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SPONTANEOUS BACTERIAL PERITONITIS AS A COMPLICATION IN ADULT PATIENTS WITH LIVER CIRRHOSIS AND ASCITES

SUMMARY

Spontaneous bacterial peritonitis (SBP) is one of many complications in patients with liver cirrhosis and ascites. It is defined as ascitic fluid (AF) infection with positive bacterial culture, where polymorphonuclear leukocytes in AF exceed the number of 250/ ml, and where there is no evident intaabdominal source of infection possible to treat surgically. If not diagnosed and treated in time the prognosis is poor, because this complication is associated with already existing chronic liver disease. In recently published studies, reported mortality in patients with liver cirrhosis and SBP has been 20 to 40%. Early diagnosis and adequate therapy of SBP can significantly improve prognosis in these patients.

Key words: **cirrhosis, ascites, spontaneous bacterial peritonitis**

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is often called primary peritonitis in literature, and that is why it is defined as an acute bacterial ascitic fluid (AF) infection where there is no evident intraabdominal source of infection possible to treat surgically. Still, the most precise definition of SBP is that it is the ascitic fluid infection with:

- positive bacterial culture;
- polymorphonuclear leukocyte (PMN) count in AF exceeding the number of 250 PMN/ ml and,
- where there is no evident intraabdominal source of infection possible to treat surgically.

Peritonitis as complication of chronic liver disease caused by Pneumococcus was described in 1983 in French literature, and peritonitis caused by Escherichia coli was first described in 1907. SBP notion appeared for the first time in 1971, although this complication of liver cirrhosis was noticed and described by Ker and authors in 1963 as well as Conn in American literature in 1964 (1). Conn thought this type of peritonitis can only be found in patients with cirrhosis caused by alcohol, but that claim was later rejected (2).

In hospitalized patients with cirrhosis and ascites diagnosis, 7% to 23% will develop SBP episode, with lethality about 17% to 50% (3). Outcome depends on: recent gastrointestinal bleeding, seriousness of infection, and degree of liver and kidney damage.

SBP occurs in patients of all ages and races, both males and females.

In order to understand SBP better, it is necessary to list the classification of AF infections.

Ascitic Fluid Infections Classification

I Primary peritonitis (spontaneous AF infections):

1. Spontaneous bacterial peritonitis, i.e., culture positive neutrocitic ascites (SBP or CPNA)- it is characterized by: positive bacterial culture and PMN exceeding the number of 250/ ml of AF. Almost two thirds of spontaneous AF infections belong to this form, and almost always are monomicrobial.

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2. Culture negative neutrocitic ascites (CNNA or probable SBP)– has got a number of PMN, as well as CPNA, but it is characterized by the AF negative bacterial culture. CNNA can be caused by badly cultivated sample or by slowly developing infection. CNNA has the same prognosis as CPNA, and that is why they have the same therapy protocol (4, 5).

3. Monomicrobial non-neutrocitic bacterascites (MNB or early form of SBP) – the culture is monomicrobial, but the PMN number is lower than 250 PMN/ ml. It occurs in two clinical forms: asymptomatic and symptomatic MNB (6). Although MNB is often caused by contamination of culture, almost 38% of these patients develop classic form of CPNA (that is why MNB is called the early form of SBP). It is very important to know that all patients that have developed the classic form of CPNA had symptomatic MNB (2). Asymptomatic MNB is only the sign of colonization, and it does not require antibiotic treatment (7).

II Secondary bacterial peritonitis - PMN number exceeds 250/ ml, AF culture isolates pathogenic bacteria (flora is polymicrobial), but what essentially differs it from SBP is the fact that there is an obvious intraabdominal source of infection surgically possible to solve. Unlike SBP, usually found in patients with cirrhosis and ascites, secondary bacterial peritonitis can be found in patients with ascites caused by many diseases other than cirrhosis (8). It is very important to make a difference between SBP and secondary bacterial peritonitis, because their symptoms are almost the same.

III Polymicrobial bacterascites– flora in AF is polymicrobial and the PMN number is lower than 250/ ml. It generally occurs in case of unintentional intestines injury in parecentesis attempt (1:1000). Risk factors are: inexperienced doctor, ileus or existing postoperative scars.

Etiology

AF polymicrobial infections are discovered in only 8% of cases, while monomicrobial infections prevail in even 92% (2).

