Secondary and Spontaneous Bacterial Peritonitis in Patients With Liver Cirrhosis and Ascites

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Introduction

Spontaneous bacterial peritonitis (SBP) is the main cause of death in patients with liver cirrhosis. SBP is a disease of the gut – after bacterial translocation of monomicrobial flora in mesenteric lymph nodes, while secondary bacterial peritonitis (SecBP) is due to an intra-abdominal source of infection – perforation or inflammation. Peritonitis in liver cirrhosis is classified as spontaneous, secondary and perforative. The frequency of SBP is ~10% of all hospitalized patients with cirrhosis and ascites, while the frequency of SecBP is ~5%, therefore SecBP reports are few. The treatment of SBP is conducted with drugs, while SecBP is treated preferably surgically. While the mortality from SBP nowadays has decreased from 90% to 20%, in SecBP it remains high (60-80%). There are three clinical forms of SBP – latent (10%), classical and fulminant (5%). The oligosymptomatic clinical form of SBP and the culture-negative neutrophilic ascites (CNNA) are the most common forms of contemporary ongoing SBP. Today SBP can be observed in half of the patients with cirrhosis in class B. Peritonitis in Child-Pugh class A cirrhosis is probably secondary. IAC (International Ascites Club) recommends the SBP diagnosis to be taken in polymorphonuclear leucocytes (PMNs) in ascitic fluid >250/mm³ regardless of the result of bacterial cultures. Leucocytes /and ascitic fluid total protein (AFTP)/ increase in ascitic fluid after diuretic treatment, but not the PMNs. In patients with AFTP<10g/L the risk of SBP increases tenfold /decreased opsonic activity of ascitic fluid/. The ascitic bacterial cultures in SBP are rarely positive. At present, half of the episodes of SBP are caused by gram-positive bacteria. Blood cultures should be performed in all patients with suspected SBP. Bacterioscites (5%) does not need treatment, but monitoring, if there are no clinical symptoms and signs of systemic inflammation or infection. SecBP should be suspected in patients who have localized abdominal symptoms or signs, presence of multiple microorganisms (aerobes and anaerobes) in ascitic culture, very high ascitic neutrophil count and high ascitic total protein concentration. A SecBP should be suspected when at least two of the following features are present in ascitic fluid: glucose levels <50mg/dL, protein concentration >10g/L, lactic dehydrogenase concentration > normal serum levels. Due to the low sensitivity and specificity of these criteria for SecBP, examination of alkaline phosphatase (>225U/L) and carcinoembryonic antigen (>5ng/ml) in ascites are recommended /Runyon’s criteria/. Patients with suspected SecBP should undergo CT.

Conclusion: The medical and surgical treatment of peritonitis in liver cirrhosis may be almost equally dangerous in wrong diagnosis.

Keywords: Spontaneous bacterial peritonitis; Secondary bacterial peritonitis; Classification of peritonitis in liver cirrhosis; Ascitic fluid

Introduction

Nowadays between 30% and 50% of patients with liver cirrhosis die due to bacterial infection [1, 2]. Spontaneous bacterial peritonitis (SBP) (H Cohn, 1963) is the main cause of death in patients with hepatic cirrhosis [1-3]. SBP is bacterial infection of ascitic fluid without any intra-abdominal source of infection [4, 5]. SBP is a disease of the gut [6] – after bacterial translocation (R Berg, 1979) of monomicrobial flora in mesenteric lymph nodes [7], while secondary bacterial peritonitis (SecBP) is due to an intra-abdominal source of infection – perforation or inflammation [8, 9]. SBP is a big complication of severe complication “ascites” in liver cirrhosis [10, 11], which does not require surgery [3], unlike most forms of SecBP in which the surgical removal of the source of peritonitis is crucial for the survival [12]. Furthermore, in 30% of patients with SecBP...
resistance to antimicrobial treatment is established [13]. Patients with suspected SecBP should undergo prompt CT scanning and early consideration for surgery [9].

The frequency of SBP is ~10% of all hospitalized patients with cirrhosis and ascites (1.5-3.5% in outpatients) [9, 14]. The frequency of SBP may increase to 19-33% 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 creatinine >88.4µmol/L / independent of the sex/ are concerned [15-18]. The frequency of SecBP is ~5% [9] (4.5-15%) of patients with liver cirrhosis and ascites [3, 8], therefore SecBP reports are few [8]. The treatment of SBP is conducted with drugs [15], while SecBP is treated preferably surgically [8, 12]. The failure of empiric treatment of SBP may be due to antimicrobial resistance or SecBP [15]. Peritonitis (SBP and SecBP) is the most frequent and serious complication of ascites in patients with cirrhosis. While the mortality from SBP nowadays has decreased from 90% to 20% [9], in SecBP it remains high (60-80%) [1]. In early surgery the SecBP mortality is 35.8%, while in non-operated patients – 81.8% [8].

