Spontaneous Bacterial Peritonitis: Pathogenesis, Diagnosis, Treatment

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Abstract

Due to inadequate defence mechanisms, cirrhotic patients with ascites have an increased susceptibility to infections, the most frequent and the most severe one being spontaneous bacterial peritonitis (SBP). SBP diagnosis is based on testing of the ascitic fluid obtained by paracentesis. A polymorphonuclear cell count of more than 250 cells/mm³ of ascitic fluid is considered diagnostic and from cultures of ascitic fluid only one germ should be isolated. 60% of the SBP episodes are produced by gram negative enteric bacilli - E. coli and Klebsiella spp. being the most frequent isolated microorganisms. The most important pathogenic mechanism for SBP is bacterial translocation. In liver cirrhosis, three mechanisms are proposed for the pathogenesis of SBP: intestinal bacterial overgrowth, the alterations (structural and functional) of the intestinal mucosal barrier and the deficiencies of the local immune response. The most appropriate antibiotic treatment is a third generation cephalosporin (Cefotaxim or Ceftriaxon) which should be administrated for 5 days. With early start of the antibiotic treatment, the short-term prognosis of cirrhotic patients with SBP has improved significantly. Unfortunately, the long term prognosis remains extremely poor due to the severity of subjacent liver disease.

Key-words
Spontaneous bacterial peritonitis - bacterial translocation - bacterial infection - sepsis - MSOF

Introduction

According to some recent statistic data, hepatic cirrhosis represents the tenth major cause of death in the USA (1). Among the major complications of cirrhosis, ascites seems to be the most frequent one, along with hepatic encephalopathy and the hemorrhage caused by the rupture of the esophageal varices (2).

Patients with cirrhosis and ascites show a higher susceptibility to bacterial infections – mainly because of the inadequate defence mechanisms. In these patients, the most frequent infectious complication that occurs (25% of the cases), and at the same time the most severe one - is spontaneous bacterial peritonitis (SBP), followed by urinary infections (about 20%), pneumonia (about 15%) and bacteremia (12%) (3).

Since 1970, when SBP was first described and up to the present, the mortality rate has been decreasing from 80% to 30%, due to a prompt diagnosis and to the early initiation of the adequate treatment (4).
Definitions

SBP is the infection of the ascitic fluid that occurs in the absence of a visceral perforation and in the absence of an intraabdominal inflammatory focus such as abscess, acute pancreatitis or cholecystitis. For SBP diagnosis, the number of polymorphonuclear leucocytes (PMN) from the ascitic fluid obtained by paracentesis must exceed 250 cells/mm³ and from bacteriological cultures only one germ must be isolated (5-7). Because SBP is in most cases a monomicrobial infection, the presence of more microorganisms in the culture (>1), must raise the suspicion of secondary peritonitis (8).

Another type of ascitic fluid infection is *culture negative neutrocytic ascites* (CNNA), the diagnosis criteria being the same as those for SBP but the cultures are negative; nevertheless, other causes of neutrocytic ascites (pancreatitis, peritonitis, tuberculosis and peritoneal carcinomatosis) must be excluded (9). Because CNNA has the same clinical and prognostic characteristics as SBP, the treatment is identical.

Monomicrobial non neutrocytic bacterascites is a form in which the cultures from the ascitic fluid are positive but the number of PMN is <250/mm³. The clinical evolution depends on the presence or absence of the signs or symptoms suggestive for infection. Patients that show infection signs have morbidity and mortality rates similar with those with SBP or CNNA (9).

The secondary bacterial peritonitis is ascitic fluid infection, diagnosed when the number of PMN exceeds 250 cells/mm³ and there is a source of infection that can be surgically treated; the cultures are positive (frequently polymicrobial). The ascitic fluid must present two of the following characteristics: the serum glucose concentration <50 mg/dl, a total protein content of >1 g/dl or LDH >225 u/ml (or higher than the upper normal limit) (9). The diagnosis of secondary bacterial peritonitis must be made early in the course of illness, because without the adequate surgical treatment, the evolution is very severe.

Another type of ascitic fluid infection is the *polymicrobial bacterascites* - in which the number of PMN is <250/mm³ and cultures of ascitic fluid (or Gram staining) demonstrate multiple organisms. This variant usually occurs as a result of inadvertent puncture of the intestine during paracentesis, being stimulated by the presence of multiple surgical scars and post-operative adhesions or by the presence of ileus. If protein concentration exceeds 1 g/dl in the ascitic fluid and the fluid activity is adequate, the colonization resolves spontaneously (9-11).

