

## Spontaneous Bacterial Peritonitis: Is It Still A Life-Threatening Issue in Cirrhosis?

Tarsila Campanha da Rocha Ribeiro, Juliano Machado de Oliveira, Fábio Heleno de Lima Pace, Juliana Ferreira de Souza, Pedro Duarte Gaburri, Liliana Andrade Chebli, Kátia Valéria Bastos Dias Barbosa, Antônio Carlos Santana Castro, Júlio Maria Fonseca Chebli

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Correspondence to: Julio Maria Fonseca Chebli, MD, PhD, Professor, Division of Gastroenterology, Inflammatory Bowel Disease Center, University Hospital of the Federal, Rua Maria Jose Leal, 296 – Bairro Granville, Minas Gerais 36036-247, Brazil.

Email: [chebli@globocom](mailto:chebli@globocom)

Telephone: +55-32 3232-4915

Fax: +55-32 3216-7122

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### ABSTRACT

Spontaneous bacterial peritonitis is the commonest and a deadly complication of cirrhosis that happens in 10% to 30% of patients admitted to hospital. The main mechanism that is being associated with its occurrence are bacterial overgrowth with translocation through the increased permeable small intestinal wall and impaired immune defense. The Gram-negative aerobic bacteria are the major pathogens responsible for SBP episodes although Gram-positive bacteria are being considered emergent agents. The ready diagnosis of SBP is a key factor for the decrease in mortality rates observed in recent years. The medical diagnosis is neither sensitive nor specific and the search for new useful and available tools to make it quicker is an important endpoint of current studies. The use of empirical antibiotics, mainly cefotaxime, improves significantly the short-term prognosis of patients with SBP. The recurrence rate is high and antibiotic prophylaxis has been recommended in high-risk scenarios. Unfortunately, the long-term prognosis remains poor.

**Key words:** Cirrhosis; Ascites; Diagnosis; Spontaneous Bacterial Peritonitis; Treatment

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### INTRODUCTION

The most common complication in cirrhosis is ascites that occurs in approximately 60% of patients with compensated cirrhosis in a ten year period of diagnosis<sup>[1]</sup>. The development of ascites is a landmark in the natural history of cirrhosis, since the mortality is 40% in one year and 50% in two years<sup>[2]</sup>. Moreover, it carries a poor prognosis and impairs quality of life recommending patient evaluation by a Liver Transplantation team as soon as possible<sup>[3]</sup>. Bacterial infections, such as spontaneous bacterial peritonitis (SBP), are worrisome in cirrhotic patients since it is known that 30% to 50% of them either have bacterial infection when admitted to a hospital or acquire them during this period with a mortality rate of near 25% in this population. SBP is one of the most common infection in cirrhotic patients.

SBP has been considered a life-threatening infection that requires a prompt diagnosis and treatment. In-hospital mortality for the first SBP episode varies from 10% to 50%<sup>[4]</sup>. The recurrence rate is also high and one-year mortality rate after the first episode of SBP has been estimated to be between 31% and 93%<sup>[5,6]</sup>. The worse scenario in the prognosis of a cirrhotic patient after an episode of infection has been proposed since that a new prognostic stage of cirrhosis, not reflected by the existing staging systems, should be defined, as the so-called “critically ill cirrhotic”<sup>[7,8]</sup>.

Cirrhotic patients have a higher risk of developing bacterial infections, sepsis, severe sepsis and therefore death. Alterations in microbiota and intestinal permeability, functional impairment of the reticuloendothelial system, neutrophilic dysfunction, impairment in opsonization of ascitic fluid and immune dysfunction are findings that make these patients susceptible to the emergence of infectious

complications. Cirrhosis-associated immune dysfunction syndrome (CAIDS) is a multifactorial state of systemic immune dysfunction, which decreases the capacity of clearing cytokines, bacteria and endotoxins from circulation which associated with portosystemic shunts allow fewer bacteria and endotoxins to be cleared by the liver from circulation. The development of bacterial infection exacerbates pre-existing circulatory dysfunction, predisposes early onset of renal dysfunction, expressed by hepatorenal syndrome, and triggers an overstressed pro-inflammatory response which can lead to organ failure (acute on chronic liver failure)<sup>[7-9]</sup>.

