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Chapter

Spontaneous Bacterial Peritonitis: Physiopathological Mechanism and Clinical Manifestations

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Abstract

Changes in intestinal permeability have been determined to influence secondary inflammatory reactions and clinical manifestations such as spontaneous bacterial peritonitis (SBP) secondary to cirrhosis. As of yet, no in-depth exploration of the changes in the microbiota and how this influences cirrhosis to differ from clinically more severe cases than others has not begun. However, at the level of pathophysiological mechanism, it must be taken into account that due to the abuse of substances such as alcohol and chronic fatty liver disease, changes in the bacterial composition and intestinal permeability are induced. This set of changes in the bacterial composition (microbiome) and modification of the intestinal permeability could be related to the presence of ascites and spontaneous peritonitis secondary to cirrhosis, being of relevance the knowledge of the mechanisms underlying this phenomenon, as well as clinical manifestation. Prophylaxis and antibiotic treatment of SBP requires clinical knowledge for the treatment decisions based mainly on the presence of ascitic fluid, accompanied of risk factors, laboratory indexes such as PMN count and culture results, in order to determine the kind of molecule that will help to the SBP recovery or to amelioration symptoms, always taking care of not exceed the antibiotic consumption and restoring the microbiome imbalance.

Keywords: bacteria, peritonitis, microbiome, cirrhosis, gut permeability

1. Introduction

In cirrhotic patients with ascites, spontaneous bacterial peritonitis (SBP), an ominous complication, occurs recurrently with an annual increase rate of 69% [1]. Furthermore, in cirrhosis with portal hypertension, SBP is a key hallmark feature in developing hepatic encephalopathy, variceal bleeding, hepatorenal syndrome and increased mortality [2]. Also, intestinal barrier dysfunction is pondered central in the pathogenesis of cirrhotic complications. In health, intestinal barrier function is

crucial against extensive and continuous exposure of the liver to the gut microbiota and their products and metabolites. Thus, gut microbiome sets the stage for the gut-liver axis [3]. Nevertheless, in cirrhosis, intestinal barrier dysfunction, increased permeability and extensive inflammation occurs due to SBP. The intestinal barrier consists of several layers, including mucus layer, intestinal epithelial cells, lamina propria and Peyer's patches. They determine the extent to which gut microbes and their products (endotoxin) can access the host vasculature [4].

Therefore, the intestinal vascular barrier is considered an important layer controlling the entry of gut bacterial products into the portal circulation and liver [5]. Gut microbiota may therefore have a prime role in a pathologic loop, which regulates portal hypertension, and thus have a role in the cirrhosis development.

SBP is a frequent and severe complication in cirrhotic patients with ascites. On the other hand, cirrhotic complication initiates dysregulation of intestinal AMP and bacterial overgrowth, which triggers mucosal inflammation. The proinflammatory cytokine milieu in the intestinal lumen plays a critical role in disrupting the tight junction protein integrity, leading to BT. Bacterial endotoxin and harmful pathogenic bacterial species translocate to the liver through portal vein further exacerbate the already prevalent hepatic inflammation and fibrosis in the liver, causing a cyclic progression of liver injury. Pathogenic bacteria and endotoxins also translocate to blood causes systemic inflammatory responses induced by cytokines, chemokines and interferons resulting cytokine storm syndrome and hemodynamic abnormalities, thereby promotes liver injury followed by multiorgan failure and eventually it causes death.

2. The pathophysiological mechanism involved in spontaneous bacterial peritonitis in cirrhosis: loss of permeability and gut microbiota

Peritonitis occurs in patients with cirrhosis and ascites, in the absence of any other intra-abdominal cause of infection, such as an abscess or intestinal perforation. The spontaneous bacterial peritonitis (SBP) is defined as an infection of the ascites fluid, which produces an inflammatory reaction of the peritoneum and as previously described. It has been associated with intestinal dysbiosis, since it leads to dysfunction of the intestinal barrier that can cause bacterial translocation of very small quantities of viable or dead bacteria, constituting a physiologically important reinforcement for the immune system. Bacterial translocation is defined as the passage of bacteria or bacterial products that go from the intestine to the mesenteric lymph nodes.