The first place among SBP carriers is assigned to gram-negative bacilli, and these are most frequently Escherichia coli and Klebsiella pneumoniae. These two bacteria are usually singled out in around 60% of isolates. The second place among potential carriers is assigned to gram-positive cocci, isolated in around 25% of cases (mainly Streptococci spp.). Anaerobes are very rarely isolated (although they are predominant in the intestinal flora) because the increased partial oxygen pressure in AF prevents their development (8). It is considered that only one third of SBP cases are caused by bacteria not of the intestine origin (9). More recent data indicate the increase of SBP cases percentage, caused by aerobic gram-positive bacteria (it is explained by the resistance of gram-positive microorganisms to fluoroquinolone, used in SBP therapy and prophylaxis).

It happens that SBP is induced by bacteria, very rarely suspected or not suspected at all. It should be considered that more than 70 species of bacteria have been isolated from AF of patients with SBP. Taking into account big samples, Enterococci cause about 5% of SBP episodes and they have a predominant place in polymicrobial SBP episodes. Most usually, these are Enterococcus faecium or Enterococcus cecorum (10, 11). There were also recorded the cases of ascites infection caused by Neisseria perflava bacterium, normally found in oropharynx, and Streptococcus milleri, Streptococcus mitis and Streptococcus sanguis bacteria. Bad condition of gums and teeth is considered to contribute to SBP pathogenesis with such etiology (12). Bacteria of Pasteurella kind cause zoonoses in people and they rarely lead to systemic infections. However, there were registered two SBP cases the etiology of which included Pasteurella dagmatis (9) and Pasteurella ureae. Also, there were registered possibilities that SBP was caused by: Burkholderia cepacia (13), Haemophilus influenzae (14), Neisseria meningitidis, Listeria monocytogenes (15), Salmonella enteritidis, Chlamydia, Brucella (16), Campylobacter jejuni, Campylobacter coli, Campylobacter fetus, Neisseria gonorrhoeae, Aeromonas hydrophilia, Morganella morganii, Aeromonas gobnia etc.

A conclusion is imposed that in SBP etiology there may be found a huge number of bacteria and that in small, but anyway, significant number of cases it is hard to come to exact etiological diagnosis and apply the right therapy.

Predisposing factors

Predisposing factors for development of spontaneous bacterial peritonitis are:

- Severity of liver disease – 70% of SBP cases occurs in patients with C level on Child's scale, and then in patients with B level.
- Gastrointestinal bleeding – patients who have chirrosis and where GI bleeding is developed, are highly predisposed to development of bacterial infections (22% develop infection within 48 hours, and 35% to 65% within 7 to 14 days (17). In more than 45% of patients with cirrhosis and ascites, presented by GI bleedings, it is just SBP that develops (18).
- Bacteriuria.
- Previous SBP episode– possibility for SBP recidive is 43% in 6 months, 69% in one year and 74% in two years.

Pathogenesis

AF infection is generally developed when its quantity is significant, but it need not be a rule. The most important factors in SBP development are: 1. liver cirrhosisis, 2. portal hypertension with ascites and 3. extensive portosystemic collateral circulation. In progressed chirrosis, even 80% of portal vein blood is shunted around the liver (so-called extrahepatic porto–systemic collateral network). In patients with cirrhosis, intrahepatic anastomoses have been proven, as well. These and such porto–systemic anastomoses provide for circulation bacteria to bypass the liver RES (which is the central defence system of an organism against bacteremia). In this way, bacteriemia becomes an usual phenomenon, and AF becomes its target (18). The infection sources are generally unknown, but it is presumed that it has to do with distant locations (e.g. urinary tract infections, pneumonias, etc.), that represent a base for the so-called hematogenous theory of SBP genesis. Everyday surgeries, and also medical procedures seeming simple in patients with progressed cirrhosis may lead to transitional bacteremia and complications like SBP (8). Medical procedures leading to bacteremia cause the so-called iatrogenous SBP (19).

Bacteria may penetrate the peritoneal cavity even through intestinal mucosa, known in literature as bacterial translocation (BT). There are three conditions contributing to this phenomenon development: overdevelopment of bacteria in small intestine (20, 21), organism immunodeficiency status and intestinal mucosa damages contributing to increased porosity of intestinal barrier (18). In patients with progressed cirrhosis the intestinal wall is edematous (that being the effect of splanchnic veins and lymphatics congestion), often inflammated, and consequently, intestinal mucosa is degenerated. When any of these three conditions becomes serious, prolonged or mutually combined, complications like SBP occur (22). Bacteria, penetrating intestinal mucosa, move into submucose tissue, and then reach mesenteric lymphatic nodos, where from they can be disseminated throughout the organism (23).