In the past few years the epidemiology of bacterial infection in cirrhotic patients has changed dramatically. Initially, SBP occurred in up to 30% of patients with cirrhosis and ascites, and had an estimated in-hospital mortality of 20%<sup>[10]</sup>. The prevalence of SBP in outpatients cirrhotic is estimated in 1.5% to 3.5% and in inpatients is about 10%<sup>[11,12]</sup>. Recent studies have shown that 60% of bacterial infections are community acquired and 40% are nosocomial<sup>[13]</sup>. Furthermore, several studies from different geographical areas, have reported a significant increase in the number of infections caused by multiresistant bacteria [MR]. The SBP prophylaxis with quinolones and other types of antibiotics, invasive procedures during hospitalization and the stay of cirrhotic patients in healthcare facilities are associated with a change in bacterial flora in these patients. More recent studies highlight the increasing emergence of gram positive cepas as quinolone-resistant organisms.

## PATHOPHYSIOLOGY

The clinical context of cirrhosis gives the patient several factors that make them more susceptible to infections, particularly SBP. These factors are markedly influenced by certain clinical conditions of cirrhosis. The presence of ascites itself confers a risk of SBP of about 10% per year<sup>[14-16]</sup>. The likelihood that it comes to occur increases by six to ten times if the protein concentration of the ascitic fluid is less than 1g/dL, as this suggests an indirect clue of reduced concentration of C3<sup>[17]</sup>. The progression of cirrhosis with the loss of liver function increases the risk of SBP and over 70% of the cases occur in patients in stage C of Child-Pugh score<sup>[5]</sup>. A bilirubin level of more than 3.2 mg/dL and platelet count lower than 98.000/ mm<sup>3</sup> are considered independently risk factors for SBP and each point in the model for end-stage liver disease (MELD) increases the risk of SBP by about 11%<sup>[16]</sup>. Gastrointestinal bleeding in patients with advanced liver disease and ascites is associated with the onset of bacteremia and /or SBP in 50% of hemorrhagic episodes<sup>[18]</sup>. Such clinical conditions keep close relationship with factors linked to the pathogenesis of SBP: bacterial translocation, increased permeability of the intestinal mucosa and local (peritoneal) and systemic immunologic defectiveness.

Bacterial translocation (BT) of enterobacteria is the main source of infectious agent to ascites fluid. Only few intestinal bacteria are able to translocate into mesenteric lymph nodes (MLN), including *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae. Interestingly, these species are the commonest agents responsible for SBP, and DNA sequencing studies reveal genotypic identity of bacteria in MLN and ascites in most of the cases. Three factors have been implicated in the development of pathological BT in cirrhosis: (1) derangement in gut microbiota; (2) increased intestinal permeability; and (3) impaired immunity.

The probability of BT'S occurrence is worsened by the trend of small bowel bacterial overgrowth (SIBO) in these patients<sup>[19]</sup>. Changes on bowel function associated with cirrhosis help bacterial small bowel proliferation. Altered small intestinal motility leads to slower

bowel transit time contributing to bacterial overgrowth<sup>[20]</sup>. Changes in peristalsis can be explained by the predominance of sympathetic stimuli and nitric oxide overproduction<sup>[21,22]</sup>. A recent meta-analysis found evidence that beta blockers increase gut motility and reduce bacterial translocation, thereby reducing the incidence of infection<sup>[23]</sup>. Conversely, Mandorfer *et al* addressed the effect of nonselective beta blockers use on patients with cirrhosis and ascites. It was demonstrated that once SBP has developed patients receiving beta blockers had a 58 % increase in mortality risk compared with patients who did not receive beta blockers<sup>[24]</sup>. Currently, the use of non selective beta blockers is been widely studied and two large studies found that they could not only be safe in patients with ascites and do not increase mortality as they could also reduce mortality in those that develop acute on chronic liver failure<sup>[25,26]</sup>.

Some studies had demonstrated that proton pump inhibitors [PPI] cannot only favor intestinal overgrowth but also affect cellular activity increasing the risk of developing bacterial infections. Garcia-Martinez *et al*<sup>[27]</sup> described in a recent paper that PPIs significantly reduce the oxidative burst activity of granulocytes and monocytes in patients with decompensated cirrhosis, which is a key mechanism of the immune system bactericidal activity. This affects the physiologic control of gastrointestinal bacterial population. Moreover, the indiscriminating use of inhibitors of gastric acid secretion is an independent risk factor to infections in patients with liver cirrhosis and increases the rate of spontaneous bacterial peritonitis among cirrhotic patients receiving pharmacologic acid suppression<sup>[28]</sup>. On the other hand, a recently published multicenter study evaluated seven hundred seventy patients with a diagnosis of decompensated cirrhosis and did not find an association between the use of proton pump inhibitors and a higher risk of SBP<sup>[29]</sup>. Khan *et al*<sup>[30]</sup> carried out a recent systematic review and meta-analysis concluded that although the studies show a statistically significant relationship between the use of PPI and SBP, it is quantitatively small. Nevertheless, these drugs should be reserved for use in well-defined therapeutic indications and for a limited period of time.