2.1 Bacterial translocation

Due to the close anatomical and physiological connections between the liver and gut, barrier dysfunction results in translocation of viable bacteria and its product to the liver via the portal circulation, thereby causing liver dysfunction. Several experimental studies showed that cirrhotic patients had increased intestinal permeability which might be a critical contributing factor to cirrhosis development [6, 7]. In addition, microbial overgrowth has been observed in intrahepatic cholestatic patients [8]. Bacterial infections such as SBP and bacteraemia are associated with the four-fold increased death rate in cirrhotic patients [9]. In this context, it was observed that the presence of bacterial DNA in the blood and ascitic fluid of cirrhotic patients developed poor prognosis compared to cirrhotic patients who had negative for bacterial DNA [10]. Bacterial translocation (BT) initiates a cycle of dysfunctional immune activation, and systemic inflammatory response, facilitating

the worsening of pre-existing hepatic and hemodynamic abnormalities in cirrhosis [11]. Identification of bacterial DNA has been associated with worsening of intrahepatic endothelial dysfunction and extra-hepatic (peripheral) vasodilation [12]. Further, lipopolysaccharide-binding protein (LBP) is a surrogate marker for BT, correlated with systemic hemodynamic abnormalities in cirrhotic patients [13]. Endotoxemia has been closely associated with hyperdynamic circulation, coagulopathy, portal hypertension, renal and cardiac dysfunction in cirrhosis [14]. Furthermore, systemic inflammatory response syndrome (SIRS) with bacterial infection shows an increased risk of 67% in cirrhotic patients suggesting that SIRS also contributing to cirrhosis prognosis **Figure 1** [15].

2.2 Gut dysbiosis

Bacterial dysbiosis is characterized by the pathogenic shift in quantity or quality from the symbiotic state existing between the host and indigenous bacteria [16, 17]. A marked alteration has been observed in the small intestinal microbiota in patients with cirrhosis compared to normal individuals. A ratio of autochthonous to non-autochthonous bacterial taxa is referred to as cirrhosis dysbiosis ratio (CDR). Patients with cirrhosis were shown to exhibit a lower CDR [16]. The pathogenic shift in the proportion of bacterial taxa is also associated with decompensation of cirrhosis. The disruption of microbial balance in cirrhosis leads to accumulation of harmful bacterial metabolites that damage the intestinal epithelial barrier [16]. Gut dysbiosis also leads to intestinal immune system dysregulation by changing the composition of short-chain fatty acids produced by the microbiota [17]. This immune dysregulation with functional proinflammatory switch