Classification of Peritonitis in Liver Cirrhosis

A small proportion of patients with liver cirrhosis may develop peritonitis due to perforation or inflammation of an intraabdominal organ, a condition known as SecBP [9, 15]. Therefore, peritonitis in patients with cirrhosis and ascites is classified as spontaneous and secondary – nonperformative and perforative [15]. On the other hand, the perforative peritonitis is not secondary peritonitis. Therefore, it is more accurately peritonitis in liver cirrhosis to be classified as spontaneous, secondary and perforative. Peritonitis occurring after successful surgical treatment of SecBP is indicated as tertiary bacterial peritonitis [19]. The increased CRP in the second postoperative day after treatment of SecBP directs to the diagnosis “tertiary peritonitis” [19]. Elevated CRP is better diagnostic marker for SBP and SecBP than leukocytosis [20].

Persistent SBP /without effect 48h after start of the treatment/ is common complication (40%) in patients with SBP and high score in the MELD (>25) [21]. MELD score /in contrast to Child-Pugh classification / is not related to SBP [22]. Peritonitis in Child-Pugh class A cirrhosis is probably secondary [16]. Mortality in patients with persistent SBP is high [21]. Spontaneous fungal peritonitis (SFP) is a rare (<5%) less recognized complication, but observational data suggest worse prognosis [23]. Clinical symptoms. Half of episodes of SBP are present at the time of hospital admission [15, 16, 24]. With asces >10L peritoneal tenderness is missing even in perforative peritonitis [25]. On one hand common clinical symptoms and tenderness of the abdominal wall can target to SBP or SecBP but cannot be differential diagnostic criteria. On the other hand, clinically suspected SBP is confirmed only in 1/3 of cases [3]. Patients with SBP may have i) signs of peritonitis, abdominal wall tenderness, vomiting, diarrhea, ileus; ii) signs of systemic inflammation; iii) worsening liver function; iv) hepatic encephalopathy; v) shock; vi) renal failure; vii) upper gastrointestinal bleeding [9, 14]. SBP in 10% of cases occurs totally asymptomatic [16, 25], particularly in outpatients [14]. There are three clinical forms of SBP – latent (10%), classical and fulminant (5%) [26]. The classical (oligosymptomatic) clinical form of SBP and the CNNA /at least in 30% of patients with SBP [15] are the most common forms of contemporary ongoing SBP.

Although SBP has been observed in 70-85% of patients with Child-Pugh class C liver cirrhosis [3], today SBP can be observed in 51-68.5% of the patients with cirrhosis in class B [27, 28]. Peritonitis in Child-Pugh class A cirrhosis is probably secondary [16]. MELD score is not related to SBP [22] and SecBP, but mortality in patients with SBP and high MELD score is high. Perihepatic blood leucocyte count ≥11x109/L and/or MELD ≥22 define poor prognosis of SBP [29]. SecBP should be suspected in patients who have localized abdominal symptoms or signs, presence of multiple organisms on ascitic culture, very high ascitic neutrophil count and high ascitic total protein concentration [8]. The differential diagnosis between SBP and SecBP is not always easy.

Polymorphonuclear Leukocytes (PMNs) in Ascitic Fluid

Peritoneal infection causes an inflammatory reaction in an increasing number of neutrophils in ascitic fluid [9]. Leucocytes / and total protein/ increase in ascitic fluid after diuretic treatment, but not the PMNs [30]. PMNs, however, increase (>250mm³) only upon infection [30]. The gold standard for ascitic neutrophil count is manual microscopy [9] but can be substituted with a flow cytometry based automated count – sensitivity and specificity close to 100% [31, 32]. The sensitivity of flow cytometry in patients with SBP /or CNNA/ and PMNs ≥250/mm³ is 86-100% [33]. The use of reagent strips (RS) has not clear evidence to support it in routine practice [9] for diagnosis of SBP. Although the specificity and the negative predictive value of RS are high (92% and 95%) [34], the sensitivity is low. Multistix 8SG RS [15] sensitivity increases when it is used in combination with the slide (PMNs <250/mm³). The RS sensitivity is high in patients with SBP and CNNA >250/mm³ [35]. In SecBP, there is a new highly sensitive point of care screen for SBP using the leucocyte esterase method [36]. Although the presence of bacterial DNA in plasma and/or ascites is associated with impairment of circulatory function [37], there are not enough data to support its use in clinical practice [38].

