [20] reported that no predictors of such an infection could be recognized.

According to the EASL guideline, the results of culture of ascitic fluid often show no growth even when performed on blood broth culture and are not considered important for the diagnosis of SBP, but should guide antibiotic therapy [11]. The reported probability of identifying a pathogen because ascitic fluid cultures are positive is 50–60% of patients with SBP [27], whereas the estimated incidence of bacterascites in patients with liver cirrhosis was 3–4% [28].

In our study, 9% had classic SBP, 36.4% had bacterascites, and 54.5% had CNNA. Mohan and Venkataraman [20] found that classic SBP in their study was diagnosed in one (14.3%) patient, bacterascites in two (28.6%), and CNNA in four (57.1%). However, in the study by Kasztelan–Szczerbinska *et al*. [25], out of nine patients with asymptomatic SBP, only two met the classic criteria of SBP, six patients had bacterascites and one patient had CNNA. On the contrary, other studies showed that all the patients with asymptomatic were culture-negative (CNNA). This could be attributed to the previous antibiotic therapy which influenced these observations, as these patients received long-term antibiotics [6,26].

In our study, the microorganism profiles isolated in five SBP cases consisted mainly of gram-positive cocci. In a similar study, Castellote *et al*. [29] reported that although one (10%) case was diagnosed with CNNA, six out of 10 (60%) cases were diagnosed with bacterascites, which was mainly caused by gram-positive cocci. Adverse effects to positive bacteria have been reported internationally and may be related to the frequent use of broad-spectrum antibiotics [30,31]. The change in the bacterial etiology may have been caused by the increase in the prescription of quinolones for bacterial prophylaxis in addition to instrumentation in patients with liver cirrhosis. Furthermore, ascites from outpatients are more likely to produce gram-positive bacteria rather than *E. coli* and *Klebsiella pneumoniae*, which are predominant in-hospitalized patients. It is accepted, therefore, that they are community-acquired infections.

Previous studies have confirmed that gram-positive bacteremia causes a less severe inflammatory response compared with gram-negative bacteremia. Differences in inflammatory reactions of bactericides and SBPs with a large number of PMNs are partly attributed to gram-positive bacteria, which are less virulent for the host, and different severity of host inflammatory reactions. According to the culture susceptibility test in this study, all patients with bactericidal SBP were resistant to cefotaxime and were sensitive to ciprofloxacin and piperacillin-tazobactam. Overall, 16.7% in CNNA also showed resistance to cefotaxime. Therefore, resistance to third-generation cephalosporins was present in 45.5% of patients with asymptomatic SBP in this study.

Elsherif *et al*. [19] stated among 19 patients with asymptomatic SBD that only 15.8% were susceptible to cefotaxime and 84.2% were resistant to cefotaxime in response to other antibiotic strains. Meanwhile, Ariza *et al*. study on symptomatic SBP found that an average global resistance to third-generation cephalosporins was 21.5%, where 7.1% were found in CA infections, 21.1% in HCA infections, and 40.9% in HA infections [32]. However, in a recent symptomatic SBP study by Jacobson *et al*., bacteria showed third-generation cephalosporin resistance.

In our study, cases with resistance to third-generation cephalosporin had responded after changing to piperacillin/tazobactam. After the evaluating the antibiotic sensitivity in 575 patients with SBP, Shi *et al*. [29] recommended cefoperazone/sulbactam or piperacillin/tazobactam as an empirical treatment of SBP. Therefore, the use of piperacillin/tazobactam as the first-option is preferred, with a reduced risk of the bacteria that has drug resistance [1].

This changing pattern of antibiotic sensitivity can be explained by changing the profile of the organisms that cause SBP. Moreover, it could be owing to frequent and long-term use of cephalosporins for empirical and prophylactic therapy of SBP [30]. Sampling of ascitic fluid for microbiology and clinical chemistry should be initiated before empirical antibiotic treatment [31]. Recently, a study by Sunjaya *et al*. [33] demonstrated that third-generation cephalosporins may provide appropriate empirical treatment for CA and HCA in patients with SBP, especially those without HCC. Therefore, determining the profile of the microorganisms and antibiotic susceptibility of asymptomatic SBP is crucial in the current era of drug

resistance. The small sample size is the main limitation of this study. Meanwhile, it was a prospective study that identified the causative organisms and their antibiotic susceptibility in asymptomatic SBP, which has a low frequency.

Conclusion

In conclusion, the prevalence of CNNA is high in asymptomatic SBP resulting mostly from gram-positive cocci. Resistance to third-generation cephalosporin was reported in 45.5% of asymptomatic SBP. Therefore, culture sensitivity on the ascitic fluid should be performed before empirical therapy.

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Conflicts of interest

There are no conflicts of interest.

References

1 Rostkowska KA, Szymanek-Pasternak A, Simon KA. Spontaneous bacterial peritonitis–therapeutic challenges in the era of increasing drug resistance of bacteria. Clin Exp Hepatol 2018; 4:224.

2 Nousbaum JB, Cadranel JF, Nahon P, Khac EN, Moreau R, Thévenot T, *et al*. Diagnostic accuracy of the Multistix 8 SG reagent strip in diagnosis of spontaneous bacterial peritonitis. Hepatology 2007; 45:1275–1281.

3 Shizuma T. Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: a literature review. World J Hepatol 2018; 10:254.

4 Oladimeji AA, Temi AP, Adekunle AE, Taiwo RH, Ayokunle DS. Prevalence of spontaneous bacterial peritonitis in liver cirrhosis with ascites. Pan Afr Med J 2013; 15:128.

