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EDITORIAL

Spontaneous bacterial peritonitis: A severe complication of liver cirrhosis

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Abstract

This report presents a survey of current knowledge concerning one of the relatively frequent and severe complications of liver cirrhosis and associated ascites-spontaneous bacterial peritonitis. Epidemiology, aetiology, pathogenesis, clinical manifestation, diagnosis and present possibilities of treatment are discussed.

Key words: Liver cirrhosis; Portal hypertension; Ascites; Spontaneous bacterial peritonitis

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is defined as an infection of initially sterile ascitic fluid (AF) without a detectable, surgically treatable source of infection[1]. It is a frequent and severe complication of cirrhotic ascites, first described in the middle of the 1960s[2]. Sometimes spontaneous infection of ascites is divided into three subgroups: (1) Spontaneous bacterial peritonitis is defined as a positive bacterial finding in ascites, together with increased polymorphonuclear leukocytes in ascites (> 250 cells/mm^3)[3]. Microorganisms responsible for SBP are isolated in 60%-70% of cases. (2) Culture-negative neutrocytic ascites (CNNA) - ascites is sterile, bacterial infection is not demonstrable by culturing, only an increased number of polymorphonuclear leukocytes above the limit of 250 cells/mm^3 is revealed. Of course, it is necessary to eliminate another cause of increased leukocytes in ascites, e.g. previous antibiotic therapy, hepatocellular carcinoma, peritoneal carcinomatosis or tuberculosis, pancreatitis or bleeding into ascitic fluid. If the sample of ascites contains blood, SBP diagnosis is made by finding more than one neutrophilic granulocyte per 250 erythrocytes. If left untreated, about one-third of cases can show, after some time, positive bacteriological findings. Both symptoms and mortality in patients with CNNA are similar to the course of disease in patients with diagnosed SBP; 33%-57% of these patients also show a positive blood culture, which provides evidence of a systemic bacterial infection. Infection is also confirmed by the fact that in patients with previous CNNA, there is a more frequent occurrence of SBP and *vice versa*[4]. (3) Monomicrobial non-neutrocytic bacterascites (or only bacterascites) has rarely been described. In this disorder, positive bacterial cultivation is presented without increased leukocytes. It is usually revealed in Child-Pugh class A patients. Recovery from bacterascites can be spontaneous (in 60%-80%), or it can develop into typical SBP. Bacterascites is often quite asymptomatic, and antibiotics should only be used if symptoms appear and cultivation finding is persistent.

As mentioned above, SBP and CNNA are identical, both from the clinical point of view and the therapeutic approach; therefore, the consensus conference of the

International Ascites Club[5] has recommended not to differentiate between these two entities; even in the case of CNNA, SBP is spoken about, and an increased number of neutrophils in ascites is sufficient for the diagnosis. A spontaneous infection complicating ascites may appear even in malignant ascites[6], however, it is found most often in cirrhotic ascites.

Early, mostly retrospective, studies described SBP in about 8% of patients with ascites; later prospective trials revealed SBP in 10%-30% of patients with ascites admitted to hospital[5,7,8]. SBP is found in about 5% of non-selected outpatients[9]. Lethality is very high. Older studies reported 80%-100% lethality connected with SBP[10], which was probably given partly by the generally worse therapeutic possibilities in cirrhotic patients and lack of availability of effective antibiotics, but better results - 20%-40% as reported in later studies[11] - are, to a certain extent, due to early diagnosis and treatment.

However, lethality has not decreased over recent years[12]. Even the long-term prognosis in these patients has been unfavourable. In 40%-70% of patients, SBP relapses within 1 year[11]. One-year survival after previous SBP patients is only 30%-40%, two-year survival is 20% and in patients with a Child-Pugh score > 10 survival is even lower[13].

AETIOLOGY

G^- bacteria are found in 65% of positive culture results- *Escherichia coli* (*E. coli*) and *Klebsiellae* are the most common and second most common agents, respectively[14]. The remaining agents are represented by G^+ cocci[1,7]. There is a difference in bacteria responsible for SBP in hospitalised and non-hospitalised patients. G^- bacteria prevail in the first group of patients, while G^+ bacteria are found in the latter[9].

Experiments modelling hepatic cirrhosis and the accompanying SBP in a rat resulted in discovery of agents in AF that differed from those in humans. It was mainly *Enterococcus faecalis* that was isolated from AF in the rat affected by cirrhosis induced by tetrachloromethane and SBP was of polymicrobial origin in one half of cases[15]. None of the above findings is typical of human patients suffering from SBP.

