Changes in the patterns and microbiology of spontaneous bacterial peritonitis : analysis of 200 cirrhotic patients

H. Al-Ghamdi[1,2], N. Al-Harbi[3], H. Mokhtar[1], M. Daffallah[1], Y. Memon[4], A. A. Aljumah[1, 2], F. M. Sanai[5]

(1) Hepatology Division, Department of Hepatobiliary Sciences and Organ Transplant, King Abdulaziz Medical City, Riyadh, Saudi Arabia ; (2) King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh ; (3) Department of Neurosurgery, King Abdulaziz Medical City, Riyadh, Saudi Arabia ; (4) Gastroenterology Division, Department of Medicine, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia ; (5) Gastroenterology Unit, Department of Medicine, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Jeddah, Saudi Arabia.

Abstract

Background & aims : **The microbiological characteristics of spontaneous bacterial peritonitis (SBP) are changing worldwide with a shift in patterns of SBP and increasing prevalence of antibiotic-resistant bacteria. We, therefore, conducted this retrospective study aiming to characterise the current patterns and microbiology of SBP in our region.**

Methods : **We performed a retrospective chart review of patients presenting with their first episodes of SBP. The demographical, clinical and laboratory parameters of all patients at first paracentesis were recorded.**

Results : **The study included 200 cirrhotic patients with SBP. Mean age was 60.4±13.5 years and 116 (58%) patients were males. Liver cirrhosis was predominantly viral in 138 (69%) patients. Ascitic fluid cultures were positive in 103 (51.5%) patients and negative in 97 (48.5%). Ninety-eight (95.1%) patients had monomicrobial bacterial growth. The most common variants of spontaneous ascitic fluid infection were culture negative neutrocytic ascites (CNNA) in 97(48.5%) patients and SBP in 65 (32.5%) patients. E.Coli was most frequently isolated microorganism in 41 (39.8%) patients followed by staphylococcus species in 19 (18.4%) patients, Klebsiella pneumonae in 14(13.6%) patients and streptococcus species in 13 (10.7%) patients. The prevalence of extended spectrum beta-lactamases (ESBL) resistant E.Coli was 29.3%. Antibiotic resistance rate for meropenem, piperacillin\ tazobactam, ceftriaxone and ciprofloxacin was 0%, 22.0%, 29.0%, and 28.6% respectively.**

Conclusions : **Changes in the patterns and microbiology of SBP are evident in our region with increasing prevalence of culture negative SBP, extended spectrum beta-lactamases resistant E.Coli, and increased resistance rate to first line antibiotics. Our data argue for relying on periodic hospital based antibiotic susceptibility data whenever SBP is treated.** (Acta gastroenterol. belg., **2019**, 82, **261-266**).

Keywords : Spontaneous bacterial peritonitis, cirrhosis, microbiology, extended spectrum B-lactamase resistance

Introduction

Spontaneous bacterial peritonitis (SBP), an infection of ascites caused by translocation of bacteria from the intestinal lumen into the systemic circulation, is a frequent event and a common cause of death in patients with cirrhosis (1,2). It is the most common infection among patients with cirrhosis and ascites with an incidence of 10-30% for hospitalised patients (3). In the early era of SBP, its mortality surpassed 90%, but a seek-and-diagnose early strategy along with appropriate treatment has reduced mortality in recent years to about 20% (4,5). The microbiological characteristics of SBP have changed (6-8), with reports from different countries indicating a shift in microbial patterns and increasing prevalence of antibiotic-resistant microorganisms raising real concerns about serious clinical outcomes in these patients. It is unknown whether the present situation of SBP in Saudi Arabia would be different from what has been reported by recent literature. We, therefore, conducted this observational study in Saudi Arabia on SBP aiming to characterise the clinical, microbiological and biochemical presentations, and the clinical outcomes of this unique infection in cirrhotic patients.