Prevention of this process is attempted by:

- selective intestinal decontamination with norfloxacin or other poorly absorbed antibiotics (24);

- changing intestinal flora with probiotics or bile acids. It is known that bile acids affect microflora and integrity of the small intestine. The oral administration of bile acids in ascitic cirrhotic rats results in reduction in bacterial overgrowth, BT and endotoxemia (25);

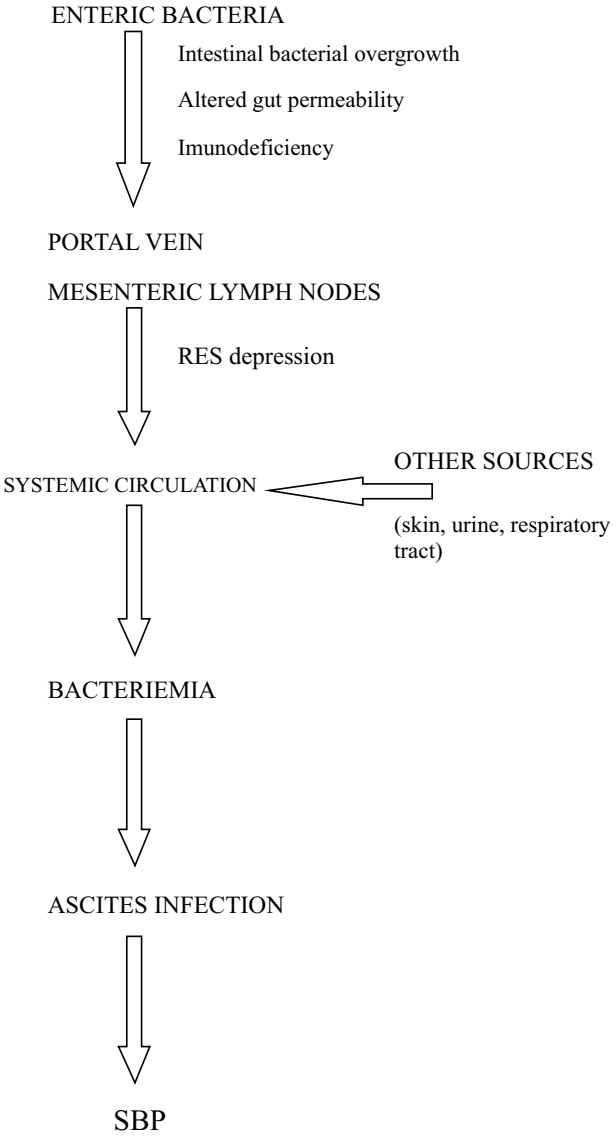

Figure 1. Pathophisiology of SBP „Spontaneous bacterial peritonitis in adult patients with liver cirrhosis and ascites“

- regulating intestinal transit with prokinetics and β- adrenergic blockers. It results with decreased possibility of bacterial overgrowth. Cisapride is effective in reducing intestinal bacterial overgrowth, but without a significant effect on the development of bacterial infections (26, 27). Much better results are registrated with propranolol in laboratory cirrhotic rats. It significantly reduces portal pressure, shortens intestinal transit time and reduces bacterial overgrowth (28). New studies imply that the dose of propranolol is extremely important for its effect (29).

It is an interesting discovery that ascitic liquid has got a very good humoral activity against gram-negative bacteria, while such activity against gram-positive organisms has not been observed. The presence of hemolitically active complement, lysosimes and immunoglobuline in AF means that

the ways of defence from bacteria in ascites are similar to those in serum. The phagocytes quantity in ascites is much lower than their number in blood under normal circumstances, while in cirrhotic patients the changes in leukocytes appearance have been observed. From all this, it is easy to conclude that the cellular defence mechanisms are not that efficient in the AF (30).