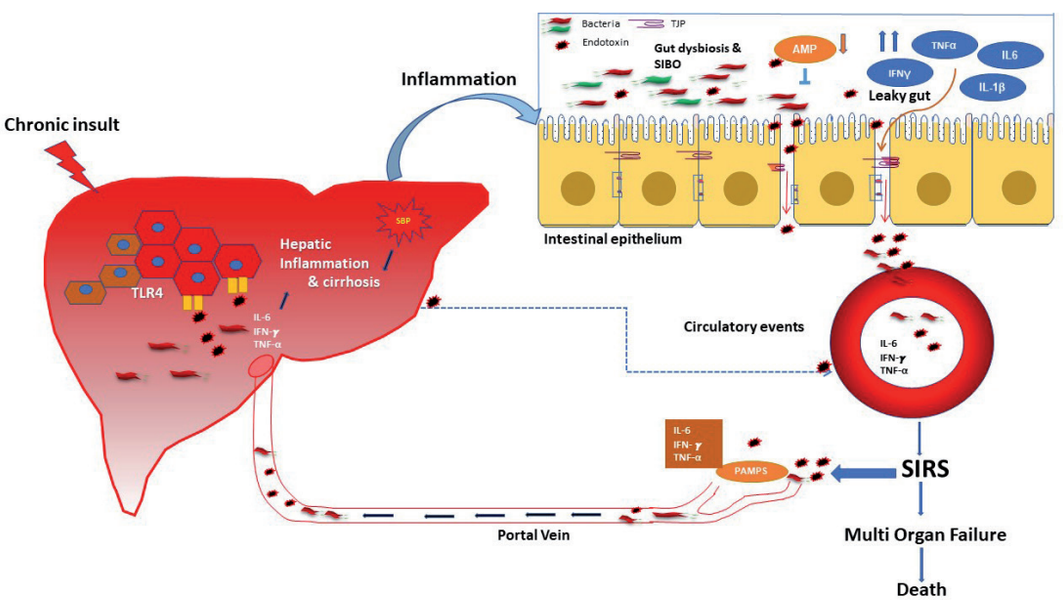

Figure 1.
The pathophysiological mechanism associated with BT and SBP in decompensated cirrhosis. SBP is a frequent and severe complication in cirrhotic patients with ascites. On the other hand, cirrhotic complication initiates dysregulation of intestinal AMP and bacterial overgrowth, which triggers mucosal inflammation. The proinflammatory cytokine milieu in the intestinal lumen plays a critical role in disrupting the tight junction protein integrity, leading to BT. Bacterial endotoxin and harmful pathogenic bacterial species translocate to the liver through portal vein further exacerbate the already prevalent hepatic inflammation and fibrosis in the liver, causing a cyclic progression of liver injury. Pathogenic bacteria and endotoxins also translocate to blood causes systemic inflammatory responses induced by cytokines, chemokines and interferons resulting cytokine storm syndrome and hemodynamic abnormalities, thereby promotes liver injury followed by multiorgan failure and eventually it causes death. Note: AMP-anti microbial peptides; BT-bacterial translocation; IFN-Interferon; IL-interleukin; IJP-tight junction protein; SBP-spontaneous bacterial peritonitis; TLR-toll-like receptor; TNF-tumor necrosis factor.

contributes to mucosal barrier dysfunction and BT [17] and thus, bile acids (BA) derangement, which plays a causal role in the gut dysbiosis.

In cirrhotic patients, intraluminal BA reduction was shown to increase deconjugation by enteric bacteria [18]. Moreover, defect in intestinal BA concentration accelerates BT and develops susceptibility to bacterial endotoxin [19]. Intestinal dysmotility is another important contributor to the development of SBP in cirrhotic patients [20].

2.3 Tight junctions and intestinal permeability

Increased intestinal permeability exerts a pivotal role in the pathogenesis of SBP in cirrhosis following elevated systemic endotoxemia. Moreover, a significant association was found between elevated portal pressure and gastro-duodenal and intestinal permeability in cirrhosis [21]. Specific ultrastructural and functional alterations in the intestinal mucosa have been identified in cirrhosis patients associated with increased intestinal permeability to BT [22]. The intestinal barrier comprises tight junction (TJ) proteins that allow specific passage of gut bacterial products and metabolites, thus maintaining intestinal structural integrity and regulating intestinal permeability following SBP [23]. Zona occludens (ZO-1), occludin and claudins are the major integral transmembrane proteins composed of TJ and maintaining the intestinal permeability [24]. The TJ proteins expression and turnover are predisposed by oxidative stress and inflammation following SBP in cirrhosis, consequently, disruption of the intestinal barrier allows bacterial endotoxin from the intestinal lumen to pass into the portal circulation and thus reaches the liver culminating hepatic complications (**Figure 1**). Significant alterations in occludin were observed in intestine of both compensated decompensated cirrhotic patients compared to healthy subjects [6, 7]. Notably, the reduction in intestinal occludin expression was associated with elevated endotoxins levels and severe variceal bleeding [6]. We found significantly decreased hepatic ZO 1 levels in patients with cirrhosis and HCC [25]. Furthermore, our rodent experimental data show evidence that in cirrhosis and HCC, diminished hepatic expression of ZO-1 and occludin was correlated with BT [25, 26].

2.4 Small intestinal bacterial overgrowth (SIBO)

Small intestinal bacterial overgrowth (SIBO) induced by prolonged gastric and small intestinal transit of bacterial products and metabolites. It is a condition in which colonic bacterial translocate into the small intestine [27]. The process of bacterial dysbiosis, coupled with SIBO, is well documented in cirrhosis [16, 28]. Increased proportion of the gram-negative Bacteroides species and the gram-positive *Enterococcus spp.* were identified in the small intestine of patients with alcoholic liver disease [28]. SIBO is also accompanied by a decrease in *Lactobacillus spp.*, which is regarded as beneficial to the host [29]. SIBO coupled with bacterial dysbiosis (**Figure 1**) leads to accumulation of bacterial endotoxins such as LPS, an specific PAMP (Pathogen Associated Molecular Patterns), which in turn results in the induction of inflammatory response culminating in intestinal epithelial damage and gut permeability [30] this mechanism will be explained deeply ahead in this chapter. Cirrhotic patients who use proton pump inhibitors are vulnerable to SBP, due to intestinal overgrowth of *Enterococcus spp*. [31, 32]. Antimicrobial peptides (AMP) are considered the first line of defence to counter bacterial overgrowth and maintain bacterial symbiosis, which are primarily produced by paneth cells and intestinal epithelial cells [33]. Decreased AMP was pronounced in the ileum, which was associated with increased BT in cirrhosis [34]. Also, human and experimental