Patients and methods

We performed a retrospective chart review between January 2010 and April 2016 of all cirrhotic patients admitted with a diagnosis of ascitic fluid infection at the liver unit in King Abdulaziz Medical City (KAMC), Riyadh. Patients were identified via a hospital-based database using International Classification of Diseases [ICD-10]. The medical records of all patients admitted with a diagnosis of ascitic fluid infection were reviewed at the time of presentation for demographic data (age, sex, date of diagnosis of SBP, aetiology of liver disease, comorbidities), clinical presentation of SBP (fever, abdominal pain, hepatic encephalopathy, variceal bleeding, worsening of ascites, presence of hypotension and shock, previous attacks of SBP and secondary prophylactic antibiotic therapy), laboratory data (liver biochemistry, renal function tests, international normalised ratio [INR], blood counts, viral serology and ascitic fluid cell count and differential, culture and sensitivity, albumin and total protein) and radiological data regarding the presence of hepatocellular carcinoma and portal vein thrombosis. The Child Turcotte Pugh (CTP) and Model of End stage liver disease (MELD) scores were calculated at the time of admission for all patients. The data were collected by the study

Correspondence to : H. Al-Ghamdi, Assistant Professor, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, P.O. Box 225264, Riyadh 11324, Saudi Arabia. Tel: +966544852277.
E-mail: alghamdiha@ngha.med.sa.

Submission date : 14/04/2018
Acceptance date : 20/11/2018

investigators in pre specified case record forms and were transferred to a specific excel sheet for final analysis by Statistical Package for Social Sciences (SPSS) software. The study was approved by King Abdullah International Medical Research Centre (KAIMRC). The inclusion criteria for the study were : adult patient ≥ 15 years, evidence of cirrhosis based on radiological criteria and/or liver histology, ascites documented clinically and/or radiologically with ascitic fluid analysis revealing high Serum Ascites Albumin Gradient (SAAG) > 11 g/L and Polymorphonuclear cells (PMN) ≥ 250/mm^3 and/or positive ascitic fluid culture. We excluded patients with evidence of surgical peritonitis or non-bacterial peritonitis such as tuberculous or fungal peritonitis or inability to complete clinical, biochemical or bacteriologic data because of missing information. Diagnosis of SBP was made if diagnostic ascitic fluid showed PMN≥ 250/mm^3 with or without positive ascitic fluid culture. SBP with culture-negative neutrocytic ascites (CNNA) was treated as SBP. Patients with positive ascitic fluid culture and PMN≤ 250/mm^3 (bacterascites) were also treated as SBP if they were symptomatic or if a second ascitic tap showed PMN≥ 250/mm^3. If patients with bacterascites were asymptomatic and the second ascitic tap showed PMN≤ 250/mm^3 they were followed up. All patients were started on an empirical intravenous (IV) antibiotic while results of culture and sensitivity were awaited. Resolution of SBP was defined as PMNs <250 /mm^3 with negative culture following 48 hrs of empirical IV antibiotics.

Statistical analysis

Descriptive statistics were displayed as a percentage and continuous data with mean and standard deviation. The median and interquartile ranges (IQR) were used if data were not normally distributed. Fisher's exact test or the Chi- square test was used to compare frequencies to assess group differences for categorical variables. Data handling and analysis were performed with SPSS version 21 (SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics of patients

We identified 386 patients admitted with a diagnosis of ascitic fluid infection. One hundred and eighty six patients were excluded because they were either within a paediatric age < 15 years (n=63), did not meet SBP diagnostic criteria (n=53), or had incomplete medical data information (n=70). The study included 200 cirrhotic patients with a first episode of SBP. Mean age was 60.4±13.5 and 116 (58.0%) patients were male. One hundred and sixty two (81%) patients had comorbid illnesses with 99 (49.5%) having type II diabetes. The characteristics of the study population with SBP including underlying aetiology of cirrhosis, presenting symptoms, serum biochemistry and ascites morphology are shown in Table 1. The most common presenting symptom was increasing ascites in 183 (91.5%) followed by abdominal pain in 162 (81.0%) patients. Portosystemic encephalopathy was seen in 65 (32.5%) : 13 (6.5%) with grade 1, 40 (20.0%) grade 2, 9 (4.5%) grade 3, and 3 (1.5%) with grade 4. Twenty five (12.5%) patients had mild (grade 1) ascites, 97 (48.5%) patients had moderate (grade 2) ascites, 78 (39.0%) patients had severe (grade 3) ascites. Twenty three (11.5%) patients were diagnosed with SBP during hospital admission for acute variceal bleeding, 58 (29.0%) patients had HCC and 27 (13.5%) patients had portal vein thrombosis. Forty-one (20.5%) and three (1.5%) patients had a history of large volume paracentesis and variceal band ligation one week prior to diagnosis of SBP, respectively. Mean CTP score was 10.2 ± 1.9 ; 66 (33%) patients were CTP class B and 134 (67.0%) patients were CTP class C. The mean MELD score was 21.9± 7.5 ; eight (4%) patients had MELD