Regarding the etiology, over 60% of the SBP episodes are produced by Gram-negative enteric bacilli - E. Coli and Klebsiella pneumonia being the most frequently isolated microorganisms (2,12).

It has been ascertained that certain E. Coli strains can translocate the intestinal mucosa more often – probably because of a higher capacity to adhere to it and because of a higher virulence that determines a higher resistance to the defence mechanisms of the host.

In about 25% of the cases, gram-positive cocci are involved: streptococci (frequently pneumococcus) and enterococci (13,14).

Although the bowel flora is predominantly anaerobic, SBP is very seldom produced by anaerobic microorganisms due to their incapacity to translocate the intestinal mucosa and due to the high volume of oxygen in the intestinal wall and in the tissues that surround it.

A special situation is represented by the patients that receive antibiotic treatment (usually fluoroquinolones) for the inhibition of the gram-negative intestinal flora (selective intestinal decontamination), with the purpose of reducing the incidence of the SBP episodes. In these patients, an increased frequency of the SBP episodes produced by gram-positive bacteria has been ascertained (15).

Pathogenesis

SBP pathogenesis in patients with cirrhosis is considered to be the main consequence of bacterial translocation (BT).

The bacterial translocation is the process through which viable or non-viable bacteria and bacterial products (bacterial DNA or endotoxins) cross the intestinal lumen and come into the mesenteric lymph nodes or extraintestinal. The BT is a perturbation of the equilibrium between the normal intestinal flora and the organism, leading to an inflammatory reaction that perpetuates, finally producing infection. Bacterial translocation also is involved in increasing the hyperdynamic state of cirrhosis and in aggravation of haemostasis disorders (3,9,12).

There are some mechanisms that are being proposed to explain BT in cirrhosis: the intestinal bacterial overgrowth, the structural and functional alterations of the intestinal mucosal barrier and the deficiencies of the local immune response (6,9).

1. The intestinal bacterial overgrowth plays a key role in BT in cirrhosis and is the result of the delayed intestinal transit existing in these patients. It seems that the sympathoadrenal stimulation, increased NO synthesis and the oxidative stress of the mucosa are the main causes for decreased intestinal motility (5,16).

   Besides, although normally in the small intestine there is a more reduced microbial density compared to that of the colon, in cirrhotic patients an increase of the colonization process of the small intestine with bacteria from the colon (approx. 30-50%) is recorded (16).

2. The barrier of the intestinal mucosa includes defence mechanisms of secretory or physical type, against the microbial penetration.

   The *secretory (first defence) mechanism* is realized through the mucus secretion, the local immunoglobulins and the bile salts.

   *The mucins* are glycoproteins secreted by the epithelial cells that form an electro-negative charged layer, and are
attached to it, preventing the direct contact between the bacteria and the intestinal membrane (12).

**Immunoglobulins** - particularly IgA - are secreted by plasmocites from the lamina propria and have three major roles:
- binding to bacteria (that prevents their adhesion to the mucosa and the bacterial colonisation);
- toxin and microorganism neutralization;
- active transport role as IgA-antigen complex from the lamina propria back to the intestinal lumen.

The bile contributes to the local defence of the intestinal mucosa against bacterial aggression by decreasing internalisation of enteric bacteria, endotoxin neutralisation and inhibition of excess intestinal flora proliferation. The bile has a trophic role for the intestinal mucosa and an antiadherence effect for bacteria as well (12).

The concentration of bile acids in cirrhosis decreases in the intestinal lumen due to the reduced secretion, as well as to the increased deconjugation under the influence of the intestinal flora. The consequences of bile acid decrease are the facilitation of BT and the increasing process of translocation induced by endotoxins.

The **physical (second defence) mechanism** is represented by the intestinal epithelium - by its lack of permeability and its antimicrobial peptide active production.

The **structure of the intestinal epithelium** with its cell junction disposal allows only the passage of very tiny molecules, preventing the bacterial or the macromolecular (lipopolysaccharides) transport (12).

In hepatic cirrhosis two processes that alter the intestinal mucosa barrier occur: increased mucosal permeability (especially in patients with sepsis) because of the mucosa oxidative stress, enterocyte mitochondria malfunction, endotoxaemia, increased NO and proinflammatory cytokine level and the mucosal structural changes. The latter include the intercellular spaces enlargement, vasodilatation, oedema, fibromuscular proliferation, decreased villi/crypts ratio, thickened muscularis mucosae and inflammation (5, 12).