ALD attributed to decreased AMP expression [33, 35]. Regenerating family member 3 alpha [Reg3A] belongs to the C-type lectin family is one of the important AMP in regulating intestinal inflammation [36] and facilitating the repair of gut mucosa in rodent models. Moreover, our recent study shows that Reg3A protein expression was significantly reduced in cirrhotic mice small intestine [37]. We also found significantly decreased Lactobacillus and increased *Bacteroides* and *Enterococcus* 16 s rRNA levels in the liver and small intestine of cirrhotic mice [37]. This reduced intestinal Reg3A expression was associated with an increased E*nterococcus* translocation to rodent cirrhotic liver. Similarly, Darnaud et al., observed that Reg3A overexpression in colitis mice attenuated intestinal inflammation and restricted BT [36]. Moreover, Reg3A expression protected against dextran sulphate sodium (DSS)-induced intestinal inflammation, intestinal permeability and BT in mice [36]. In addition, intestinal Reg3A has been reported to promote the enrichments of *Lactobacilli sp* [38] and depletion of *Bacteroidetes* population [36], indicating Reg3A could be a critical factor in restricting BT by averting bacterial dysbiosis. Cathelin-related antimicrobial peptide (CRAMP) is an AMP produced by intestinal epithelial cells exhibits potent antibiotic activity against various strains of gram-negative bacteria [39]. Deficiency of CRAMP expression correlated with impaired microbial clearance and elevated proinflammatory cytokine response in glial cells exposed to bacterial endotoxins [40]. We found CRAMP cellular expression in the small intestine of cirrhotic mice albeit, no significant difference between control and cirrhotic mice [37].

2.5 Inflammation in spontaneous bacterial peritonitis

Inflammation and oxidative stress are other key players contributing to mucosal damage and cirrhosis progression by triggering cytokine productions. Activation of Kupffer cells and the recruitment of proinflammatory monocyte subsets could propagate both intra-hepatic and extra-hepatic (systemic) inflammation [41, 42]. Of note, the cirrhotic patients with bacterial infections exhibited elevated systemic levels of inflammatory and pyrogenic cytokines IL-6 and TNF-α compared to septicemia patients without cirrhosis [43]. IL-6 levels in cirrhotic patients correlated with immune cell activation, organ failure, and portal hypertension [14, 44]. Moreover, soluble TNF-α receptor levels in hepatic venous and portal venous blood correlated with endotoxin concentration as well as hemodynamic derangements in cirrhosis [45]. Hence endotoxin-induced proinflammatory cytokines serve as important mediators of SIRS induced-hemodynamic abnormalities in cirrhosis. In this context, our experimental data show evidence that significantly elevated ascitic fluid cytokine concentrations in cirrhotic mice [37]. Gastrointestinal tract inflammation was contemplated as a major mediator of TJ disruption. Decreased TJ proteins ZO-1 and occludin were reported in gastric carcinoma with inflammation [46]. In cirrhosis with SBP, intestinal barrier disruption has been precipitated by inflammation [26]. Proinflammatory cytokines such as TNF alpha, IL-I beta and IFN gamma trigger barrier damage on the gut epithelium by inducing endocytosis of TJ proteins and increased expression of myosin light chain kinase protein, thereby causing TJ permeability [17, 26]. Intestinal mucosa covered by the mucus layer provides a first line of defence mechanism against harmful bacteria and endotoxin from invading the microvillus environment [30]. Inflammatory mediators, LPS and growth factors affect the secretion of mucin, which is present in the mucus layer. In particular, nuclear factor-κB [NF-κB] binds with the specific site of the promoter region of mucin and affect its secretion [47]. Therefore, modulation of bacterial adherence to the gut mucosal surface by intestinal mucus results in loss of gut barrier function [48]. In this context, a previous experimental study

shows evidence in cirrhotic rats ileum that increased mucin 2&3 mRNA expression compared to control [49]. Moreover, increased mucus content in the small intestine was found following chronic alcohol supplementation to rats [30].

In cirrhosis, SBP is a major precipitating factor initiates gut-liver axis dysfunction. It is mainly due to the fact that intestinal microbiota dysbiosis, bacterial overgrowth and bacterial translocation [4], which originates intestinal mucosal dysfunction and damage at the systemic immune cell functions [50]. Moreover, inflammation and oxidative stress are other contributing factors that can influence the barrier function of both the small and the large intestine and probably result in the occurrence of SBP in cirrhosis.