Table 1. — **Characteristics of two hundred patient with first episode of SBPS**

Parameter	**Value**	
Age (Years)	60.4 ± 13.5	
Male	116 (58.0)	
Female	84	(42.0)
Etiology of cirrhosis		
HCV	80	(40.0)
Cryptogenic	43	(21.5)
HBV	50	(25.0)
HBV/HDV co-infection	8 (4.0)	
Schistosomiasis	7 (3.5)	
Autoimmune hepatitis	5 (2.5)	
Alcohol	5 (2.5)	
Other aetiology	2 (1.0)	
Symptoms of SBP		
Abdominal pain	162 (81.0)	
Fever (temperature ≥38 C)	67	(33.5)
Increasing ascites	183 (91.5)	
Hypotension with systolic blood	43	(21.5)
pressure < 90 mmHg		
Portosystemic encephalopathy	65	(32.5)
Grade I	13	(6.5)
Grade II	40	(20)
Grade III	9 (4.5)	
Grade IV	3 (1.5)	
Total serum bilirubin*	76.5 µmol/L (43-168.3)	
Serum albumin	27	± 5.8 g/L
INR	1.8 ± 0.6	
Serum creatinine	136 ± 107.7 µmol/L	
CTP score	10.2 ± 1.9	
MELD	21.9 ± 7.5	
Ascitic fluid PMN*	652/mm^3 (301.6-2278)	
Ascitic fluid total protein	13.3 ± 7.7 g/L	
Ascitic fluid Albumin	6.4 ± 4.6 g/L	

Data presented as n, (%) or mean ± standard deviation. * median (IQR [interquartile range])

score 6-10, 91 (45.5%) patients had MELD score 11-20 and 101 (50.5%) patients had MELD score 21-40 (data not shown).

Microbiology of ascitic fluid

Ascitic fluid cultures as shown in Table 2 were positive in 103 (51.5%) patients and negative in 97 (48.5%). Ninety-eight (95.1%) patients had monomicrobial bacterial growth ; 64 (65.3%) and 34 (34.7%) patients had gram-negative and -positive microorganisms, respectively. Five (4.9%) patients had polymicrobial bacterial growth with two patients had ascitic fluid PMNs <250/mm^3 ; giving an overall prevalence of 1% risk for paracentesis needle-induced gut wall perforation. In the other three patients with polymicrobial cultures (1.5%), the ascitic fluid PMNs were > 250/mm^3 but none had evidence of surgical abdomen. Culture negative neutrocytic ascites (CNNA) was most common and diagnosed in 97 (48.5%) of patients followed by classical SBP in 65 (32.5%) patients.

The most common bacterial microorganisms were E.Coli in 41 (39.8%) patients followed by staphylococcus species in 19 (18.4%) patients. Staphylococcus aureus diagnosed in four patients (3.9%) whereas coagulase negative staphylococcus species were diagnosed in 12 (11.7%).

Extended spectrum beta lactamase (ESBL) E.Coli was isolated in 12 (29.2%) patients.

Data for bacterial culture and sensitivity are summarised in tables 2b and 3a. The antibiotic resistance of gram-negative microorganisms was highest for trimethoprim/sulfamethoxazole (46.7 %) and completely absent with meropenem (0%).

