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Clinical and Laboratory Forms of Conteporary Manifestation of Spontaneous Bacterial Peritonitis

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1. Abstract

1.1. Objective: Spontaneous Bacterial Peritonitis (SBP) is a big complication of severe complication "ascites" in patients with cirrhosis. There are three clinical forms of SBP (1982) – latent, classical and fulminant. Classic symptoms of peritonitis in SBP are usually absent. Diagnosis of SBP is established if polymorphonuclears (PMNs) in ascitic fluid are >250/mm^3 – SBP (PMNs >250/mm^3 and positive bacterial cultures) and culture negative neutrophylic ascites (CNNA) or bacterascites (positive bacterial cultures from ascitic fluid and PMNs <250/mm^3).

1.2. Aim: The aim of this study is to separate forms of contemporary course of SBP, based on combination of all clinical (classical, oligosymptomatic, fulminant, latent, extraperitoneal) and laboratory forms (SBP, CNNA and bacterascites).

1.3. Patients and Methods: 302 patients with liver cirrhosis and ascites grade II and III have been investigated over a ten-year period (2007-2016). 68 patients were admited in hospital more than once time. SBP was diagnosed in 54 patients (14,6% of all 370 hospitalizations). Latent clinical form of SBP is deffined as a form without any clinical symptoms and laboratory abnormalities. Patients with classical form have at least two of three main clinical symptoms (pain, fevere, leukoytosis). Patients with olygosymptomatic form have only one of three main clinical symptoms. Extraperitoneal form is deffined as latent form with hepatic encephalopathy or hepatorenal syndrome. Fulminant form is deffined as form that manifests with septicaemia, shock, ileus, hepatic or multiorgan failure.

1.4. Results: Diffuse abdominal pain was significantly more frequent ($p = 0{,}00001$) in patients with SBP (31,5%) compared to patients with cirrhosis and sterile ascitic fluid (3,6%). patients with SBP were significantly more frequent (p = 0,006) febrile (29,7%) than patients with cirrhosis and sterile ascitic fluid (11,7%). Leukocytosis had been observed in 1/4 (24,1%) of patients with SBP. Only one patient (1,8%), with fulminant form of SBP, have had all clinical and laboratory symptoms (pain, fever and leukocytosis). Five different clinical forms of SBP were separated – classical (20,4%), oligosymptomatic (64,8%), fulminant (1,8%), latent (0%), extraperitoneal (13%) – latent form with hepatic encephalopdthy and/or hepatorenal syndrome. Frequency of typical SBP was 14,8%; CNNA – 83,3%; bacterascites – 1,8%.

1.5. Conclusion: The combination of oligosymptomatic form with CNNA (the most frequent laboratory form in the study) was established in 61,1% of all patients with SBP.

2. Background

Peritonitis in patients with liver cirrhosis and ascites is classified as spontaneous, secondary and perforative [1]. Nowadays between 30% and 50% of patients with hepatic cirrhosis die due to bacterial infec-

tions [2, 3]. Spontaneous bacterial peritonitis (SBP) is a big complication of severe complication "ascites" in patients with cirrhosis [4-6]. SBP is the main cause of death in patients with cirrhosis [3, 5]. The frequency of SBP is ≈10% of all hospitalized patients with cirrhosis and ascites (1,5-3,5% in outpatients) [7]. The frequency of SBP may increase to 19-33% of patients with cirrhosis and ascites as far as the cases with: i) culture-negative neutrophilic ascites (CNNA), which is a variant of SBP; ii) ascitic fluid total protein (AFTP) <10g/L, and iii) double elevated serum bilirubin and/or serum creatinin >88,4μmol/L (independent of the sex) are concerned [8-11].

There are three clinical forms of SBP (1982) – latent, classical and fulminant [12]. Classic symptoms of peritonitis often absent in patients with SBP [13]. Completely asymptomatic course of the SBP have 10% of patients [14]. However only in third (31,7%) of patient's clinical suspicion for SBP is confirmed [15].

The ascitic bacterial cultures are rarely positive (≈40%) in SBP [8] due to the low concentration of microorganisms in ascitic fluid (1 bacteria/1mL [9]), even if collected in blood culture bottles (≈70% [8]).

According to IAC (International Ascites Club) the SBP diagnosis is considered to be placed in polymorphonuclears (PMNs) >250/mm^3 [16], including the cases of culture-negative neutrophilic ascites (CNNA) - variant of SBP [8], as there is no significant difference in mortality between SBP and CNNA [17]. There are three laboratory forms of SBP – classical form of SBP (PMNs >250/mm^3 and positive bacterial cultures) and Culture Negative Neutrophylic Ascites (CNNA) or bacterascites (positive bacterial cultures from ascitic fluid and PMNs <250/mm^3) [8]. PMNs in ascitic fluid increase >250/mm^3 in gram-negative flora, but it is not clear whether this is the same in gram-positive microorganisms [18]. At present, half of the episodes of SBP are caused by gram-positive bacteria [19].