2.6 Microbiota in spontaneous bacterial peritonitis consequence

The gut microbiota plays a key role in spontaneous bacterial peritonitis due to intestinal dysbiosis and bacterial translocation. A study conducted by Lachar & Bajaj, 2016, demonstrated that patients with spontaneous bacterial peritonitis presented intestinal dysbiosis, and thus concluded that it can be a useful quantitative index to describe the microbiome alterations that accompany the progression and complications of cirrhosis [51].

The term microbiota refers to the community of living microorganisms that reside in a specific ecological niche. In the gastrointestinal tract, the microbiota is a dynamic system that maintains a symbiotic relationship with the intestinal mucosa. This relationship imparts metabolic, protective and immune functions that contribute to the well-being of the host, which are modified by environmental factors. Additionally, it participates in metabolic processes that connect the intestine with liver, muscle and brain [52, 53]. The eubiosis microbiota comprises a balance between symbiotic microorganisms [bacteria with homeostasis-promoting functions] and pathobionts [commensal bacteria with the ability to induce pathology]. However, the dysregulation of this balance can determine a state of dysbiosis [54] (**Figure 2A**). Therefore, alterations in the intestinal microbiota are important in the pathogenesis of several complications that arise in liver disease, such as spontaneous bacterial peritonitis. This is usually caused by the presence of one or more species of aerobic and anaerobic enteric bacteria that act in synergy [55–59] (**Figure 2B**).

The most common microorganisms associated with this disorder are Gram-negative bacteria, such as *Escherichia coli* and *Klebsiella* species, and infections by Gram-positive bacteria such as *Staphylococcus*. Gram negative bacilli, especially *Escherichia coli*, which are found in low concentrations in the small intestine of healthy subjects, these are increased as jejunal microbiota in many cirrhotic patients, especially in those patients with more advanced cirrhosis and a greater decrease in the intestinal motility. *Escherichia coli* is known to be the main cause of SBP and is more frequently isolated in ascites fluid, in previous studies it has been described that the isolation rate is 66.6%. An increase in endotoxin levels in patients with advanced cirrhosis has been shown to promote the production of multiple pro-inflammatory elements, so the activation of this cytokine cascade in spontaneous bacterial peritonitis has been associated with greater complications leading to death [60–62].

In recent years the prevalence of Gram-positive bacteria in SBP has increased. In addition, there is a growing resistance to multiple drugs such as quinolones, which is of particular importance since norfloxacin represents the antimicrobial of choice for SBP. But this has changed dramatically, as multidrug resistant organisms (MDRO) have been described [63]. A study carried out by Mücke *et al.*