Antibiotic resistance for piperacillin\tazobactam, ceftriaxone and ciprofloxacin was 22.0%, 29.0% and 28.6%, respectively, while for gram-positive strains it was 57.9%, 52.6% and 0% with cefazolin, clindamycin and vancomycin, respectively. Resistance rate to E.Coli was 35.9%, 43.9%, 28.2%, and 65.9% for ceftriaxone, ciprofloxacin, piperacillin\tazobactam, and trimethoprim/sulfamethoxazole respectively (Figure 1).

Data on initial empirical IV antibiotic were available in 188 patients. The most commonly used empirical IV antibiotics were ceftriaxone in 142 (75.5%) patients followed by piperacillin/tazobactam in 30 (16.0%) patients, ciprofloxacin in eight (4.3%), cefotaxime in three (1.6%), meropenem in three (1.6%), and one (0.5%) each for ceftazidime and moxifloxacin.

All patients were placed on secondary SBP prophylaxis after the diagnosis of their first episodes of SBP. Antibiotics utilized for secondary prophylaxis showed that 166 patients (83%) were on fluoroquinolones and 34 patients (17%) were on Trimethoprim/sulfamethoxazole (P = 0.004). Thirty-six (18.0%) patients had recurrent episodes of SBP (mean episodes 2.5 ± 0.8). Among those on fluoroquinolones prophylaxis, 39.2% had recurrent SBP while 26.5% on Trimethoprim/sulfamethoxazole developed recurrence (P = 0.178).

There was no significant difference in terms of antibiotic resistance for gram-negative coverage by ceftriaxone vs. piperacillin/tazobactam (28.9% vs. 22.0%, respectively, *P* = 0.066). However, when ciprofloxacin was used as secondary SBP prophylaxis, it had a lower resistance rate than trimethoprim/sulfamethoxazole (28.6% vs. 46.7%, respectively, *P* = 0.02).

Discussion

Our study presents the largest data on SBP from Saudi Arabia. We performed this retrospective study to evaluate the clinical presentations, identify microbial patterns and antibiotics resistance profile in 200 patients with cirrhosis and SBP. Patients with SBP may have different clinical presentation ranging from asymptomatic infection to a life threatening disease. The vast majority of our patients were symptomatic at the time of SBP diagnosis. The most common symptoms and signs associated with SBP in our cohort were increasing ascites (91.5 %,) followed by abdominal pain (81%), jaundice (75%) and fever (33.5%). In the study by Bibi et al (9) clinical features in SBP patients observed in descending order were abdominal pain (65.8%), fever (52.6%), constipation (50%) and jaundice. In their study, they further observed

Table 2. — **Microbiology of spontaneous ascitic fluid infection and classification**

SBP Microbiology	**n=103 (%)**	**SBP subclass €**	**n=200 (%)**
E. Coli ∏	41(39.8)	SBP	65(32.5)
Klebsiella pneumonae	14(13.6)	CNNA	97(48.5)
Streptococcus Species	13(12.6)	MNB	36(18.0)
Enterococcus Species	3(2.9)	PB	2(1.0)
Enterobacter Species	4(3.9)		
Staphylococcus Species¶	19(18.4)		
Acinetobacter Species	2(1.9)		
Mixed organisms	3(2.9)		
Others rare single organism¥	4(3.9)		

∏ 12 extended-spectrum beta-lactamases E.Coli. 15 coagulase negative staphylococcus. ¥ 1 Salmonella non-Typhi, 1 ochrobacterium antropi, 2 pseudomonas aeruginosa. SBP= Spontaneous bacterial peritonitis, CNNA= Cul ture negative neutrocytic ascites, MNB= monomicrobial non neutrocytic bacterascites, PB= Polymicrobial non neutrocytic bacterascites.