Another intestinal epithelium defence mechanism is the secretion of molecules with antimicrobial role (natural antibiotics), which have the capacity of destroying the microorganisms. Among these molecules a major role have the α-defensins, synthesized as a reaction to the presence of bacteria or lipopolysaccharides, and also the lysozyme and secretory phospholipase A2. These antimicrobial peptides are synthesized in the Paneth cells localized at the bottom of each intestinal crypt, mostly in the jejunal and ileal region. Besides, most epithelial cells from the small intestine and the colon can secrete β-defensine - a peptide involved in the defence against commensal bacteria (6, 12).

In addition to the mucosal local defence mechanisms (secretory and mechanical), there is at the intestine level the **gut-associated lymphoid tissue (GALT)** - considered the best immunologically represented “organ” and which includes four compartments:

1- Peyer’s patches;

2- lymphocytes from the lamina propria (including the dendritic cells);

3- intraepithelial lymphocytes;

4- mesenteric lymph nodes (MLN).

The structures that form GALT react to the presence of germs from the intestinal lumen by intraepithelial lymphocyte proliferation, germinative center appearance in the lymphoid follicles and in the lamina propria and an increase of the secreted Ig level.

In return, bacteria that form the commensal intestinal flora interact with the intestinal epithelium and can start up the primary immune response as well as the adaptive one (12, 17).

The primary immune response is realized through the monocytes and dendritic cells from the intestinal mucosa and requests some specific bacterial ligands recognition (PAMP = pathogen-associated molecular pattern) from corresponding receptors existing in mononuclear cells (PRR = pattern recognition receptor). These receptors belong to a group named TLR (toll like receptor), the most important being TLR 2, 4 and 9. The stimulation of these receptors by bacterial ligands (lipopolysaccharides, lipoteichoic acid, peptidoglycans) activates the cytokine and chemokine synthesis and the antimicrobial gene transcription. The chemokines synthesized by the epithelial cell recruit dendritic cells in the mucosa (12).

Luminal bacterial antigens are presented to dendritic cells by two mechanisms: indirect, using M cells or direct, using local antigen presenting cells (APC). M cells are specific cells from the epithelial layer, which overtake the antigen by endocytosis and transport it to the dendritic cells and local macrophages (12).

The direct mechanism consists of the takeover of antigens from local APC by emission of pseudopodes among the epithelial cells.

Then, APC presents the microbial peptides to B and T lymphocytes from the intestinal mucosa or from the MLN, by using lymphatic afferent vessels. APC will determine the type of the immune response stimulating Th “naive” lymphocytes followed by their transformation in effector Th1, Th2 or mixed phenotype lymphocytes. The bacterial antigen presentation to the B lymphocytes determines secretion of IgA (or IgG) with a protective role for the intestinal mucosa (12).

Another defence mechanism against bacterial aggression is represented by the lymphocyte T migration from the Peyer’s patches after their exposure to antigen, to the lamina propria and the epithelium, where they mature and convert to T cytotoxic lymphocytes.

The link between the primary immune response and the adaptative one is made by dendritic cells, which present bacterial antigens to B and T lymphocytes from the submucosa, but can transport them also to the MLN, where they determine a local immune response (12). Bacterial destruction from the MLN (by mononuclear cells) is not followed by systemic immunity or intestinal inflammation.
In cirrhosis, because of the local and systemic immune deficiencies, the BT process is followed by bacteremia and ascitic fluid inoculation. If the ascitic fluid complement level is low, this will determine a low bactericidal activity and thus a higher risk of SBP (9, 14).

The Kupffer cells have a special role in preventing infections in these patients. In healthy people, these local macrophages collaborate with neutrophils in the process of bacterial extraction from the circulation, followed by their destruction. In patients with hepatic cirrhosis, because of intra- and extrahepatic shunts (due to portal hypertension), circulant bacteria do not come in contact with Kupffer cells, the result being bacteremia with ascitic fluid inoculation (12).

Qualitative neutrophile abnormalities (decreased phagocytosis capacity), low complement serum levels and the decreased function of macrophages’ Fcy receptors can favour SBP (12).