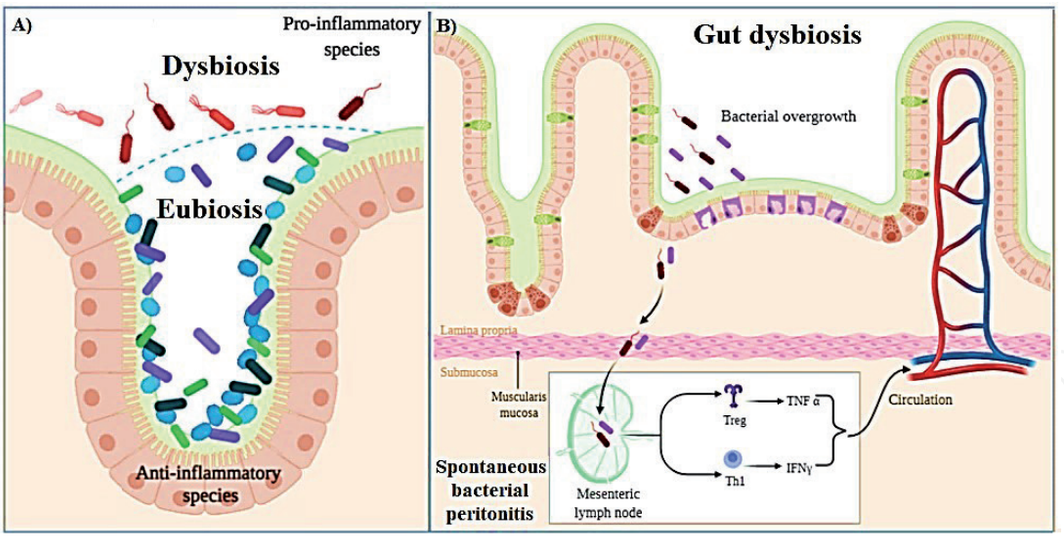

Figure 2.
The role of the gut microbiota in spontaneous bacterial peritonitis. (A) Ecology of the gut microbiota. Ecological community in balance of symbiotic microorganisms (anti-inflammatory species) and pathobionts (pro-inflammatory species) that share a certain niche and are considered an important factor in health or disease. (B) Bacterial translocation in spontaneous bacterial peritonitis. From the intestinal lumen, in a state of dysbiosis, bacteria (gram-negative bacilli of enteric origin and to a lesser extent gram-positive) cross the intestinal barrier and infect the mesenteric lymph nodes, a process known as bacterial translocation, and from there they reach the blood circulation through of the lymphatic pathway leading to the hepatosplenic and systemic circulation. Which leads to the development of an inflammatory reaction in the mesenteric lymph nodes themselves with the release of pro-inflammatory cytokines. TRL-4 is responsible for the production of TNF-α in response to endotoxin, while Th1 cells release interferon γ.

demonstrated that the presence of MDRO and quinolone-resistant Gram-negative bacteria (QR-GNB) has been associated with the failure of antimicrobial prophylaxis [64].

There is great concern worldwide about the increase in antimicrobial resistance, which has now been associated with SBP. Appropriate antimicrobial therapy should be administered as soon as possible, as inappropriate administration increases hospital mortality. Unfortunately, it has been reported that treatment protocols still support the use of third-generation cephalosporins as a first line of therapy [65–67]. In a meta-analysis carried out by Iogna *et al.*, showed that there is significant uncertainty about the choice of antimicrobial therapy that is best in people with SBP. It is important to highlight that the short-term mortality from spontaneous bacterial peritonitis (SBP) is high, approximately 25% [68]. Therefore, having the result of the culture, and an antimicrobial regimen with a narrower spectrum should be started. Based on these findings, it is essential to perform a microbiological surveillance for the use of the correct use of antimicrobials.

3. Clinical manifestations of spontaneous bacterial peritonitis and diagnostic

Patients with liver cirrhosis (LC) and ascites are at a high risk of developing bacterial infections, spontaneous bacterial peritonitis [SBP] can be a life-threatening infection in these patients [69]. The diagnosis of SBP is based on the patient's signs and symptoms, in addition to the findings at diagnostic paracentesis in a patient with ascites fluid. The patient with peritonitis may have symptoms such as abdominal pain, nausea, vomiting, diarrhea and signs of a systemic inflammatory response (hyper or hypothermia, chills, altered white blood cell count, tachycardia, and/or

tachypnea), also presenting with worsening of liver function, hepatic encephalopathy, shock, kidney failure and gastrointestinal bleeding. However, it is important to note that SBP can be asymptomatic particularly in outpatients [70].

Diagnostic paracentesis should be performed in all patients who present symptoms is extremely important, as the PMN count in the ascitic fluid plays an essential role in obtaining a diagnosis of SBP [71]. However, clinical signs and symptoms are occasionally absent in patients with SBP [72]. The diagnosis of SBP is confirmed based on a PMN count of >250 cells/mm3 in the ascitic fluid cell analysis (**Figure 3**). The cutoff value of 250 PMN cells/mm3 has the greatest sensitivity, whereas 500 PMN cells/mm3 exhibits the greatest specificity [73].

The gold standard for ascitic neutrophil count is manual microscopy, but it is labor intensive and associated with interobserver variability, time and costs. In most places this has been substituted with automated counts based on flow cytometry for counting and differentiating cells. This technique has been documented to have high linearity with manual microscopy and thus sensitivity and specificity close to 100% [74].

3.1 Clinical manifestations of spontaneous bacterial peritonitis.

For Spontaneous bacterial peritonitis (SBP) the diagnosis is established based on positive ascitic fluid bacterial cultures and the detection of an elevated absolute fluid polymorphonuclear neutrophil (PMN) count in the ascites (>250/mm^3) without an evident intra-abdominal surgically treatable source of infection (**Figure 3**). In addition, ascitic fluid cultures are negative in approximately 10–60% of patients with clinical manifestations of SBP [75].

The Secondary Bacterial Peritonitis, that differs of Spontaneous bacterial peritonitis (SBP) consists of ascitic fluid infection due to intraabdominal infections, for example, perforation of gastrointestinal tract or abscess. It is much less frequent, but has still high mortality rate compared with SBP in patients with LC [76].