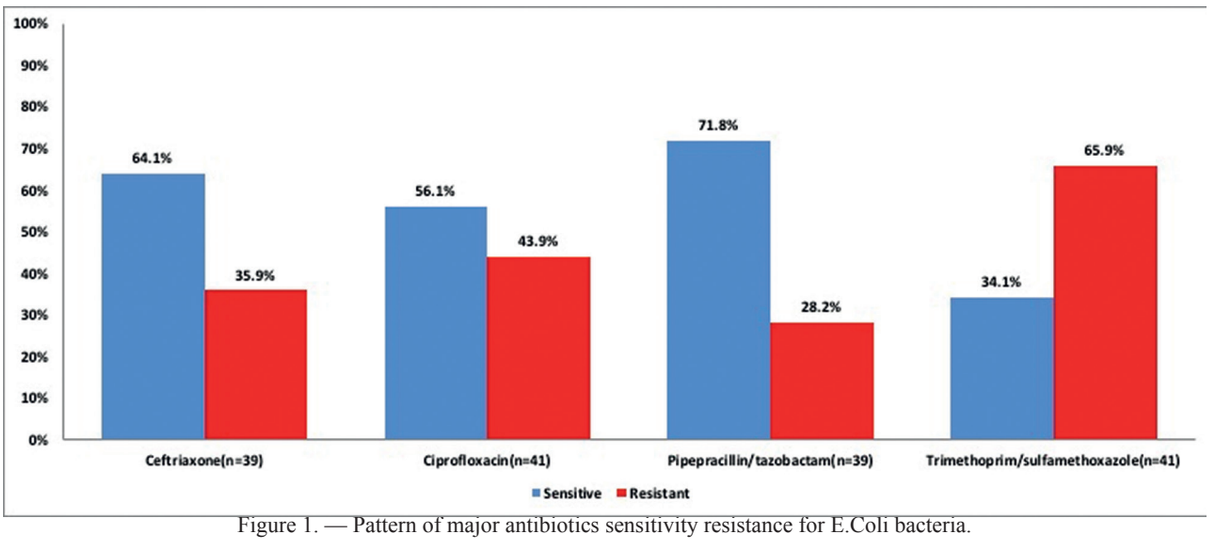

Figure 1. — Pattern of major antibiotics sensitivity resistance for E.Coli bacteria.

Table 3a. — **Antibiotics resistance and sensitivity for Gram-negative microorganisms from monomicrobial cultures**

	Ceftriaxone (n= 62)		Piperacillin/Tazobactam (n=59)		Meropenem (n=54)	Ciprofloxacin (n=63)		Trimethoprim/ Sulfamethoxazole (n=60)	
	R % (n)	S % (n)	R % (n)	S % (n)	S % (n)	R % (n)	S % (n)	R % (n)	S % (n)
Escherichia coli	35.9% (14)	64.1% (25)	28.2% (11)	71.8% (28)	100% (36)	43.9% (18)	56.1% (23)	65.9% (27)	34.1% (14)
Klebsiella pneumonae	0% (0)	100 % (14)	0 % (0)	100% (14)	100% (12)	0 % (0)	100% (13)	0% (0)	100% (14)
Klebsiella pneumonae	50 % (2)	50 % (2)	50 % (2)	50 % (2)	100% (4)	0 % (0)	100% (4)	0 % (0)	100% (4)
Acinetobacter sp.	50 % (1)	50% (1)	NR	NR	NR	0 % (0)	100 % (2)	100% (1)	0 % (0)
Other rare single organisms	33.3 % (1)	66.7% (2)	0 % (0)	100% (2)	100 % (2)	0 % (0)	100% (3)	NR	NR
Total	29 % (18)	71% (44)	22% (13)	78% (46)	100% (54)	28.6% (18)	71.4% (45)	46.7% (28)	53.3% (32)
P - value	0.094		0.066		NA	0.009		0.001	

S = sensitivity, R = Resistance, NA = Not Applicable, NR = Not Reporte, n = number of patients

that there is no clear association or specificity between these signs/symptoms when compared to non-SBP patients.

In our study, CNNA was the most common variant of spontaneous ascitic fluid infection. Different recent studies displayed CNNA as the most common variant of spontaneous ascitic infection in cirrhotic patients (10, 11).

In this study, we found that gram negative and gram-positive bacteria accounted for 65.3% and 34.7% of cases respectively. This result is consistent with the findings observed by other studies (12,13). The pathogenesis of SBP is related to bacterial translocation from gut hence the commonly isolated pathogens are usually enteric gram-negative bacilli. On the other hand, some studies have also reported the predominance of gram-positive microorganisms but this is uncommon and is often due to some prophylaxis or prior intervention (14).