PATHOGENESIS

Bacteria participating in SBP come from the digestive tract. Extraintestinal bacteria such as those from the respiratory apparatus, urogenital tract or skin are much less frequent. Catheters and other equipment used during invasive procedures represent another possible source of infection. It is currently hypothesised that SBP follows an episode of bacteremia during which, due to the constant exchange of fluids between the peritoneal and intravascular space, AF gets infected[14]. The development of SBP thus depends on the antibacterial capacity of AF (the so-called opsonin activity) which is positively correlated to the content of the total protein in AF and the immunocompetence of the patient. The organism reacts to the infection of AF by activating neutrophilic granulocytes which migrate into the peritoneal cavity and trigger a complex cytokine cascade; the fact being documented, for example, by increased concentrations of interleukin 6 and tumour necrosis factor α in AF.

There are four key elements of SBP pathogenesis: (1) small intestinal bacterial overgrowth, (2) increased intestinal permeability, (3) bacterial translocation, and (4) immunosuppression. These key elements are not separate, but interlinked.

Small intestinal bacterial overgrowth (SIBO)

Considering bacteria commonly found in the gastro-intestinal tract, only some of them frequently participate in translocation. The most frequent bacteria are *E. coli*, *Proteus spp.*, *K. pneumoniae* and other *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *enterococci*, *streptococci* and *staphylococci* - i.e. organisms causing infections in immunocompromised individuals. Bacterial small intestinal overgrowth creates conditions favourable for translocation of the above-mentioned bacteria. Liver cirrhosis is one of the conditions accompanied by SIBO. The main reasons for SIBO in patients affected by liver cirrhosis can be summarised as reduced intestinal passage, abnormalities in bile secretion, hypochlorhydria, abnormalities in IgA production and malnutrition[16]. A total of 20%-60% cirrhotic patients are affected by bacterial overgrowth. SBP is more often diagnosed in alcoholics affected by liver cirrhosis and SIBO as compared to patients affected in the same way but without SIBO[17]. Some authors are doubtful about the importance of SIBO in the pathogenesis of SBP[18]; according to this study, SIBO is associated with the use of drugs decreasing secretion of HCl and this therapeutic approach can increase the risk of SBP. Bacterial translocation found in a healthy individual after ingestion of extremely high numbers of microorganisms[19] can serve as a distant parallel of the relationship between SIBO and bacterial translocation.

Increased intestinal permeability

In severely ill patients, such as those with liver cirrhosis, small intestinal motility is impaired, resulting in bacterial overgrowth and the related translocation of microbes through dysfunctional mucosal barrier. The increased intestinal permeability and thus impaired function of the intestinal barrier are mainly due to portal hypertension. The consequences are dilated vessels in the intestinal mucosa, oedema of the lamina propria mucosae, fibromuscular proliferation, hypertrophy of the lamina muscularis mucosae and compromised integrity of the intestinal mucosa. Portal hypertension can play an important role, as can the toxic effects of alcohol, bile secretion disorders, malnutrition, decreased secretion of growth factors (insulin-like growth factor I), changes in the composition and flow of bile, or higher levels of nitric oxide. Increased intestinal permeability is likely to be proportional to the degree of portal hypertension, but independent of the severity and aetiology of liver disease[20,21].

Bacterial translocation

The term bacterial translocation was first used in 1979[22].

Bacterial translocation is defined as either active or passive penetration of living microorganisms and their toxic products through the mucosal epithelial layer to the lamina propria mucosae. From there, microbes migrate to mesenteric lymph nodes and/or extraintestinal sites. Under normal circumstances, there are only small numbers of bacteria readily destroyed by the immune system in the lamina propria mucosae. Translocation is only possible if their numbers are high, up to 10^8 bacteria in 1 g of faeces[17].

According to clinical significance, there are four degrees of bacterial translocation. Degree 0: Bacteria and/or their components penetrate the mucosa by various mechanisms: active intracellular penetration, diffusion, absorption, endocytosis or phagocytosis by macrophages; Degree 1: Bacteria and/or their components enter the mesenteric lymphatic system and penetrate it centripetally; Degree 2: Bacteria and/or their components are already detectable in the systemic circulation and certain organs. They may also pass directly into small intestinal venules and from there into the portal circulation. Some of the bacteria are probably even capable of intracellular passage through the muscularis propria into the peritoneal cavity; Degree 3: The organism is systemically overwhelmed by bacteria and/or their components, leading to a septic response.

Bacteria escaping both phagocytosis and destruction by the complement system may even get into the bloodstream. *Enterobacteria*, *staphylococci* and *enterococci* are capable of translocation, i.e. passing live across the intestinal epithelium to the mesenteric lymph nodes, blood and other organs, whereas most anaerobic organisms lack this ability. Bacterial translocation may be confirmed by positive culture from the mesenteric lymph nodes. The main mechanisms underlying the translocation are deficient local mucosal immune response, lower phagocytic activity of both macrophages and neutrophils, increased permeability of the intestinal barrier and the above-mentioned intestinal bacterial overgrowth[16,17].