SIBO and BT are topics of major concern in the discussion of SBP and general infection on patients with liver cirrhosis. New studies in this field not only would help understanding the pathogenesis but would also allow new recommendations for this group of patients.

Rifaximin is an antibiotic with broad-spectrum activity against gram-positive and gram-negative microorganisms within the gastrointestinal tract usually used for hepatic encephalopathy prevention. Its main advantage is being nonabsorbable with few side effects. The use of rifaximin in SBP prophylaxis has been studied with controversial results. Kalambokis *et al*<sup>[31]</sup> first described in cohort of 16 cirrhotic patients with no previous episode of SBP that rifaximin can reduce SIBO and BT decreasing the incidence of SBP. These results were corroborated by a retrospective study conducted by Hanouneh *et al*<sup>[32]</sup> in 404 cirrhotic patients in which rifaximin was used for hepatic encephalopathy and avoided the occurrence of SBP. However, two others recently published studies could not confirm these results. Lutz *et al*<sup>[33]</sup> studied 152 cirrhotic hospitalized patients that underwent a diagnostic paracentesis. Patients treated with rifaximin for hepatic encephalopathy prophylaxis have not had a reduction in the incidence of SBP, however, the etiology of it had changed with *Klebsiella* species being found in 75% of patients under rifaximin treatment and no enterococci or *Escherichia coli* had being observed. A multicenter prospective study evaluated the use of long-term antibiotics, including rifaximin, and proton pump inhibitor in predicting the development of infection in cirrhotic patients. Although the use of rifaximin reaches statistical significance in univariate analysis in increasing subsequent

infections, this was not observed in multivariate analysis. These studies confirmed the controversial issue of rifaximin use and its association in increasing the risk of SBP<sup>[34]</sup>. Further prospective studies are needed to recommend rifaximin as a prophylactic agent against SBP.

Another issue involved in bacterial translocation is the change in the intestinal barrier. One of the factors that lead to loss of the intestinal barrier function is the structural damage of the intestinal wall with increasing permeability of bacteria into systemic circulation, especially in advanced stages of liver disease that is already associated with altered bacterial flora<sup>[35,36]</sup>. Portal hypertension induces enteropathy with intestinal wall thickening, capillary dilatation, edema of the lamina propria and reduction of villus/crypt ratio that can influence bacterial translocation<sup>[37]</sup>. These factors alone may not be enough for the occurrence of the passage of the bacteria through the intestinal wall. However, such changes associated with variations of intestinal microbiota and the immune system provides higher risk of bacterial translocation in cirrhotic patient.

In order to reach the systemic circulation from the intestinal lumen, the bacteria must overcome two immunological barriers besides those of the mucosa. The first one is the intestinal immune system, which comprises Peyer's patches, lymphocytes of the lamina propria, intraepithelial lymphocytes, and mesenteric lymph nodes. The second barrier is composed by the reticuloendothelial system [RES], responsible for phagocytosis of bacteria that reach the bloodstream. In the liver, the RES is represented by the Kupffer cells. Even after defeating these barriers, bacteria need to find fertile territory without adequate immune defense system.

Patient with cirrhosis, especially on advanced stages, may fail at all stages of immune control. The activity of intraepithelial lymphocytes and their proliferative capacity is decreased in cirrhotic rats<sup>[37]</sup>. The control played by the mesenteric lymph nodes is compromised, probably by the overload of bacterial exposure. Phagocytosis capacity of Kupffer cells is reduced and portosystemic shunts deviate bacteria from hepatic RES<sup>[38]</sup>. As a consequence of bacterial translocation, several cytokines and nitric oxide are produced. This leads to inflammatory damage of the liver and to the gut mucosa, thus perpetuating the bacterial translocation cycle<sup>[39]</sup>. From the systemic circulation, bacteria tends to proliferate in tissues or fluids more susceptible in an immunological point of view. The housing of bacteria in the peritoneum of patients with liver cirrhosis is facilitated because of the immune fragility. The stimulus for chemotactic attraction of neutrophils from local macrophages is decreased in alcoholic cirrhosis<sup>[40]</sup>. Another remarkable failure on defense against colonization of ascitic fluid is the reduced opsonization of bacteria, especially due to low levels of C3<sup>[41,42]</sup>. Total protein concentration on ascitic fluid also reflects opsonization capacity and is inversely related to the risk of SBP<sup>[43]</sup>.