Our study indicated that E. coli is still the most common microorganism for culture positive SBP. This corresponds to data obtained from other studies (15, 16). Our study reported a lower prevalence of staphylococcus aureus SBP 3.9% (4/103) than what was found by Cheong et al. (15) showing a prevalence of staphylococcus aureus SBP in their patients as 5.1% (12/236). However, 12 out of 19 patients with staphylococcus species SBP were secondary to coagulase negative staphylococcus species. In all these patients, ascitic fluid neutrocytosis

Table 3b. — **Antibiotics resistance and sensitivity of Gram-positive microorganisms from monomicrobial cultures**

	Vancomycin (n= 35)	Clindamycin (n=19)		Cefazolin (n=19)		Ceftriaxone (n=6)	Piperacillin/Tazobactam (n=6)
	S % (n)	R % (n)	S % (n)	R % (n)	S % (n)	S % (n)	S % (n)
Streptococcus sp.	100% (13)	NR	NR	NR	NR	100% (6)	100% (6)
Enterococcus sp.	100% (3)	NR	NR	NR	NR	NR	NR
Staphylococcus sp.	100% (18)	52.6% (10)	47.4% (9)	57.9% (11)	42.1% (8)	NR	NR
Total	100% (35)	52.6% (10)	47.4% (9)	57.9% (11)	42.1% (8)	100% (6)	100% (6)

S = sensitivity, R = Resistance, NR = Not Reported, n = number of patients

was evident. It is our observation, which is currently supported by other studies (17,18) that keeping pigtail ascitic drainage catheters for more than several hours after ascitic drainage can lead to SBP with coagulase negative staphylococcus species.

The prevalence of Enterococcus SBP in our study was 2.9%. In a study by Reuken et al (19) the prevalence of Enterococcus SBP increased from 11% to 35% over the 12 year study period. This was different from our findings. However, the prevalence of Enterococcus SBP may represent regional differences in different parts of the world. For instance, it was reported to be a 4% in China (1996–2010) ;(20) and 11–35% in France (1996-2003) (21.22). In our study, 12/41 (29.2%) patients infected with E. coli had ESBL- E.Coli (29.2%). Fernández et al (14) noted an increased frequency of infections caused by ESBL- E.Coli in cirrhotic patients from 1.2% in 2002 to 8.7% in 2010-2011. The reported risk factors were nosocomial origin of infection and previous treatment with beta-lactamase or quinolones.

In this study, best antibiotic sensitivity results (100%) were identified with meropenem for gram-negative microorganisms and Vancomycin for gram-positive microorganisms. In a local combined study from Egyptian and Saudi patients (23), meropenem sensitivity in SBP patients was reported as 90 and 85% to E-coli and Klebsiella isolates, respectively. Sensitivity pattern is quite variable throughout the world with a trend toward increased resistance to first line empirical antibiotics for SBP especially third generation cephalosporins (3GCs) and fluoroquinolones.

In our study, 29% and 22% of gram-negative bacteria were resistant to 3GCs and piperacillin/tazobactam respectively. However, the use of piperacillin/tazobactam as an initial antibiotic in our study showed a trend toward better gram-negative coverage (P = 0.066). One recent study (24) evidenced antibiotic coverage by piperacillin/tazobactam to be better than cephalosporins (73% vs. 57%). A recent systematic review and meta-analysis (25) found a resistant rate to 3GCs to be a 54.3% and 33.8 % for gram-negative nosocomial-SBP and community acquired-SBP respectively. There are various studies comparing efficacy of trimethoprim/sulfamethoxazole to quinolones, especially norfloxacin. Lontos et al (26) observed similar efficacy for both of these antibiotics in prevention of SBP. In our study resistance pattern of ciprofloxacin was better as compared to trimethoprim/sulfamethoxazole (ciprofloxacin resistance 28.6% vs. Trimethoprim/sulfamethoxazole resistance 46.7% ; p = 0.02). Therefore, when these two drugs were used for secondary SBP prophylaxis, ciprofloxacin remained superior to trimethoprim/sulfamethoxazole.