Microbes found in peritoneal cavity are considered to induce activation of three types of defence mechanisms: removal mechanisms (where pathogene microorganisms are removed by absorption via diaphragma lymphatic vessels), killing mechanisms (where the existing phagocytes act as effector cells, opsonization and phagocytose mechanisms) and sequestration mechanisms (acting according to the principle of "fibrine capturing" and forming of adhesions between omentum and visceral surfaces). In fact, these mechanisms are a side effect of an organism inflammatory response. Although macrophages and PMN in peritoneal cavity proved to have almost the same phagocytic abilities, predomination of macrophages at the moment of microorganism appearing in ascitic liquid has shown that these cells, together with translymphatic absorption represent the first defense line in case SBP occurred. Till PMN appearance, the number of bacteria has already been limited by macrophages reaction.

A very significant parameter for prognosing patient's ability to defend from possible ascitic infection is protein concentration in the AF. The concentration of protein in AF is proportional to opsonic activity and complements level. It means that SBP pathogenesis implies the existence of bacteremia with settling of AF in which the concentration of total proteins is lower than 10 g / l (8, 31, 32).

Clinical presentation

It should be kept in mind that SBP symptoms and signs are related to disturbances preceeding its very occurence, and these are cirrhosis and ascites. SBP clinical presentation depends on the moment of diagnosis establishing. When SBP is discovered in the very initial phase, most of the affected persons have got asympomatic presentation (which is the case in almost one third of patients). What might arouse suspicion are the following: increased body temperature – 69% or hypothermia – 17%, abdominal pain – 59%, sensitivity of abdomen to palpation – 49%, hepatic encephalopaty – 54%, diarrhea – 32%, ileus – 30%, shock – 21%, hypotension – less than 20% of patients. Rigidity is not the characteristic of infected ascites due to a big quantity of free liquid, disabling spinal reflex activation.

Diagnosis

A justified suspicion to SBP must be eliminated in every patient with cirrhosis who has ascites and develops any sign of decompensation (e.g. encephalopathy, refractory ascites, renal insuficiency etc.). The next step is refering patient to diagnostic paracentesis. The risk of paracentesis performing is small, regardless of the presence of almost persistent coagulation disturbance in such patients. It is only 1% risk for generation of more significant hematoma in abdominal wall, 0.01% for hematoperitoneum generation and 0.01% risk from iatrogene infection. However, one should be extremely careful, particularly with patients who have organomegaly, pregnant patients, patients with intestines obstruction, intraabdominal adhesions and patients with urine retention (33). Diagnostic paracenthesis implies: AF inspection, biochemical, microbiological and citological analysis of AF.

In order to confirm SBP diagnosis, the inspection should show unclear, stinking ascites. In terms of AF biochemical analyses for diagnosis establishing, the following results are useful: glucose, proteins, albumin and cholesterol levels. In fact, microbiological and cytological analysis of AF establish SBP diagnosis. Optimal therapy depends on causal organism isolation precision. However, conventional seeding methods give positive SBP cultures only in about 40% of cases (34). Just for that reason, different SBP culture techniques are used, which, unlike conventional ones, are sensitive to low bacterial concentrations. One of such techniques implies bottles inoculation with blood base „by the bed". By introducing this method, the percentage of positive cultures increased from 42% to 91%. It is important to stress that in microbiological analysis results obtaining, the following are not considered as pathogenic bacteria: Staphylococcus epidermidis, Bacillus species and diphteroides. Repeating paracenthesis is not necessary if the response to therapy is dramaticly fast and if the infection is monomicrobial.

The methods to shorten the time period necessary for exact diagnosis establishing of this potentially lethal complication are currently in the focus of all those dealing with SBP. Ascites pH measurement was the original solution for fast establishing of SBP diagnosis, but it came out that this method is not reliable, and as such, it was eliminated (18, 35). Researches from 2006 favored the so-called Dipstik test. Dipstik test was previously used only for proving the existence of urine infection, but it proved to be useful with cerebrospinal, pleural, sinovial, as well as with peritoneal liquid. Big enthusiasm about the use of this fast way of SBP diagnosis is decreasing because in case of potentially

lethal pathology existence, which is yet characterized by good response to antibiotics therapy, a test rendering just a little or no falsely negative results at all should be used. According to new researches' results, it is not the case with Dipstik test. These indicate that classic diagnostic methods, such as AF cytological and bacteriological analyses, should be returned into practice (36).

Therapy

The therapy should be started empirically if SBP is clinically suspected, regardless of the possible lack of laboratory analyses or the AF PMN number less than 250/ ml (18).