IAC (International Ascites Club) recommends the SBP diagnosis to be taken in PMNs in ascitic fluid >250/mm³, although the greatest specificity is reached with cut-off of 500 neutrophils/mm³ [9, 24], regardless of the result of bacterial cultures [15, 39]. The ascitic bacterial cultures are rarely positive [9, 15]. Clear ascitic fluid appearance /PMNs <250/mm³/ and negative bacterial cultures /can rule out SBP [40]. Delayed diagnostic paracentesis in patients with
SBP />12h after admission/ is associated with 2.7-fold increase in mortality [41]. Diagnostic paracentesis should be performed in all patients with cirrhosis and ascites at the time of hospital admission [10]. In negative bacterial cultures and PMNs in ascitic fluid >250/ mm³ (CNNA), the isolated bacteria from blood cultures should be considered a causative agent of SBP [42]. Blood cultures should be performed in all patients with suspected SBP before starting antibiotic treatment [9]. Blood cultures are positive in a significant proportion of patients with SBP /and CNNA/. Bacterioscites (BA) (positive bacterial cultures from ascitic fluid and PMNs <250/ mm³) is rarely observed - 5%. BA does not need treatment, but monitoring, if there are no clinical symptoms [15] and signs of systemic inflammation or infection [9]. BA is abortive form of SBP, but at more advanced stage of cirrhosis BA might progress to SBP - patients should undergo a second paracentesis [9].

In patients with SecBP PMNs in ascites are also >250/mm³, and most often significantly higher [15]. Limiting demarcation for SecBP different from that of SBP (>250/mm³) does not exist. PMNs between 250/mm³ and 1000/mm³ is a “gray zone” for the diagnosis of SecBP. The ascitic fluid in the cirrhotic without SBP usually has fewer than 300–500 white blood cells/mm³; nevertheless 10–15% may have more than 500 cells and 5% more than 1000 cells [43-45]. More than 70% of these white cells are mononuclear leukocytes /very small proportion of patients with cirrhosis and sterile ascitic fluid may have PMNs ≥250/mm³/. In contrast, in cirrhotic patients with SBP, the ascitic fluid usually contains more than 500 white blood cells/mm³ (frequently more than 2000), with more than 70% of them being PMNs [45, 46]. PMNs in ascitic fluid increase >250/mm³ in gram-negative flora, but it is not clear whether this is the same in gram-positive microorganisms [47]. At present, half of the episodes of SBP are caused by gram-positive bacteria [48].

**Ascitic Fluid Total Protein (AFTP)**

Total ascitic protein concentration ranges between 0.5 and more than 6 g/dL [49] and is greater than 3 g/dL ("exudative ascites") in up to 30% of patients with otherwise uncomplicated cirrhosis [43]. Significant PMN increase in ascitic fluid, and increased AFTP is observed in SecBP [9, 15, 16]. In 1/4 of patients with SecBP one of two of the main criteria for the diagnosis of SecBP /significant PMN increase in ascitic fluid, and increased AFTP/ are absent. In patients with AFTP<10g/L the risk of SBP increases tenfold [3]. After diuretic treatment AFTP decreases in 2/3 of patients [30] and SBP may occur at higher values of AFTP (usually <15g/L) [9, 15]. Leukocytes also increase in ascitic fluid after diuretic treatment, but not the PMNs [30]. Almost all patients with SBP have been treated with diuretics, because SBP occurs in the third year of the appearance of ascites in 1/4 of patients [16] (7-30% per year). The opsonic activity of ascitic fluid in cirrhosis is directly correlated with the total protein level in ascites and with the concentration of defensive substances, such as immunoglobulins, complement and fibronectin [44, 45]. Diuresis in cirrhotic ascites increases its opsonic activity and may help prevent SBP [50]. It is questionable whether diuretic therapy, which increases AFTP and the opsonic activity of ascitic fluid, prevents from the occurrence of SBP. It is necessary the diagnosis of SBP to be revised if AFTP is ≥15g/L. AFTP in patients with SBP may be even ≥25g/L, but only in 0-6% [49]. Most likely SecBP is concerned in these cases [15, 51]. High AFTP values (because of exudation - infection causes an inflammatory reaction), established in most patients with SecBP, are a consequence and not a prerequisite of peritonitis [51]. AFTP, apart from the transudate/exudate conception, is still used today to determine the risk of SBP in cirrhotic patients, for differentiation of SBP from SecBP and in cardiac ascites [49] /high AFTP and high serum-ascites albumin gradient/. AFTP depends on serum total protein and portal hypertension [52-54].

**Serum-Ascites Albumin Gradient (SAAG)**

SAAG does not change after paracentesis and diuretic therapy [49]. SAAG can be <11g/L in 5% (up to 15-16%) of patients with liver cirrhosis [53], but in SBP SAAG significantly exceeds 11g/L, due to the low values of AFTP - the proportions of albumin in the total protein concentration is approximately 45% [43]. In SBP the permeability of peritoneal membranes is not altered as that of the pleura and meninges in infection, therefore AFTP remains at low values in SBP [49]. The same refers to the majority of patients with SecBP. Regardless of the considerations expressed, the majority of patients with mixed genesis of ascites in cirrhosis /every fifth ascites in patients with cirrhosis/ [10] have a high SAAG, due to portal hypertension [52, 54].

