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# Nanotechnology used in Spontaneous Bacterial Peritonitis: A Review

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**Abstract** Spontaneous bacterial peritonitis is the most frequent bacterial infection in patients with cirrhosis. The reported incidence varies between 7% and 30% in hospitalized patients with cirrhosis and ascites, representing one of their main complications. Outcomes in patients with spontaneous bacterial peritonitis are poor since acute kidney injury, acute-on-chronic liver failure, and death occur in as much as 54%, 60%, and 40% of the patients, respectively, at midterm. Early antibiotic treatment of spontaneous bacterial peritonitis is crucial. However, the landscape of microbiological resistance is continuously changing, with an increasing spread of multidrug-resistant organisms that make its current management more challenging. Thus, the selection of the empirical antibiotic treatment should be guided by the severity and location where the infection was acquired, the risk factors for multidrug-resistant organisms, and the available information on the local expected bacteriology. The use of albumin as a complementary therapy for selected high-risk patients with spontaneous bacterial peritonitis is recommended in addition to antibiotics. Even though antibiotic prophylaxis has proven to be effective to prevent spontaneous bacterial peritonitis, a careful selection of high-risk candidates is crucial to avoid antibiotic overuse. In this article we review the pathogenesis, risk factors, and prognosis of spontaneous bacterial peritonitis, as well as the current evidence regarding its treatment and prophylaxis.

**Keywords** Nanotechnology, Bacterial Peritonitis

## Introduction

Spontaneous bacterial peritonitis is the most frequent bacterial infection in patients with cirrhosis, followed by urinary tract infection, pneumonia, skin and soft tissue infections, and spontaneous bacteremia. During or after an episode of spontaneous bacterial peritonitis, patients frequently present signs of decompensation such as development or progression of ascites or hepatic encephalopathy, gastrointestinal bleeding, and extrahepatic organ compromise such as renal failure. In fact, the most common cause of death in patients with cirrhosis admitted for bacterial infections is the development of acute-on-chronic liver failure, characterized by a high mortality rate due to multiorgan failure. In daily practice, the diagnosis of spontaneous bacterial peritonitis and other infections might be challenged by the fact that typical signs and symptoms, like fever or leukocytosis, are frequently absent. Therefore, a high index of suspicion is usually necessary for early diagnosis and treatment, which is associated with better outcomes [1].

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/$mm^3$ and from bacteriological cultures only one germ must be isolated [13-15]. 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.

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. Because CNNA has the same clinical and prognostic characteristics as SBP, the treatment is identical [2].

**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].

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 [4].

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.
   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 .
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.

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.

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.

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 malfunctioning, 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.

Another intestinal epithelium defence mechanism is the secretion of molecules with antimicrobial role (natural antibiotics), which have the capacity of destroying the microorganisms

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).

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 [5].

**Signs and Symptoms**

Signs and symptoms of spontaneous bacterial peritonitis (SBP) include fevers, chills, nausea, vomiting, abdominal pain and tenderness, general malaise, altered mental status, and worsening ascites. Thirteen percent of patients have no signs or symptoms [6].

**Diagnosis**

A diagnostic paracentesis should be performed in all cirrhotics with ascites and: (1) upon admission to the hospital, (2) who develop any change in clinical status including fever, abdominal pain, mental status changes, ileus, or septic shock, (3) who develop laboratory abnormalities such as a leukocytosis, acidosis, or renal failure, or (4) during episodes of gastrointestinal bleeding prior to the administration of antibiotics.

When suspicion of infection exists, ascitic fluid should be sent for cell counts, total protein, glucose, lactate dehydrogenase, amylase, Gram's stain, and culture. A serum and ascitic fluid albumin should also be sent if the serum-ascites albumin gradient has not been previously calculated. Other tests such as ascitic fluid pH and lactate are of limited value and more confusing than helpful. The fluid PMN count (when using a threshold of 250 cells/$mm^3$) is the most sensitive and single best test in diagnosing ascitic fluid infection

Secondary bacterial peritonitis should be suspected if the ascites PMN count is 6250 cells/mm3 and two of the following three ascitic fluid values are met:

(1) glucose 50 mg/dl, (2) total protein 1 1 g/dl, and (3) lactate dehydrogenase greater than the upper limit of normal for serum.