There are some predisposing factors for SBP: severity of the liver disease, decreased protein and C3 level in the ascitic fluid, acute gastrointestinal bleeding, urinary tract infection, iatrogenic factors and previous SBP episodes. From these factors, the most important one is the severity of liver disease: about 70% of the patients which develop SBP are in Child C class. Besides, a serum bilirubin level >2.5 mg/dl is an independent predictive factor of SBP (17).

The low bactericidal activity of the ascitic fluid, demonstrated by a protein concentration <1g/dl, can favour SBP.

Bacteriuria, frequent mostly in female cirrhotic patients, can be another factor that favours SBP; this is why screening and treatment of urinary infections have to be performed even in asymptomatic patients, and urinary catheterization must be avoided (if possible).

Regarding acute gastrointestinal bleeding, it has been ascertained that approx. 20% of the patients have SBP at the time of admission to the hospital and 30-40% develop bacterial infections during hospitalization for digestive hemorrhage – a possible explanation being that the hemorrhagic shock increases BT and intestinal permeability. Also for preventing bacteremia, vascular catheterization has to be reduced to a minimum.

It has been documented that SBP surviving patients have an increased risk to recurrence (3, 9).

The SBP diagnosis is established by analysis of the ascitic fluid obtained at paracentesis. The main indications for paracentesis in a patient with hepatic cirrhosis include: unexplained clinical deterioration, the onset of complications (hepatic encephalopathy and gastrointestinal bleeding), new onset ascites and at every hospitalization. Paracentesis should be avoided only in case of a suspicion of fibrinolysis or DIC (3).

Although patients with cirrhosis have coagulation disturbances, the paracentesis is associated with a very low risk of complications: abdominal wall hematoma (1%), hemoperitoneum (0,1%) and iatrogenic infections (0,1%).

From the ascitic fluid a series of tests can be performed, namely: routine tests - mandatory even in the case of a therapeutic paracentesis (leucocyte count with formula, serum and ascitic fluid albumin levels, cultures in blood-culture bottles), optional tests (total amount of proteins, glucose level, LDH and amylase levels, Gram staining) and special tests (Ziehl-Nielsen stain and cultures on Lowenstein medium, cytology, bilirubin and triglyceride concentration). SBP is suspected when the PMN number in the ascitic fluid is over 250/mm³.

After paracentesis, the ascitic fluid should be inoculated immediately (at the patient's bedside) into blood-culture bottles (10ml in each bottle). Using these recipients instead of the usual ones increases the diagnosis rate of ascites with neutrophils from 50 to 80%.

The assessment of albumin quantity in the ascitic fluid is useful to calculate the albumin serum / ascites gradient, a gradient ≥ 1.1 g/dl being characteristic for portal hypertension presence.

If the clinical aspect is suggestive for SBP, the cultures from the ascitic fluid are monomicrobial and the clinical response to treatment is prompt, a second paracentesis is not required. If there are elements that suggest a secondary peritonitis or the ascitic fluid has the characteristics of a monomicrobial non neutrocytic bacterascites, paracentesis must be repeated after 48 hours (9, 11).

Because almost half the SBP cases are associated with bacteremia and any bacterial infection in cirrhotic patients can lead to manifestations similar to SBP, blood and urine cultures from these patients are useful (3).

The chest x-ray can show a right hydrothorax. If infection is suspected (and SBP diagnosis has been ruled out), thoracentesis is necessary in order to establish diagnosis because the spontaneous bacterial empyema can occur even without ascites or SBP. From the pleural fluid, common tests (some as for ascitic fluid) and inoculation into blood-culture bottles can be performed.

**Diagnosis**

Clinical manifestations of SBP are unspecific. The most frequently encountered symptoms and signs are fever (69%), abdominal pain (59%), signs of hepatic encephalopathy, abdominal tenderness (very rare), diarrhea, ileus, shock and hypothermia. Approximately 10% of the patients with SBP are asymptomatic (8, 9, 18).

At physical examination, patients with ascites and SBP do not have a rigid abdomen because the ascitic fluid in great amounts prevents the contact between the peritoneal membranes (visceral and parietal) (19).

**Treatment**

**Antibiotics.** Many years ago, the usual treatment for cirrhotic patients with ascites and SBP was the combination of a β-lactam plus an aminoglycoside. Because patients with SBP are very sensitive to the nefrotoxicity associated with
use of aminoglycosides, this initial treatment scheme has been replaced with a third generation cephalosporin - Cefotaxim. Starting with 1985, after some clinical studies, Cefotaxim has been considered the first choice empiric antibiotic in SBP treatment. Its efficiency is better than that of the initial therapeutic scheme (85% to 56%) and the doses (2g i.v. every 8 hours) do not need adjustment in renal or hepatic failure. The duration of treatment is 5 days, even in patients with bacteremia. With similar efficiency and security profile as Cefuroxim are also Ceftriaxon (2g every 24 hours for 5 days) and the association Amoxicillin + clavulanic acid (1.2g every 6-8 hours for 2 days) (2,11,13,20-22).