There are numerous therapeutic protocols used in SBP treatment.

I Third Cephalosporines Generation

If the third Cephalosporine generation protocol is used, Cephotaxim is most frequently applied intravenously (IV), 2 g each at every 8 hours, 5 days. It was shown to be very successful, because it cured SBP episodes in even 85% of cases (3). Cephotaxim is considered to cover 95% of possible SBP carriers. However, attention should be paid to the fact that more recent researches indicate that Cefotaxim is not successful as the first defense line in even 40% of cases and that it is to think about other protocols to take over up-to-date leading role of Cephalosporine in SBP therapy (8). From the medicaments of the same group, Ceftriaxon is also used, IV, 2 g dose, every 24 hours.

II Combination of Amoxicillin and Clavulinic Acid

The use of this protocol is not widespread. Therapeutic scheme looks like this: 1 g/ 0, 2 g every 6 to 8 h– IV, 2 days, and then, 500 mg/ 125 mg, per os, every 8 h, 6 to 12 days. (19) Advantages of this kind of therapy in regard to already described protocol are as follows: it has more efficient effect against enterococcal infections, it is cheaper and it may be applied orally (18).

III Aminoglucosides

Amicacin has shown to be less effective than Cephotaxim, but it has not shown higher nephrotoxicity, as expected (37).

IV Fluoroquinolones

From this group of medicaments – Levofloxacin, a combination of Gatifloxacin and Moxifloxacin and Ofloxacin were singled out as the most effective. Levofloxacin is applied in 500 mg dose, IV or per os every 24 hours. Then, the combination of Gatifloxacin and Moxifloxacin, IV or orally, in 400 mg dose, every 24 h. Within this group, Ofloxacin proved to be the best in SBP therapy. It is applied orally in 400 mg dose, every 12 hours. Studies comparing treatment with Cephotaxim- IV and Ofloxacin- orally, in 5 day-period, have shown that the percentage of cure is almost the same (85% and 84%). However, these two protocols are still the subject of dispute, because there is no study big enough to support one or the other (38). Ofloxacin is currently applied as an alternative therapy only in patients with uncomplicated ascites, who have not had quinolones administered prophylactically. The advantage of Quinolones therapy, in regard to the therapy with third generation of Cephalosporine, is only in the fact that they have a good intestinal absorption and excellent bioavailability in the ascitic liquid (better than any other kind of intravenous therapy) (18). From this group of medicaments, Cyprofloxacin, applied intravenously, and then continued in the form of oral therapy has also been proved as effective (39).

Regardless of the therapeutic protocol applied, it has been concluded that it should last 5 days if the repeated paracentesis (48 hours after the start of the therapy) showed the successfulness of the therapy.

It is necessary to take care that the doses be adjusted to kidneys function, generally disturbed by the presence of the basic disease, i.e., cirrhosis (19). It is an alarming fact that one third of patients with chirrosis, who have had SBP diagnose established, will develop irreversible renal insufficiency. For that reason, an attempt has been made to apply albumin together with standard Cephotaxim therapy. Cephotaxim+ Albumin therapy has shown enviable results! Albumin was applied in a dose of 1, 5 g/ Kg of bodily weight at the moment of diagnosis, and then, on the third day it was continued with 1 g/ kg of bodily weight. Such prophylactic therapy lowered the percentage of renal damage from 30% (in patients treated by Cephotaxim only) to 10%, and lethality from 29% to 10% only (3). It is even more important that this combination indicates its usefulness even three months after application, as well as its impact on cardial function rehabilitation (18). However, a routine use of this prophylactic protocol is being avoided due to high cost of IV Albumin therapy. It should be kept in mind that patients in whom kidneys failure is obvious, entailing long-term dialysis treatment, according to all standards, would mostly benefit from Cefotaksim+ Albumin treatment (40).

Prophylaxis

Prophylaxis should be taken into consideration in: patients with ascites and cirrhosis in whom there is occurrence of gastrointestinal (GI) bleeding, patients with ascitic protein level< 1 g/ dl (primary prophylaxis), as well as in patients with previous SBP episode (secondary prophylaxis). The greatest chance for recurrent SBP episode occurrence is in patients with previous SBP episode.