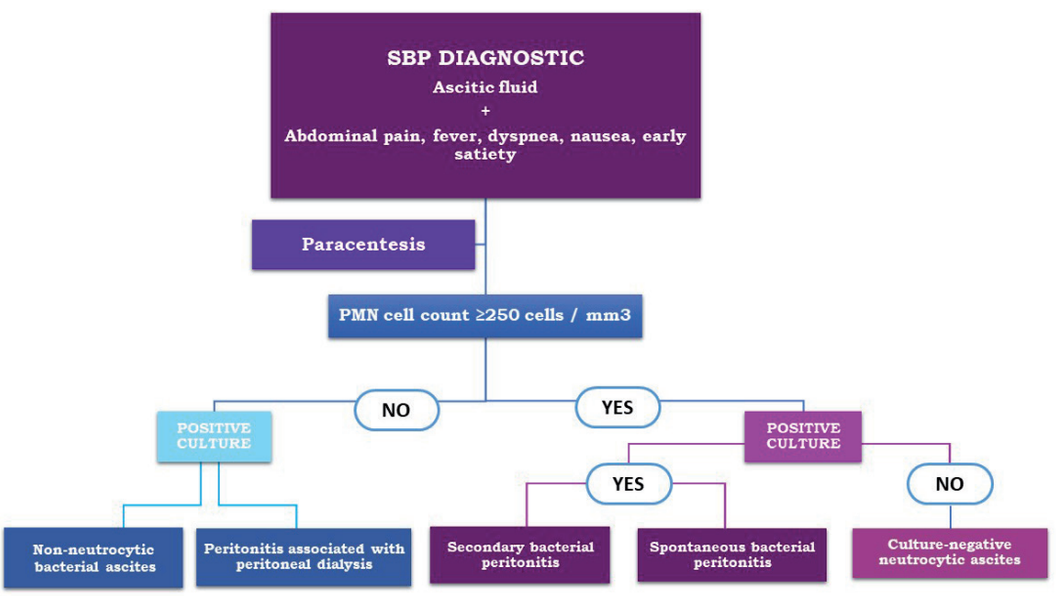

Figure 3.
*Recommended empirical antibiotic treatment for SBP. Community-acquired agents are treated with 3rd generation Cephalosporins, Amoxicilin/Clavulanic acid, Ciprofloxacin, Ofloxacin or Piperacilin/Tazobactam. Health care associated and nosocomial agents are treated with Piperacilin/Tazobactam or a Carbapenem antibiotic. For profilaxis of SPB, Norfloxacin is the agent of choice. (Figure adapted from [66]). *In case of multidrug resistant organism.*

Non-neutrocytic bacterial ascites or Bacterascites: is an ascitic fluid polymorphonuclear -neutrophil (PMN) count below 250/μL and a positive ascitic fluid culture results in the absence of an evident intra-abdominal, surgically treatable source of infection. It is a different clinical entity than spontaneous bacterial peritonitis (SBP), which is characterized by a neutrophil reaction in ascites regardless of the bacterial culture result. Bacterascites is prevalent in 8–11% of all patients with cirrhosis and ascites, and the clinical significance seems to vary according to how the infection was acquired [77].

3.2 Treatment of spontaneous bacterial peritonitis

Even though the spectrum of this chapter does not contemplate treatment modalities we thought it best to give an updated brief view of the treatment involved in SBP in an easy diagram (**Figure 4**). First step is to acknowledge and apply the indication of a paracentesis, which are the following according to multiple clinical practice guidelines: All patients with new onset grade 2 or 3 of ascites, in those hospitalized for worsening of ascites or any complication of cirrhosis. Other indications are new onset of ascites, any patient admitted to the hospital with preexisting ascites, regardless of the reason for admission and ascites who has signs of clinical deterioration [78]. Once the diagnosis of SBP is made the treatment modalities must be applied as soon as possible (**Figure 4**). These empiric treatment schemes should also be administered if the patient has a diagnosis of culture-negative neutrocyte ascites and monomicrobial non-neutrocytic bacterial ascites or bacterial ascites. Particularly the treatment decision differs from the community acquired SBP from the nosocomial one, considering the risk factors, other comorbidities treatment and the previous use of antibiotic (3 months at least) to prescribe the specific drug, because the microbiome involucrate in each case requires a different antibiotic. For example, the use of 3rd. generation cephalosporines in community acquired SBP, not such as the treatment suggested in the nosocomial acquired SPB that the carbapenem is indicated as first therapeutic option.