3. Aim

The aim of this study is to separate forms of contemporary course of SBP, based on combination of all clinical (classical, oligosymptomatic, fulminant, latent, extraperitoneal) and laboratory forms (SBP, CNNA and bacterascites).

4. Patients and Methods

302 patients with liver cirrhosis and ascites grade II and III were investigated for ten-year period (2007-2016) - 74 wemen and 228 men [mean age 59 (30-86) years]. 302 patients were admited in hospital 370 times.

SBP have been diagnosed in 14,6% [54/370 of hospitalized patients with cirrhosis and ascites grade II or III], who was compared to 243 patients with cirrhosis and sterile ascites [Nine patients (9/307 - 2,9%) had secondary bacterial peritonitis (Sec BP)].

Routine hematological, biochemical, immunological, virological and instrumental examinations (ultrasonography, upper gastrointestinal endoscopy) were performed in all patients.

Ascitic fluid was investigated biochemically, with differential count (PMNs), bacterial cultures and cytologically in all patients.

Latent clinical form of SBP is deffined as a form without any clinical symptoms and laboratory abnormalities.Patients with classical form have at least two of three main clinical symptoms (pain, fevere, leukocytosis). Patients with olygosymptomatic form have only one of three main clinical symptoms. Extraperitoneal form is deffined as latent form with hepatic encephalopathy or hepatorenal syndrome. Extraperitoneal form with combination with other symptoms (overlap - e.g. fever) is deffined as other (e.g. olygosymptomatic). Fulminant form is deffined as form that manifests with septicaemia, shock, ileus, hepatic or multiorgan failure.

5. Statistical Methods

In accordance with the aims of the research it was necessary to do comparisions between proportions of two independent groups on a dichotomous dependent variable. In order to determine whether the difference in two proportions was statistically significant the Z-test was applied for samples with sizes more than 50 and T-test for rest of the cases. The significance of the results given below is represented by corresponding p-values.

6. Result

Diffuse abdominal pain was significant more frequent $(p = 0{,}00001 < 0{,}05)$ in patients with SBP compared to patients with cirrhosis and sterile ascites (31,5% v/s 3,6%).In more than half (57,4%) of the patients with SBP in the study there was no abdminal pain or tenderness at all.

Leukocytosis was established in 24,1% of patients with SBP. Mean level of leukocytosis was 16,5.10^9 (10,8-35,3.10^9), and only in 7,4% of patients with SBP leucocytoasis was >15.10^9.

Combination of the three main clinical and laboratory symptoms (pain, fever, leucocytosis) had only one patient (1,85%) with fulminant form of SBP.

Five clearly differentiated clinical forms of SBP were established in the study – classical, olygosymptomatic, latent, extraperitoneal and fulminant.

Olygosymptomatic clinical form of SBP was three times more frequent (64,8%) than classical form (20,4%). Seven of the patients with extraperitoneal form of SBP had hepatic encephalopathy or hepatorenal syndrome.

Clinical symptoms of hepatic encephalopathy (stage II-IV by West Haven) have been established in 1/5 (20,4%) of patients with SBP and 17,7% of patients with cirrhosis and sterile ascites.

Renal dysfunction was also established in 1/5 (20,4%) of patients with SBP and in 23,5% of patients with cirrhosis and sterile ascites.

CNNA was significant more frequent form (83,3%) than classical SBP (14,8%). Bacterascites was present in only one patient (1,85%).

Positive bacterial cultures from ascitic fluid in patients with SBP in the study were very low – 16,7%. Gram-negative microorganisms were insignificantly more frequent than Gram-positive - 9,3% v/s 7,4%.

Combination of olygosymptomatic clinical form with CNNA (61,1%)was significant more frequent $(p < 0,0001)$ in comparison to other combinations of forms of SBP in the study.