In patients with ascites and cirrhosis, in whom GI bleeding occurs, the greatest probability for infection development is in the first few days after the very bleeding occurrence. The possibility of SBP occurrence is therefore very high, ranging from 30 to 50%. Intestinal origin bacteria are most frequently in the etiology of such generated SBP, and the very infection in this case has a very bad prognosis. As prophylaxis in such patients, Norfloxacin is applied orally, 400 mg/ 12 h, for 7 days. Cyprofloxacin prophylaxis is also possible, in 500 mg/ day dose, orally, 7 days. If there is active bleeding, there is no dilemma - the prophylaxis should include the application of IV Ofloxacin.

In patients the ascitic protein level of whom is< 1 g/ dl, Norfloxacin prophylaxis is used orally, 400 mg/ day. In this case, it is possible to apply the combination of Trimetoprim and Sulfametoxasol (TS)- 160 mg/ 800 mg, 5 days in a week (so called "Monday– Friday" scheme).

Patients with previous SBP episode use Norfloxacin per os, 400 mg/ day as a prophylactic treatment, for non-defined period of time. The TS (160 mg/ 800 mg) therapy, 5 days a week also proved to be successful. All described therapies in patients with previous SBP episode last indefinitely or until the liver transplantation. Application of Norfloxacin, in already described way, decreased the occurrence of recurrent SPB episode, from 68% to only 20% for one-year period.

The risk in such, obviously useful prophylaxis, is the appearance of resistant bacteria in intestinal flora and possibility of such bacteria to induce SBP. The latest discoveries indicate that fluoroquinolones prophylaxis should be reconsidered because there is a large number of bacteria which developed resistance to them. There is no significant difference in SBP occurrence either in patients who are on Norfloxacin prophylaxis and in those treated with TS. These studies even give advantage to TS combination due to the very fact that TS therapy is cheaper (41).

The latest investigations of SBP prophylaxis are oriented to completely new direction, to IGF– I. IGF– I is an anabolic hormone synthethized by the liver and it has primarily hepatoprotective role. In 2006, it was proved on an animal model that this hormone slowed down chirrosis development, lowered portal hypertension, improved the intestinal barrier function and decreased BT. For that reason, it is considered that IGF– I hormone therapy could be successful in prevention of SBP development in patients with chirrosis and ascites (42).

Prognosis

When defined as a notion for the first time, SBP had lethal effect in 80% or, according to some statistical data, even in 100% of cases. In the '90s, lethality ranged from 30 do 50% (3). In recently published studies, this percentage got decreased to 15 to 20% only (18).

Prognosis is good if the diagnosis is established quickly and adequate SBP therapy started, as well as if the infection is observed before the occurrence of renal failure and shock. Renal failure is the parameter, most reliably forecasting a lethal outcome. Statistical data show that lethality in patients affected by SBP and progressive renal insufficiency is 100%, while in those with SBP and stable renal insufficiency it is only 31– 40% (19).

AF protein level is considered to be a reliable prognostic parameter. Patients with AF protein level less than 10 g/ l have the chance to develop SBP in one year in 20 of 43% of cases, while the chance of those, the protein level of whom exceeds 10 g/ l, is almost irrelevant in the period of 3 years.

Long-term SBP prognosis is bad, because this complication is associated with already existing serious liver disease. Percentage of one-year and two-year survival ranges from 30% do 50% (one year) and 25– 30%, (two years) (3).

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SPONTANI BAKTERIJSKI PERITONITIS KAO KOMPLIKACIJA KOD ODRASLIH BOLESNIKA SA CIROZOM JETRE I ASCITESOM

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SAŽETAK

Jedna od brojnih komplikacija kod bolesnika sa cirozom jetre i ascitesom je spontani bakterijski peritonitis (SBP). Definiše se kao infekcija ascitne tečnosti (AT) sa pozitivnom bakterijskom kulturom, gde broj polimorfonuklearnih ćelija prelazi 250 po ml AT- i i kod koje ne postoji evidentan, intraabdominalni izvor infekcije koji se može hirurški tretirati. Ukoliko se ne dijagnostikuje i ne tretira na vreme, ima lošu prognozu, jer je ova komplikacija udružena sa već postojećom teškom bolešću jetre. Po najnovijim studijama SBP dovodi do smrtnog ishoda u 20 do 40% slučajeva. Pravovremeno prepoznavanje i adekvatna terapija mogu značajno da poboljšaju prognozu kod ovih bolesnika.

Ključne reči: **ciroza, ascites, spontani bakterijski peritonitis**