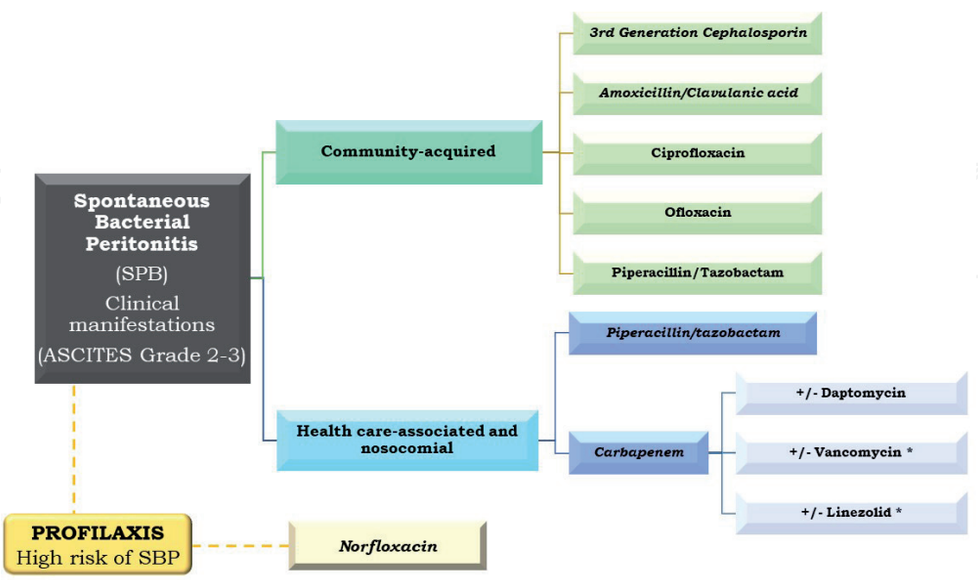

Figure 4.
Diagnostic algorithm of SBP. The diagnosis of SBP is established based on positive ascitic fluid bacterial cultures and the detection of an elevated absolute fluid polymorphonuclear neutrophil (PMN) count in the ascites (>250/mm^3) without an evident intra-abdominal surgically treatable source of infection, except in peritonitis associated with peritoneal dialysis, where bacteria can enter the body through the open ends of the PD catheter during exchanges.

The efficacy of antibiotic therapy should ideally be revised doing a second paracentesis at 48 hours from the starting treatment. One should suspect either resistance to antibiotics, secondary bacterial peritonitis or fungal peritonitis if the patient exhibits worsening clinical signs and symptoms or does not have a marked reduction in the leucocyte count of at least 25% [78, 79]. In addition to the antibiotics administered it is vital to administer albumin 1.5 g/kg body weight at diagnosis followed by 1 g/kg on day three. This in order to significantly decrease the incidence of type 1 Hepatorenal syndrome and mortality in up to 30% of the cases [78].

Another important topic is the prophylaxis of SBP in high risk patients which in which in summary are three: (1) Patients with acute gastrointestinal hemorrhage; (2) Patients with less than 15 g/L of ascitic fluid protein; (3) Patients with previous history of SBP. For the prophylaxis of SBP in high risk patients the recommended prophylaxis schemes are with norfloxacin [79]. Healthcare providers must be very conscious when they are considering the use of prophylactic antibiotics balancing the risks of generating gastrointestinal complications secondary to gut dysbiosis *vs* the benefits of preventing an event of SBP. As healthcare workers one must avoid the abuse of antibiotic use, it is important to know and apply these indications, and imperative to be clear in which antibiotic can be used in these specific cases, and avoid the use of broad spectrum antibiotics.

4. Conclusions

In cirrhotic patients, the intestinal barrier dysfunction increased permeability, and extensive inflammation occurs due to Spontaneous Bacterial Peritonitis. Clinically, the SBP is a frequent and severe complication in cirrhotic patients with ascites. It is well documented that bacterial endotoxin and harmful pathogenic bacterial species translocate to the liver through portal vein further exacerbate the already prevalent hepatic inflammation and fibrosis driven by hepatocytes destruction and loss of biochemical functionality, thereby these phenomena promote liver injury followed by multiorgan failure and eventually death in a high percentage of cirrhotic patients.

In this analysis were described that microbiota plays an essential role in this pathological process, but it is also related to gut permeability loss due to previous treatments or the inflammation sustained signalling by hepatic lesion immunological response.

Clinically, a flux for diagnostic and treatment was proposed for SBP, that includes de analysis of ascitic fluid and polymorphonuclear cells as consequence.

It is suggested that there is a lot of task to do in public health, in order to control the self-medication and the excess of antibiotic therapy, in order to avoid microbiota dysbiosis and SBP.

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Conflict of interest

The authors declare no conflict of interest.

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