7. Discussion

Nevertheless that diffuse abdominal pain was significant more frequent (31,5%) in patients with SBP versus patients with cirrhosis and sterile ascites (3,7%) (Figure 1), lack of abdominal pain or tenderness (57,4%) does not exclude SBP. Abdominal pain may be absent in patients with ascites >10L, even in patients with perforated peritonitis [13]. On one hand patients with SBP were significant more frequent sub febrile and febrile (29,7%) (Figure 1), while elevated temperature had only 11,7% of patients with cirrhosis and sterile ascites. On the other hand, 70,3% of patients with SBP and 88,3% of patients with cirrhosis and sterile ascites were afebrile Accepting "febris hepatica" as possible cause of febrile syndrome should be very carefully thought of. Not all bacterial infections (mainly pulmonary and uroinfections) are proved [19]. Leukocytosis was present in 1/4 (24,1%) of patients with SBP. In patients with diabetes mellitus type 2 (23,9% of patients with cirrhosis and ascites in the study compared to 9% in Bulgarian population) febrile syndrome and leukocytosis may be absent in patients with infections.

Half of the patients with contemporary clinical course of SBP have no pain, temperature or leukocytosis [6], but results of the study are even lower, especially in combination of these main clinical and laboratory symptoms (Figure 1). Hepatic encephalopathy and renal dysfunction may be the only presentation of SBP [2, 20].

Patients with SBP have at least one of the following seven symptoms:

- Abdominal pain, abdominal tenderness, vomiting, diarrhea, ileus;
- Signs of systemic inflammation: hyper or hypothermia, chills, tachycardia, tachypnea, leukocytosis;
- Deterioration of liver function;
- Hepatic encephalopathy;
- Shock;
- Renal failure;
- Gastrointestinal bleeding [8].

SBP may have completely asymptomatic course [8].

Apart from the well-known three clinical forms of SBP described in 1982 – latent, classical and fulminant [12], there are additional two forms – olygosymptomatic and extraperitoneal (Figure 2). The last two forms truly exist in the contemporary course of SBP. Fulminant forms of SBP decrease all over the world while latent increase (10%) [14].

The reason of lack of patients with completely asymptomatic course of SBP (latent form) in the study is the relation of SBP with hepatic encephalopathy and hepatorenal syndrome, which are separate forms of SBP – extraperitoneal form (13%). The last form is a latent form of SBP without pain, fever or leukocytosis but with clinic manifestation - encephalopathy or hepatorenal syndrome.

Bacterial cultures from ascitic fluid with routine examination are rarely positive (≈40%) in patients with SBP [8]. Positive bacterial cultures in the study were 16,7% (Figure 3) - SBP and bacterascites. In India bacterial cultures from ascitic fluid in patients with SBP are positive in 22,2% and in Portugal – 26% [21]. The ascitic bacterial cultures are rarely positive in SBP (1 bacteria/1mL ascitic fluid) [9], even if collected in blood culture bottles (≈70%) [8]. Detection of bacterial DNA in ascitic fluid is with no clinical relevant [7, 22].

Olygosymptomatic clinical form (64,8%) (Figure 2) and CNNA (83,3%) (Figure 3) and their combination (61,1%) (Table 1) were the most frequent forms of contemporary course of SBP in the study.

Bacterascites (BA) is rare - 5% [8] (1,85% in the study) and usually abortive form of SBP (more often in patients with cirrhosis Child-Pugh class B).BA does not require treatment, if there are no clinical symptoms and/or systemic manifestations, but observation (and second investigation of ascitic fluid) because BA can progress to classic SBP [8].

SBP, CNNA and BA are three forms of SBP [8]. Very high frequency of CNNA is typical for Bulgaria [possible as well in othher contries], because bacterial cultures are rarely positive during conventional microbiological investigation. However positive bacterial cultures from ascitic fluid in patients with SBP are no more than 70%, even ascitic fluid is obtain in blood cultures bottles by patient's ped [8]. This mean that frequency of CNNA is at least 25-30%, even ascitic fluid is obtain in blood cultures bottles by patient's bed and that combination between olygosymptomatic clinical form of SBP and CNNA if it is not the most frequent form, it is the second frequent form in the world.

Table 1: Frequency of clinical forms of spontaneous bacterial peritonitis in combination with forms according to bacterial cultures and polymorphonuclear leukocytes in ascitic fluid.

Forms of SBP	SBP *	CNNA**	BA***	Total
Fulminant	1,85% (1/54)	-	-	1,85% (1/54)
Classical	11,11% (6/54)	9,26% (5/54)	-	20,37% (11/54)
Olygosymptomatic	1,85% (1/54)	61,11% (33/54)	1,85% (1/54)	64,81% (35/54)
Extraperitoneal	-	12,96% (7/54)	-	12,96% (7/54)
Latent	-	-	-	-
Total	14,81% (8/54)	83,33% (45/54)	1,85% (1/54)	100% (54/54)

*SBP – spontaneous bacterial peritonitis
**CNNA –culture negative neutrophylic ascites
***BA –bacterascites