Immunosuppression

Patients with liver cirrhosis suffer from decreased phagocytic activity of neutrophilic granulocytes and the mononuclear phagocytic system, deteriorated humoral immunity and decreased opsonin activity of AF[23]. Neutrophilic granulocytes of patients with hepatic cirrhosis show not only a decrease in the phagocytic activity, but also intracellular destruction of bacteria, deteriorated metabolic activities, frequent apoptosis and considerably reduced chemotaxis. For proper protection against bacteria, neutrophilic granulocytes have first to adhere to the vascular endothelium, then migrate to the endothelial cellular junctions, pass through by diapedesis and migrate further into the target tissue. Neutrophilic granulocytes of cirrhotic patients adhere to the vascular endothelium to a greater extent and their transendothelial migration is thus decreased[24]. Neutrophilic granulocytes show decreased chemotaxis probably due to the presence of inhibitors of chemotaxis in the blood plasma of the cirrhotic.

The opsonin activity of AF correlates with the concentration of immunoglobulins, complement, fibronectin and total protein in AF[5,25]. Patients with a reduced total protein content in AF are prone to the development of SBP.

CLINICAL MANIFESTATION

SBP is particularly revealed in patients with more severe liver functional damage (Child-Pugh classification C), often after bleeding from the upper gastrointestinal tract due to portal hypertension and often recurs. The clinical picture is non-specific. In a lot of cases the infection is quite asymptomatic, common signs - subfebrile states, diffuse abdominal pain - are not very conspicuous. They are frequently manifested only by the occurrence or deepening of symptoms that accompany the course of liver cirrhosis - increased ascites and failure of diuretic therapy, deteriorated encephalopathy, vomiting, *etc*. Therefore, an active search for the ascites infection is necessary.

Diagnostic paracentesis with leukocyte investigation is recommended in all patients with ascites admitted to hospital as well as in cirrhotics (whether in hospital or not) with worsened ascites, who have presented with signs of abdominal or systemic infection (abdominal pain or tenderness, disturbed intestinal passage, fever, acidosis, peripheral leukocytosis) or with encephalopathy or worsened renal functions[5]. An active approach to the SBP diagnosis is extraordinarily important even from the prognostic point of view. If SBP is diagnosed at the first paracentesis carried out in all patients hospitalised with ascites, this infection has no influence on the patient's prognosis. However, if SBP appears over the course of studying these patients, the risk of lethality increases two-fold[26]. This can probably be explained by the damaged renal function under a longer-lasting untreated infection.

High lethality is not primarily associated with the severity of the infection, and patients do not die of sepsis. An infection only worsens the changes present in cirrhotic patients, especially blood supply and renal function[27]. Splanchnic vasodilatation occurring in cirrhotics is worsened due to endotoxemia; effective arterial blood volume decreases which can damage renal function and can cause hepatorenal syndrome. Patients who showed a higher level of urea and higher portal pressure at the moment of diagnosis of an infection are threatened with renal failure and the associated high lethality[28].

DIAGNOSIS

Diagnosis is relatively easy. SBP is diagnosed by revealing polymorphonuclear leukocytes in ascites > 250 cells/mm^3 (less accurately at the increase of all leukocytes over 400/mm^3). Reagent papers used for examining leukocytes in urine could be used for the immediate detection of leukocytes in ascites[29] although the sensitivity is not sufficient. A positive cultivation finding is not necessary for diagnosing SBP, it is usually revealed in about 30% of cases. Some trials have mentioned a higher bacteriological

detection if ascites is inoculated on the medium at the bedside as it is carried out for the investigation of blood culture - BactAlert test[30]- however, the advantage of this test has not been demonstrated by other studies[8,31].

In the case of diagnostic doubts, the serum procalcitonin level (the limit of 0.75 ng/mL has 95% sensitivity, and 98% specificity) or the interleukin 6 level in ascites (the limit of 5.0 ng/mL has 100% sensitivity) may be determined[32]. Nowadays, examination of the ascites pH (for the diagnosis of SBP < 7.35) or arterial: ascites pH gradient (> 0.1) as recommended previously is no longer used.