It is important to note that in our study, the resistance to Ceftriaxone and Ciprofloxacin, which are recommended as first line therapy for patients with SBP was 29% and 28.6%, respectively.

The rates of cephalosporins resistance in patients with SBP were shown to be 21 to 45% in other studies (27, 28).

In conclusion, our data confirmed the changes in the patterns and microbiology of SBP in our region with increasing prevalence of culture negative SBP, extended spectrum beta-lactamases resistant E.Coli and increasing resistance to first line antibiotics recommended as initial and empiric drugs for SBP. Our data argues for relying on periodic hospital based culture surveys whenever prescribing empirical antibiotics for SBP.

References

1. NAVASA M., RIMOLA A., RODES J. Bacterial infections in liver disease. *Semin Liver Dis*., 1997, **17** : 323-333.

2. WONG F., BERNARDI M., BALK R., CHRISTMAN B., MOREAU R., GARCIA-TSAO G., PATCH D., *et al.* Sepsis in cirrhosis : report on the 7th meeting of the International Ascites Club. *Gut*, 2005 May, **54(5)** : 718-25.
3. SUCH J., RUNYON B.A. Spontaneous bacterial peritonitis. *Clin Infect Dis*., 1998, **27** : 669-674.
4. TANDON P., GARCIA-TSAO G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis*., 2008, **28** : 26-42.
5. GARCIA-TSAO G. Current management of the complications of cirrhosis and portal hypertension : variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology*, 2001, **120** : 726-748.
6. FERNÁNDEZ J.I., NAVASA M., GÓMEZ J., COLMENERO J., VILA J., ARROYO V., RODÉS J. Bacterial infections in cirrhosis : epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*, 2002, **35(1)** : 140-148.
7. PIROTH L., PECHINOT A., DI MARTINO V., HANSMANN Y., PUTOT A., PATRY I., HADOU T., *et al*. Evolving epidemiology and antimicrobial resistance in spontaneous bacterial peritonitis : a two-year observational study. BMC Infect Dis., 2014, May 23, **14** : 287.
8. ALEXOPOULOU A., PAPADOPOULOS N., ELIOPOULOS D.G., ALEXAKI A., TSIRIGA A., TOUTOUZA M., PECTASIDES D. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int*., 2013, Aug. **33(7)** : 975-81.
9. BIBI, S., AHMED, W., ARIF, A., KHAN, F., ALAM, S.E. Clinical, laboratory and bacterial profile of Spontaneous Bacterial Peritonitis in Chronic Liver Disease patients. *J Coll Physicians Surg Pak*., 2015 Feb., **25(2)** : 95-9.
10. NA S.H., KIM E.J., NAM E.Y., SONG K.H., CHOE P.G., PARK W.B., BANG J.H., *et al*. Comparison of clinical characteristics and outcomes of spontaneous bacterial peritonitis and culture negative neutrocytic ascites. *Scand J Gastroenterol*., 2017, Feb., **52(2)** : 199-203.
11. KIM S.U1., KIM D.Y., LEE C.K., PARK J.Y., KIM S.H., KIM H.M., CHOI E.H., *et al*. Ascitic fluid infection in patients with hepatitis B virus-related liver cirrhosis : culture-negative neutrocytic ascites versus spontaneous bacterial peritonitis. *J Gastroenterol Hepatol.*, 2010, Jan., **25(1)** : 122-8.
12. MUKHTAR AHMAD, MOHAMMAD MUMTAZ, AAMIR ABBAS, AMEER ABBAS ALI, JAVED IQBAL. Spontaneous Bacterial Peritonitis ; Microbiological Analysis of Ascitic Fluid in Patients with Complicated Liver Cirrhosis. *Professional Med J*., Oct-Dec 2011, **18(4)** : 557-561
13. CALY, W.R., STRAUSS, E. A prospective study of bacterial infections in patients with cirrhosis. *J Hepatol*., 1993, **18** : 353-358.