5 Khalid M, Samiullah R, Khalid SR. Frequency of asymptomatic spontaneous bacterial peritonitis in outdoor patients with liver cirrhosis. Pak Armed Forces Med J 2015; 65:278–281.

6 de Mattos AA, Costabeber AM, Lionço LC, Tovo CV. Multi-resistant bacteria in spontaneous bacterial peritonitis: a new step in management?. World J Gastroenterol 2014; 20:14079.

7 Jeffries MA, Stern MA, Gunaratnam NT, Fontana RJ. Unsuspected infection is infrequent in asymptomatic outpatients with refractory ascites undergoing therapeutic paracentesis. Am J Gastroenterol 1999; 94:2972–2976.

8 Liver EAftSot. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69:406–460.

9 Cadranel JF, Nousbaum JB, Bessaguet C, Nahon P, Nguyen-Khac E, Moreau R, *et al*. Low incidence of spontaneous bacterial peritonitis in asymptomatic cirrhotic outpatients. World J Hepatol 2013; 5:104.

10 Runyon BA. Committee APG. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009; 49:2087–2107.

11 Liver EAFTSOT. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010.53:397–417.

12 Ison MG. Empiric treatment of nosocomial spontaneous bacterial peritonitis: one size does not fit all. Hepatology 2016; 63:1083–1085.

13 Peck KR, Cheong HS, Kang CI, Lee JA, Moon SY, Joung MK, *et al*. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clin Infect Dis 2009; 48:1230–1236.

14 Fernández J, Acevedo J, Castro M, Garcia O, Rodríguez de Lope C, Roca D, *et al*. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012; 55:1551–1561.

15 Fong TL, Akriviadis EA, Runyon BA, Reynolds TB. Polymorphonuclear cell count response and duration of antibiotic therapy in spontaneous bacterial peritonitis. Hepatology 1989; 9:423–426.

16 Murray PR, Baron E, Jorgensen J, Pfaller M, Yolken R. *Manual of clinical microbiology*. 8th ed. Washington, DC: American Society of Microbiology; 2009.

17 Forbes BA, Sahm DF, Weissfeld AS. *Study guide for Bailey & Scott's diagnostic microbiology*. USA: Mosby; 2007.

18 Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, *et al*. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000; 32:142–153.

19 Elsherif AA, Eldahshan MA, Hussein MS, Mohamed AM. Asymptomatic spontaneous bacterial peritonitis in adult Egyptian patients with decompensated liver cirrhosis: a prospective cohort study. Int J Adv Biomed 2016; 1:5–9.

20 Mohan P, Venkataraman J. Prevalence and risk factors for unsuspected spontaneous ascitic fluid infection in cirrhotics undergoing therapeutic paracentesis in an outpatient clinic. Indian J Gastroenterol 2011; 30:221.

21 Bellot P, Francés R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. Liver Int 2013; 33:31–39.

22 Dever J, Sheikh M. spontaneous bacterial peritonitis–bacteriology, diagnosis, treatment, risk factors and prevention. Aliment Pharmacol Ther 2015; 41:1116–1131.

23 Guarner C, Solà R, Soriano G, Andreu M, Novella MT, Vila MC, *et al*. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. Gastroenterology 1999; 117:414–419.

24 Obstein KL, Campbell MS, Reddy KR, Yang YX. Association between model for end-stage liver disease and spontaneous bacterial peritonitis. Am J Gastroenterol 2007; 102:2732–2736.

25 Kasztelan–Szczerbinska B, Słomka M, Celinski K, Serwacki M, Szczerbinski M, Cichoz-Lach H. Prevalence of spontaneous bacterial peritonitis in asymptomatic inpatients with decompensated liver cirrhosis–a pilot study. Adv Med Sci 2011; 56:13–17.

26 McDonald DP, Leithead JA, Gunson BK, Ferguson JW. Subclinical spontaneous bacterial peritonitis at the time of liver transplantation does not impact on outcomes. Eur J Gastroenterol Hepatol 2016; 28:101–106.

27 Adhikary R, Joshi S, Venugopa R, Ganjoo N. Spontaneous bacterial peritonitis caused by S. paratyphi A. J Assoc Physicians India 2013; 61:930–931.

28 Lutz P, Goeser F, Kaczmarek DJ, Schlabe S, Nischalke HD, Nattermann J, *et al*. Relative ascites polymorphonuclear cell count indicates bacterascites and risk of spontaneous bacterial peritonitis. Dig Dis Sci 2017; 62:2558–2568.

29. Castellote J, Girbau A, Maisterra S, Charhi N, Ballester R, Xiol X. Spontaneous bacterial peritonitis and bacterascites prevalence in asymptomatic cirrhotic outpatients undergoing large-volume paracentesis. Journal of gastroenterology and hepatology 2008;23(2):256–259.

30. Friedrich K, Nüssle S, Rehlen T, Stremmel W, Mischnik A, Eisenbach C. Microbiology and resistance in first episodes of spontaneous bacterial peritonitis: implications for management and prognosis. Journal of gastroenterology and hepatology, 2016. 31(6): 1191–1195.

31. Fernández J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, *et al*. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. Journal of hepatology, 2019. 70(3): 398–411.

32. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, *et al*. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. Journal of hepatology, 2012. 56(4): 825–832.

33. Sunjaya DB, Lennon RJ, Shah VH, Kamath PS, Simonetto DA. Prevalence and Predictors of Third-Generation Cephalosporin Resistance in the Empirical Treatment of Spontaneous Bacterial Peritonitis. in Mayo Clinic Proceedings. 2019. Elsevier.