In patients with uncomplicated SBP (no gastrointestinal bleeding, hepatic encephalopathy, ileus, shock or renal failure), treatment with Ofloxacin or other oral quinolones for 8 days can be administrated (10,15,18,22).

A good response to therapy can be evaluated by clinical criteria (disappearance of infection signs and symptoms), but the most important parameter remains the decrease to a half (from the pre-treatment value) of the PMN number in the ascitic fluid obtained by paracentesis after two days of treatment (11).

Studies that require further confirmation propose the association of albumin (1.5 g/kg body weight the first day, then 1g/kg three more days) to the Cefotaxim treatment for patients with renal failure and SBP. Albumin in these patients may improve the renal function by increasing the intravascular volume, because vasodilatation induced by cytokines released in excess reduces the effective arterial volume (18,23).

Other adjuvant therapies in patients with SBP include prokinetics and probiotics.

Prokinetics are used to shorten the intestinal transit time, reducing thus the intestinal bacterial overgrowth and the risk of bacterial translocation.

Encouraging results have been obtained by using Cisapride and Propranolol, the latter’s β blocking effect antagonises the increased adrenergic tone existent in patients with cirrhosis and responsible for the decreased intestinal motility.

Probiotics are used for intestinal flora reequilibration, in favour to anaerobic protective bacteria. Bacteriotherapy with Lactobacillus seems to correct intestinal bacterial overgrowth, to stabilize mucosal barrier function and to stimulate the local defence mechanisms (3,12).

Oral treatment with conjugated bile acids (cholyglycine and cholylsarcosine) for preventing BT is under evaluation (12).

**SBP prevention**

There are three categories of cirrhotic patients which are more at risk of developing SBP: patients with digestive hemorrhage; patients with ascitic fluid protein level <1 g/dl; and patients who survived a prior SBP episode.

For preventing SBP in patients with low ascitic fluid protein level, Norfloxacin is administrated during hospitalization.

Patients with digestive hemorrhage are more at risk in developing SBP; it is considered that 20% of them have SBP at admission and 30-40% will develop an infection during hospitalization. These patients will receive 800 mg/ day Norfloxacin through the nasogastric tube for 7 days (3,22).

In patients who survive an episode of SBP, a long term prophylactic treatment (for preventing recurrence) with Norfloxacin 400 mg/day will be administered.

When the oral administration or the administration by nasogastric tube of Norfloxacin is not possible, Ciprofloxacin can be administered i.v. In patients with intolerance to quinolones, the association trimethoprim/sulfamethoxazol for 5 days/ week can be used.

Patients who receive primary or secondary prophylactic treatment with Norfloxacin can develop resistant gram-negative bacilli strains. Fortunately, no crossed resistance between third generation cephalosporines and quinolones has been observed, thus infections caused by quinolone resistant germs can be treated with Cefotaxim or Ceftriaxon.

Other prophylactic measures include:

- diuretics, which reduce the ascites volume and increase the ascitic fluid opsonic activity;
- local infections treatment and eradication, before their dissemination;
- porto-caval shunts and TIPS (transjugular intrahepatic portosystemic shunt) for digestive hemorrhage or ascites risk reduction, reducing indirectly SBP risk;
- abstinence from alcohol in case of alcoholic cirrhosis (9).

**Conclusions**

In cirrhotic patients, endotoxaemia and infection are very frequent. These damage systemic and splanchnic haemo-
dynamics, impair coagulation, worsen liver function and may trigger variceal bleeding (14).

In patients with critical status, the digestive tract is right to be considered the MSOF’s “engine”. The management of these patients is based more and more on a multi-disciplinary collaboration, early diagnosis and treatment being decisive for their evolution and prognosis.

Once the diagnostic criteria have been defined and a prompt treatment decided (before renal failure or shock occurrence), the short term prognosis for patients with SBP has significantly improved. Unfortunately, for patients who have survived a SBP episode, long term prognosis is extremely poor because of the associated severe impairment of liver function. This is why for these patients liver transplantation must be an option.

References