TREATMENT

Therapy should be initiated immediately after revealing increased leukocytes in ascites. Empiric antibiotic therapy, e.g. an intravenous third-generation cephalosporin, preferably cefotaxime in a single dose of 2 g is the recommended antibiotic drug. Mostly, it is sufficient to administer cefotaxime every 8 h as this regimen is as effective as its administration every 6 h[33]. Even a shorter length of application is possible, cefotaxime administered every 8 h for 5 d has the same effects as its 10 d application and from a practical and financial point of view, this regimen seems to be the most suitable. Two 3rd generation cephalosporins may alternatively be used-cefonicid (2 g every 12 h) or ceftriaxone 2 g/d[34]. In uncomplicated SBP (i.e. if diagnosed during preventive examination of ascites without clinical signs of infection) a combination of amoxicillin, clavulanic acid[35], or ofloxacin 400 mg may be administered every 12 h for a period of 7-10 d[36]. Although more than 10 therapeutic studies have been published since 1985, clear proof of the efficacy of these antibiotics supported by evidence-based medicine is still missing, and treatment is based more on clinical experience[37]. Moreover, there are reports on increasing occurrence of enterobacteria resistant to the 3rd generation cephalosporins[38], therefore, a large, well-designed randomised trial is necessary to ensure explicit demonstration of the effectiveness of each antibiotic drug.

As mentioned above, the high lethality is associated with damaged renal function due to impaired hypovolemia. Therefore, the efforts of expansion of intravascular volume could be contributory, and some studies have demonstrated that simultaneous application of albumin (as plasma expander) at a dose of 1.5 g/kg during the first 6 h and 1 g/kg on the 3rd d together with antibiotics decreased both the occurrence of renal damage and lethality[39]. This albumin replacement is recommended in patients with even clinical suspicion of SBP and serum creatinine > 1 mg/dL, blood urea nitrogen > 30 mg/dL, or total bilirubin > 4 mg/dL.

Preventive treatment

Three groups of patients are at higher risk of SBP-patients with gastrointestinal bleeding, patients who have survived an episode of SBP and patients with low opsonic activity of ascites.

Preventive administration of antibiotics is recommended in the first two groups. Intravenous ceftriaxone for 7 d or norfloxacin 400 mg twice a day for 7 d should be administered to prevent bacterial infections in patients with cirrhosis and gastrointestinal bleeding. Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (400 mg once a day)[40] or trimethoprim/sulfamethoxazole. In these patients, liver transplantation should be considered as the lethality after passed SBP is higher than that after liver transplantation[5,13]. If transplantation is indicated, antibiotics should be applied until the operation. If transplantation is not indicated, according to literature, they should be applied for the rest of the patient's life. However, in clinical practice, an individual approach to each patient has been recommended.

Preventive application of antibiotics in the last group of patients at higher risk of infection - patients with the ascitic fluid protein < 15 g/L (i.e. with low opsonin activity) has not been generally recommended so far[41]. Long-term use of norfloxacin (or trimethoprim/sulfamethoxazole) can be justified in these patients if at least one of the following is present together with a low level of protein: serum creatinine > 1.2 mg/dL, blood urea nitrogen > 25 mg/dL, serum sodium < 130 mEq/L or Child-Pugh > 9 points with bilirubin > 3 mg/dL[42].

Intraperitoneal re-infusion of concentrated ascites can effectively increase the protein level and opsonic activity of ascites[43]. On the other hand, it is not clear if just this procedure can reduce the risk of SBP in patients with low ascitic fluid protein.

Reports on possible influencing of bacterial translocation (and thus the development of SBP) using prokinetics[44,45] or probiotics[46] have appeared in the literature.

CONCLUSION

Spontaneous infection of ascites is a very frequent and severe complication of ascites occurring in a high number of patients admitted to hospital with ascites. This infection must be actively searched for. Diagnostic paracentesis must be performed with examination of polymorphonuclear leukocytes in ascites in all patients suffering from ascites at the moment of their admission to hospital as well as in all cirrhotics with a sudden increase of ascites or worsening of their general condition.

If the number of polymorphonuclear leukocytes in ascites exceeds 250 cells/mm^3, a positive bacteriological finding is not necessary, SBP is diagnosed and cefotaxime at the minimum dose of 2 g every 8 h for 5 d is administered. If patient has no clinical symptoms and SBP was diagnosed during preventive examination, ofloxacin 400 mg every 12 h for 7-10 d is an alternative. Although more studies are lacking, prevention of the development of simultaneous renal damage due to severe hypovolemia by administration of plasma expander (albumin at a dose of 1.5 g/kg during the first 6 h, and 1 g/kg on the third day) seems to decrease lethality.

Preventive application of antibiotics is indicated in two groups of patients with a high risk of developing SBP. Norfloxacin 400 mg twice a day is recommended

in patients with bleeding from the upper gastrointestinal tract and portal hypertension. The other group involves patients with previous SBP. As secondary prevention, norfloxacin 400 mg once a day is administered. Liver transplantation is recommended and antibiotics are applied until the surgery. Long-term administration (lifelong according to literature) is indicated in patients who are not indicated for transplantation.

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