The finding of more than one organism on Gram's stain or culture of ascitic fluid should prompt a similar urgent evaluation for perforation. If multiple organisms are detected on either modality but the PMN count is ! 250 cells/$mm^3$, the diagnosis is likely polymicrobial bacterascites due to puncture of the bowel with the paracentesis needle. This is a rare occurrence (less than 0.6% of paracenteses), is associated with low morbidity, and surgical intervention does not appear to be necessary [7].

**Treatment**

Empirical antibiotic therapy for SBP should begin as soon as infection is suspected (i.e. PMN count 6250 cells/ $mm^3$) and not delayed pending culture confirmation of the organism and sensitivities. Delaying treatment until the results of the culture are known may result in death of the patient from overwhelming sepsis. Accordingly, patients with CNNA also warrant early antibiotic therapy as they are similar to SBP with regard to symptoms, ascitic fluid analysis, rate of blood culture growth, and mortality [8].

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 [9].

**Antibiotic therapy of SBP**

Gram-negative enteric organism and streptopneumonia are the causative pathogens in over 80% of instances of SBP. Hence, the choice of antibiotics should cover these most likely agents. Early studies have used combination of ampicillin and aminoglycoside. However, aminoglycosides have a narrow therapeutic band over which nephrotoxicity occurs. Within this range, antibiotics level may not be adequate. Furthermore, the volume distribution of aminoglycoside is unpredictable in ascites.

Several studies have proved, in randomized controlled studies that third generation cephalosporins are more effective than the combination of ampicillin and tobramycin. This drug covers 98% of the SBP flora and resulted in no nephrotoxicity, and at the same time achieved an adequate ascitic fluid level.

Reported mortality in patients with SBP is improving with early literature reporting 100% death in SBP, while newer studies quote a figure of 50%. This could be as consequence of the awareness of the physician, early performance of paracentesis and use of more effective drugs [10].

**Oral antibiotics**

Oral fluoroquinolones are generally acceptable for uncomplicated SBP (i.e. absence of sepsis and patients at risk for aspiration). Fluoroquinolones have excellent oral bioavailability ranging from 70% for ciprofloxacin to 95% for levofloxacin. In a randomised controlled trial, oral ofloxacin and IV cefotaxime resolved SBP at the same rate (84% vs. 85%) respectively [11].

**Switch therapy**

In a randomised study in 2000, Terg *et al*. showed that patients with SBP can be adequately treated with oral ciprofloxacin after a short course of IV ciprofloxacin. Switch therapy with oral ciprofloxacin was as effective as IV ciprofloxacin at infection resolution in a randomised study involving 116 patients with SBP and was more cost effective [12].

**Prevention**

- Albumin infusion prevent HRS and improves survival in SBP.
- Pentoxifylline 1200mg /day superior to placebo in preventing HRS in cirrhotics with ascites and creatinine clearance 41-80 ml /min.
  -Prevents HRS in severe ETOH hepatitis
  -Subsequent metanalysis showed no benefit on HRS or mortality
- Norfloxacin 400 mg QD prevents SBP in low protein and previous SBP 400 mg BID for pts with variceal hemorrhage
- Oral antibiotics do not prolong survival [13].

**Use of Nanotechnology in Spontaneous Bacterial Peritonitis**

We report here the application of a photonic interferometer biosensor based on a bimodal waveguide (BiMW) for the rapid and label-free detection of bacteria directly in ascitic fluid.

The current standards for detecting bacteria are microbial culture or gene analysis, which need complex equipment and professional technicians to operate in specific environments. Recent studies show that colorimetric biosensors, fluorescence imaging or microelectronics can be useful for Gram-positive and Gram-negative bacteria detection[14].

AuNPs (gold nanoparticles) are widely applicable as colorimetric biosensors, drug delivery carriers, antibacterial agents, and photothermal therapy material. Our group has developed a series of small molecule-modified AuNPs that can kill multidrug-resistant bacteria. We also report a number of colorimetric sensors based on AuNPs since their use can avoid the necessity of bulky instruments by obtaining signals with the naked eye. A number of investigators have reported bacterial biosensors based on AuNPs. Scientists have developed cetyltrimethylammonium bromide (CTAB)-coated AuNPs to detect bacteria. CTAB is positively charged such that it can target the negatively charged bacterial surface. Researchers also use antibodies or aptamers to decorate AuNPs for bacterial targeting. Unfortunately, these strategies are based on charge interactions and easily interfered by surroundings such as pH values, metal ion or proteins. A stable, easily available and navigable platform for the detection of pathogens is urgently needed [15].