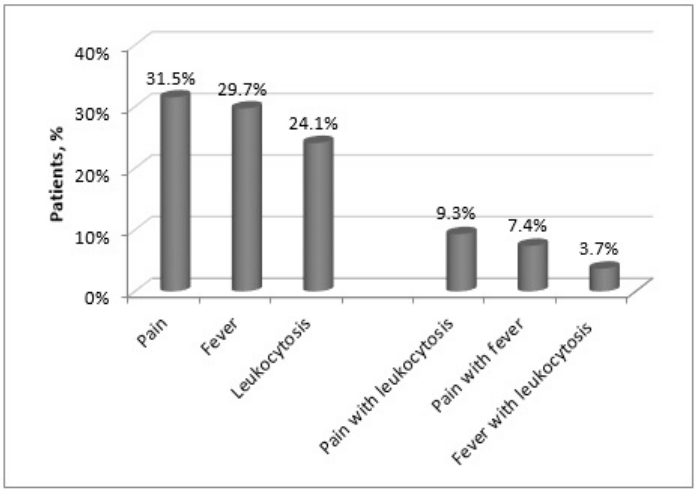


Figure 1: Most frequent clinical and laboratory symptoms (pain, fever, leucocytosis) of spontaneous bacterial peritonitis and their combination.

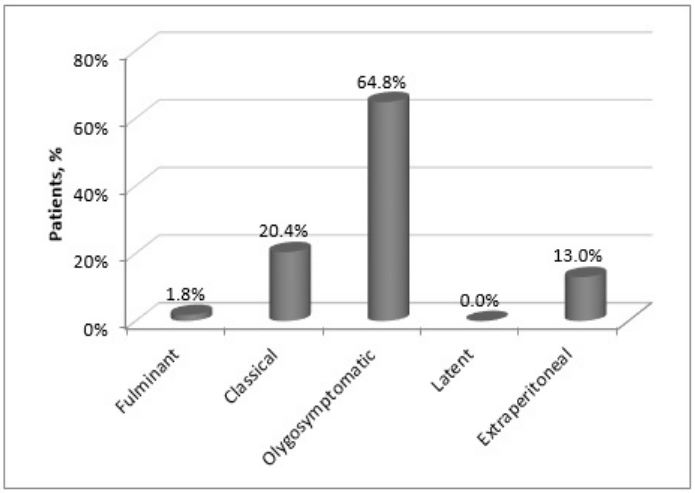
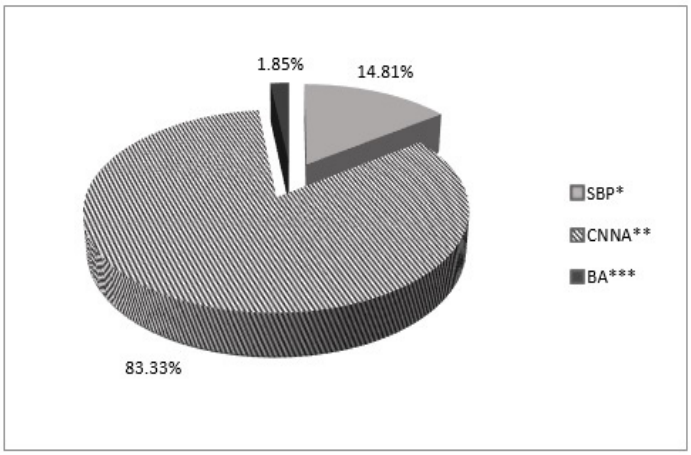


Figure 2: Frequency of five established clinical forms of spontaneous bacterial peritonitis



*SBP – *spontaneous bacterial peritonitis*
**CNNA –*culture negative neutrophylic ascites*
***BA –*bacterascites*

Figure 3: Frequency of the forms of spontaneous bacterial peritonitis according to bacterial cultures and polymorphonuclear leukocytes in ascitic fluid.

The problem concerning management (empirical treatment or observation) of patients with cirrhosis and negative bacterial cultures from ascitic fluid and PMNs in fluid ≤250/mm^3 but with clinical symptoms (including hepatic encephalopathy or hepatorenal syndrome) remain unsolved. It is questionable if in part of those patients it is referring to bacterascites with clinical symptoms (bacteremia) and false-negative results of bacterial cultures from ascitic fluid (including hemocultures). Bacterascites with clinical symptoms and/or systemic manifestations is indication for treatment as in patients with SBP [8].

8. Conclusion

Contemporary course of SBP is not usual. Five clinical forms of SBP are separated – latent, olygosymptomatic, classical, fulminant and extraperitoneal. Combination of olygosymptomatic clinical form of SBP (64,8%) and CNNA (83,3%) is the most frequent form of SBP (61,1%) in the study.

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