14. FERNÁNDEZ J1., NAVASA M., GÓMEZ J., COLMENERO J., VILA J., ARROYO V., RODÉS J. Bacterial infections in cirrhosis : epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*, 2002, Jan., **35(1)** : 140-8
15. CHEONG H.S., KANG C.I., LEE J.A., MOON S.Y., JOUNG M.K., CHUNG D.R., KOH K.C., *et al.* Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis*., 2009, May 1, **48(9)** : 1230-6.
16. FERNÁNDEZ J1., ACEVEDO J., CASTRO M., GARCIA O., DE LOPE C.R., ROCA D., PAVESI M., *et al*. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis : a prospective study. *Hepatology*, 2012, May, **55(5)** : 1551-61.
17. KATHPALIA P., BHATIA A., ROBERTAZZI S., AHN J., COHEN S.M., SONTAG S., LUKE A., *et al*. Indwelling peritoneal catheters in patients with cirrhosis and refractory ascites. *Intern Med J*., 2015, Oct., **45(10)** : 1026-31.
18. TASHIRO M., IZUMIKAWA K., ASHIZAWA N., NARUKAWA M., YAMAMOTO Y. Clinical significance of methicillin-resistant coagulase-negative staphylococci obtained from sterile specimens. *Diagn Microbiol Infect Dis.* ,2015, Jan., **81(1)** : 71-5.
19. REUKEN P.A.., PLETZ M.W., BAIER M., PFISTER W., STALLMACH A., BRUNS T. Emergence of spontaneous bacterial peritonitis due to enterococci-risk factors and outcome in a 12-year retrospective study. *Alimentary Pharmacol. Therapeutics*, 2012, **35(10)** : 1199-1208
20. GOU Y.-Z., LIU B., PAN L., YU H.-T., WANG J.-P., WANG D.-C. Pathogens of spontaneous bacterial peritonitis change in northern China. *Saudi Med J*., 2010, **31** : 1152-6.
21. BERT F., ANDREU M., DURAND F., DEGOS F., GALDBART J.O., MOREAU R., BRANGER C., *et al.* Nosocomial and community-acquired spontaneous bacterial peritonitis : comparative microbiology and therapeutic implications. *Eur J ClinMicrobiol Infect Dis*., 2003, **22** : 10-5.
22. CAMPILLO B., RICHARDET J.-P., KHEO T., DUPEYRON C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients : impact of isolate type on prognosis and characteristics of infection. *Clin Infect Dis.*, 2002, **35** : 1-10.
23. HASSAN-ELBANNA M.A.Y., JIMAN-FATANI A.A.M. Spontaneous Bacterial Peritonitis in Egyptian and Saudi Patients with Liver Cirrhosis. J. of King Abdulaziz University : Medical Sci., 2011, **18(3)** : 29-46.
24. NOVOVIC S., SEMB S., OLSEN H., MOSER C., KNUDSEN J.D., HOMANN C. First-line treatment with cephalosporins in spontaneous bacterial peritonitis provides poor antibiotic coverage. *Scand J Gastroenterol*., 2012, Feb., **47(2)** : 212-6..
25. FIORE M., GENTILE, MARAOLO A.E., LEONE S., SIMEON V., CHIODINI P., PACE M.C1., *et al*. Are third-generation cephalosporins still the empirical antibiotic treatment of community-acquired spontaneous bacterial peritonitis? A systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.*, 2018, March, **30(3)** : 329-336.
26. LONTOS S., GOW P.J., VAUGHAN R.B., ANGUS P.W.J. Norfloxacin and trimethoprim-sulfamethoxazole therapy have similar efficacy in prevention of spontaneous bacterial peritonitis. *Gastroenterol Hepatol.*, 2008, Feb., **23(2)** : 252-5.
27. PARK M.K., LEE J.H., BYUN Y.H., LEE H.I., GWAK G.Y., CHOI M.S., KOH K.C., *et al*., Changes in the profiles of causative agents and antibiotic resistance rate for spontaneous bacterial peritonitis : an analysis of cultured microorganisms in recent 12 years. *Korean J Hepatol*., 2007, Sep., **13(3)** : 370-7.
28. ARIZA X., CASTELLOTE J., LORA-TAMAYO J., GIRBAU A., SALORD S., ROTA R., ARIZA J., *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** : 825-832.