In recent years, we have been faced with an explosion in the design, development and characterization of novel nanofabricated devices for drug delivery. Nanotechnology is being used, as follows:

- drug discovery (including combinatorial chemistry and synthesis on the molecular and macromolecular scale),
- nanoanalysis including bioanalysis using miniaturized probes, microarrays and lab-on-a-chip approaches,
- utilizing approaches used by the body in fluid flow and targeting,
- drug delivery systems having sizes in the nanometer range (e.g. liposomes, nanoparticles, micro-emulsions, dendrimers, etc.),
- implantable devices that can sense blood levels and automatically administer drugs,
- nanoscale biomaterials including biomimetics,
- biological macromolecules (e.g. proteins, enzymes, DNA and RNA based nanostructures, molecular assemblies, biomolecules, cells, biochips, etc.),
- molecular sensors and biosensors, as well as clinical diagnostic techniques,
- gene delivery and expression [16].

**Conclusions**

These results indicate that spontaneous bacterial peritonitis in cirrhotic rats is mainly due to intestinal bacteria translocated to mesenteric lymph nodes. Portal blood could be a less frequent route [17].

Primary prophylaxis with norfloxacin has a great impact in the clinical course of patients with advanced cirrhosis. It reduces the incidence of spontaneous bacterial peritonitis, delays the development of hepatorenal syndrome, and improves survival [18].

**Refrences**

[1]. European Association for the Study of the Liver Electronic address: easloffice@easloffice.eu, EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69(2):406–460.

[2]. Levison ME, Bush LM. Peritonitis and intraperitoneal abcesses. In Mandell GL, Bennett JE, Dolin R. Principles and Practice of Infectious Diseases. 6th Edition, Elsevier, Churchill Livingstone, Philadelphia, 2005, Vol 1, 927- 951

[3]. Garcia-Tsao G. Bacterial infections in cirrhosis: treatment and prophylaxis. J Hepatol2005;42:585-592

[4]. Guarner C, Soriano G. Bacterial translocation and its consequences in patients with cirrhosis. Eur J Gastroenterol Hepatol 2005; 17: 27-31

[5]. Berg RD. Mechanisms promoting bacterial translocation from the gastrointestinal tract. Adv Exp Med Biol 1999; 473: 11- 30.

[6]. Koulaouzidis, A; Bhat, S; Saeed, AA (7 March 2009). "Spontaneous bacterial peritonitis". World Journal of Gastroenterolog. 15 (9): 1042-9. doi:10.3748/wjg. 15.1042. PMC 2655193. PMID 19266595.

[7]. Runyon BA: Management of adult patients with ascites due to cirrhosis. Hepatology 2004; 39: 841–856.

[8]. Garcia-Tsao G: Treatment of spontaneous bacterial peritonitis with oral ofloxacin: inpatient or outpatient therapy? (letter). Gastroenterology 1996; 111: 1147–1149.
[9]. Wiest R, Garcia-Tsao G. Bacterial translocation in cirrhosis. Hepatology 2005; 41: 422- 433
[10]. Runyon BA. Spontaneous bacterial peritonitis: an explosion of information. Hepatology 1988; 8(1):171-5.
[11]. Navasa M, Follo A, Llovet JM, *et al*. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996; 111: 1011–7.
[12]. Angeli P, Guarda S, Fasolato S, *et al*. Switch therapy with ciprofloxacin vs. intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. *Aliment PharmacolTher* 2006; 23: 75–84.
[13]. Madrid A, Hurtado C, Venegas M. *et al* Long term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. Am J Gastroenterol 2001961251–1255.
[14]. Chen Y, Xianyu Y, Jiang X. Surface modification of gold nanoparticles with small molecules for biochemical analysis. Accounts Chem Res. 2017; 50:310–319.
[15]. Ray PC, Khan SA, Singh AK, Senapati D, Fan Z. Nanomaterials for targeted detection and photothermal killing of bacteria. Chem Soc Rev. 2012; 41:3193–3209.
[16]. Rytting H. Pharmaceutical nanotechnology: a new section in IJP. Int. J. Pharm. (2004) 281
[17]. Llovet, Josep M., et al. "Translocated intenstinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence." Journal of hepatology 28.2 (1998): 307-313.
[18]. Fernández, Javier, et al. "Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis." Gastroenterology 133.3 (2007): 818-824.