**Bacterial Cultures from Ascitic Fluid**

The ascitic bacterial cultures are rarely positive (≈40%) in patients with SBP [9, 15] due to the low concentration of microorganisms in ascitic fluid /1 organism/mL or less/ [16], even if collected in blood culture bottles (>70%) [15]. Ascites is an unfavorable environment for existence of not only bacteria, but also blood cells /mainly red blood cells/, including leukocytes. Application of primary quinolone prophylaxis with expanded indications and broad-spectrum antibiotics in immunocompromised patients with liver cirrhosis decreases the few bacteria in ascites and selects gram-positive bacteria. Currently half of the episodes of SBP are caused by gram-positive flora (and in naive patients) [42, 48]. Diagnostic paracentesis usually is not performed at the onset of SBP or SecBP, but in suspected infection or during hospitalization thus only increased PMNs [51] in ascites are often established. Neutrophil phase continues several days [51]. Since intra-abdominal source of infection persists in SecBP, bacterial cultures are often positive [51], and the microflora is polymicrobial with anaerobes [55]. Despite the high frequency of positive bacterial cultures in SecBP (40-80%) in comparison with SBP and the more frequent Gram-negative flora isolated, these
criteria cannot be used for differential diagnosis between SecBP and SBP, if polymicrobial flora and anaerobes are absent.

**Runyon’s Criteria for Secondary Bacterial Peritonitis**

A SecBP should be suspected when at least two of the following features are present in ascitic fluid: glucose levels <50mg/dL, protein concentration >10g/L, lactic dehydrogenase (LDH) concentration > normal serum levels [56, 57]. Increased total protein and LDH in ascites were found in almost all patients with SecBP but they may be also elevated in peritoneal carcinomatosis without blastoma cells in ascitic fluid /in 6,7% of patients after twice cytological examination of fluid/ [10]. The lower ascitic glucose values /<2,78 mmol/L and/or lower to serum glucose/ may have higher diagnostic value in perforative peritonitis due to the consumption of glucose from bacteria [51]. Examination of LDH and glucose in ascitic fluid is not recommended by EASL for the diagnosis of SecBP, but more studies are needed to reject the significance of these indicators /Level B1/ [15]. Due to the low sensitivity and specificity of these criteria for SecBP, examination of alkaline phosphatase /ALP/ (>225U/L) and carcinoembryonic antigen /CEA/ (>5ng/ml) in ascites are recommended [56, 57]. The sensitivity of Runyon’s criteria is 66,6% and the specificity - 89,7%, but if they are combined with polymicrobial flora, which is rare in nonperformative SecBP, in 95,6% of cases SecBP is established [8]. These criteria lead to the SecBP diagnosis and indicate the conducting of CT.

**Instrumental Diagnosis of SecBP**

Ultrasonography is not only a screening in patients with liver cirrhosis, but a particularly valuable method for detecting intra-abdominal source of infection. CT placed an accurate diagnosis in 85% of intraoperatively and/or autopsy verified cases with SecBP [8]. Diagnostic laparoscopy is indicated in all cases of suspected acute surgical abdomen, especially for perforative peritonitis. Moreover, laparoscopy can be performed in emergency at any time of the day [51].

**Diagnostic Approach (Algorithm) for SecBP**

Diagnosis of SecBP can pass through three stages: 1) clinical, hematological, biochemical tests (including CRP), blood cultures, ultrasonography, and investigation of ascites - AFTP, PMN, microbiological examination of ascitic fluid in blood culture bottles, cytological examination of ascitic fluid; 2) Determination of Runyon’s criteria for SecBP; 3) Conduction of CT and/or laparoscopy.

**Conclusion**

SecBP should be suspected in patients who have localized abdominal symptoms or signs, presence of polymicrobial organisms in ascitic culture, very high PMN and AFTP, or in those patients with an inadequate response to empirical therapy for SBP. SecBP diagnosis and differential diagnosis between SecBP and SBP is not always so easy and sometimes creates serious difficulties. The use of other tests such as measurement of glucose or LDH in ascitic fluid has been suggested to help with the diagnosis of SecBP. Patients with suspected SecBP should undergo CT. The medical and surgical treatment of peritonitis in liver cirrhosis may be almost equally dangerous in wrong diagnosis. The misdiagnosis of SBP and SecBP is an "error of art".

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**Conflict of Interest**

No conflict of interest.

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