## DIAGNOSIS

Spontaneous bacterial peritonitis (SBP) is defined as the presence of more than 250 polymorphonuclear cells/mm<sup>3</sup>(PMN) in ascitic fluid with a positive ascitic fluid culture in the absence of an intra-abdominal source of infection or malignancy. The most frequent condition, however, is the finding of an elevated PMN count without a positive ascitic culture that is called culture-negative neutrocytic ascites (CNNA). Individuals with CNNA have comparable clinical presentation and outcomes as patients with SBP and should be treated similarly.

Furthermore, we can find positive culture results without PMN count elevation in the ascitic fluid, an entity known as non-neutrocytic bacterascites that can occur in 2% to 3% of outpatients

and in up to 11% of hospitalized patients. In this case, if the patient has no symptom suggested of SBP, paracentesis should be repeated after 24-48 hours because this situation can represent either a transient and spontaneously reversible phenomenon of a colonization phase of ascitic fluid or the first step in the development of SBP<sup>[12]</sup>. If the patient has any symptom suggestive of SBP, some authors recommend that this patient should be managed as having SBP.

Although previous studies have shown that a positive culture of ascitic fluid could be achieved with bedside culture bottles inoculation in approximately 93%, nowadays near 60% of ascitic fluid samples with a PMN count > 250 cell mm<sup>3</sup> do not show evidence of bacterial growth<sup>[44,45]</sup>. The low positivity of ascitic fluid culture was confirmed in a study conducted by our group which found a positive culture in only 36% of studied population<sup>[46]</sup>. One can speculate that this is the result of the low bacteria population in ascitic fluid associated with the increasingly use of prophylactic antibiotics.

Independently of culture results, antibiotic treatment should be promptly started in every cirrhotic patient with an ascitic PMN count greater than 250 cells/mm<sup>3</sup> as soon as the cultures are obtained due to the high morbidity and mortality risks of SBP.

Frequently, patients with SBP are asymptomatic and even if they present any symptom, most of them are unspecific. Therefore, cirrhotic subjects who have ascites and present any type of decompensation (e.g. abdominal pain, encephalopathy or renal dysfunction) or who have been admitted in a hospital for some reason should be considered at potential risk of SBP. Encephalopathy is the most common feature related to SBP, followed by abdominal pain and fever<sup>[47,48]</sup>. In such cases, patients must undergo diagnostic paracentesis. Conversely, it is important to take into account that in cirrhosis all the classical signs and symptoms of infection do not hold true because it is per se a state of partial systemic inflammatory response syndrome and patients can present without fever, leukocytosis or other infectious signs. Hence, the higher suspicion is very important in these patients.

A wide range of different tests has been investigated to render SBP diagnosis easier and faster, but none has been proved to be better than the traditional polymorphonuclear count in the ascitic fluid. The utility of urinary dipstick (leukocyte esterase detection resulting from activated neutrophils) has been proposed to reach such targets, but as they were originally developed for use in urinary tract infection the cut-off values are different and the number of false negative is high. Nevertheless, none of the recent guidelines recommends the use of these reagent test strips to assess leucocyte esterase activity of activated PMNs for the diagnosis of SBP owing to unacceptable diagnostic accuracy, mostly because of the high value of false negative results<sup>[46,49-52]</sup>. Recently, a new reagent strip test has been calibrated for ascitic fluid with a cut-off of 250 PMN/mm<sup>3</sup>. Validity scores achievable were reported to be 100% sensitivity and 100% negative predictive value. However, this needs to be confirmed in further studies, but it could be an important tool for a bedside diagnosis of SBP if the results are confirmed<sup>[53]</sup>.

Analyses of lactoferrin or serum procalcitonin is another measure that can be useful for the diagnosis of ascitic inflammatory activity, but initial results need reproduction in studies with greater number of subjects. Neutrophil gelatinase associated lipocalin (NGAL) is a protein involved in iron metabolism that links to bacterial DNA in ascitic fluid. The use of NGAL to differentiate bacterial peritonitis from non-bacterial peritonitis has been studied and the results reported a high diagnostic accuracy, mostly if lactate dehydrogenase (LDH) is added to NGAL<sup>[54,55]</sup>. However, the use of these markers need to be confirmed and are not yet widely available.

Some biochemical parameters are especially useful on differential diagnosis. The presence of elevated levels of LDH and total protein level associated with low glucose level on ascitic fluid should raise the hypothesis of secondary bacterial peritonitis. The latter usually occurs on the clinical setting of acute abdomen caused by a surgically treatable intra-abdominal source with higher frequency of abdominal pain and clinical decompensation. The diagnosis of secondary peritonitis lay on the presence of 2 out of three of the following criteria: LDH greater than the upper limit of normal for serum, glucose less than 50 mg/dL and protein greater than 1g/dL. The occurrence of multiple organisms on Gram's stain and a polymicrobial culture increase the possibility of its diagnosis<sup>[15]</sup>.

Besides ascitic fluid analyses, blood parameters also assist in patient evaluation. Blood count and culture may be useful in confirming the presence of infection and in the identification of the causative agent. Renal function assessment is compulsory due to the great risk of decompensation and the need of immediate therapeutic intervention.

## TREATMENT

The development of new antibiotics and the possibility of an earlier diagnosis of SBP have dramatically changed the natural history of resolution from 25% before 1980 to 70% - 90% in the last few years<sup>[15]</sup>. Although the in-hospital mortality is low and predicted by the presence of renal impairment and a higher MELD score, in-hospital non-infection-related mortality can be as high as 20% to 40%<sup>[56-58]</sup>. The one and two-year mortality rates are approximately 70% and 80% percent, respectively<sup>[59]</sup>. Hence, the occurrence of SBP is still a life-threatening event in cirrhotic patients and liver transplantation should be seriously considered.

Relatively broad-spectrum therapy is warranted in patients with suspected ascitic fluid infection until the results of susceptibility tests are available and it can be narrowed after the results of culture become known. Delaying treatment until the ascitic fluid culture grows bacteria may result in death from overwhelming infection. Nowadays, it seems very important to take into account not only the type and severity of infection, but also the site of acquisition of it, since the strain of bacteria causing SBP may depend mainly on it<sup>[8,60-62]</sup>.

In patients with no previous hospitalization and no prior antibiotic treatment, the causative bacteria still usually belongs to the easily treatable Enterobacteriaceae family. Several antibiotics have been recommended for the initial treatment of SBP. Felisart and colleagues demonstrated the first evidence of cefotaxime efficiency for SBP. The comparison of cefotaxime with the association of ampicillin and tobramycin showed a higher rate of infection resolution with neither nephrotoxicity nor inferiority in those treated with cefotaxime<sup>[63]</sup>. Since that, cefotaxime has been considered the standard of care for treatment of SBP<sup>[14,64]</sup>. However, one study compared two different doses of cefotaxime in 143 patients with SBP, using 2 g every 6 h and 2 g every 12 h. The rate of infection resolution was the same in both groups (77% versus 79%)<sup>[65]</sup>. The interval between doses could be less frequent, mainly in patients with renal function impairment. A similar third generation cephalosporin, as ceftriaxone 2 g intravenous daily, is considered a reasonable choice for suspected SBP, in empiric therapy, while the result of ascitic fluid culture is not known<sup>[60,66]</sup>. These antibiotics used can cover 95% of the flora including the 3 most common isolates: *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcal pneumoniae*. The efficacy of the treatment was demonstrated to be similar if the antibiotics are used for 5 or 10 days<sup>[57]</sup>.

Other antibiotics have been studied and are an alternative for SBP treatment, but caution should be taken in avoiding those that have nephrotoxicity and increased risk of multiresistant bacteria development. The use of amoxicillin/clavulanate seemed to be secure and an efficient alternative<sup>[67]</sup>. Ofloxacin (400 mg bid for an average of eight days) has been demonstrated to be as effective as intravenous cefotaxime in treatment of patients with SBP without vomiting, shock, grade II (or higher) hepatic encephalopathy or serum creatinine greater than 3 mg/dL. The only drawback of this treatment is the recent observation of quinolone-resistant organism emergence<sup>[58]</sup>.

The widespread use of quinolones to SBP's prophylaxis in high-risk subgroups of patients as well as frequent hospitalizations with invasive procedures associated with the exposure to broad-spectrum antibiotics have led to a change in intestinal flora with more gram-positives and the occurrence of extended-spectrum b-lactamase producing Enterobacteriaceae in recent years<sup>[68-70]</sup>. Some risk factors have been identified as important factors for the emergence of multiresistant infections as nosocomial origin of infection, long-term norfloxacin prophylaxis, recent infection with multiresistant bacteria, and recent use of beta-lactam antibiotics. Infections with these resistant organisms are associated with a higher mortality rate<sup>[8,62,68,70]</sup>. Moreover, none of the international guidelines to date differentiate between nosocomial and community-acquired SBP with regard to the type of antibiotic regimen to be used and new guidelines are urgently needed.

In the setting of nosocomial SBP the recommended antibiotics have recently been proved to achieve not only disappointing but also unacceptable low rates of resolution with third-generation cephalosporins and quinolones reaching levels of resistance of 23% to 44% and 38% to 55%, respectively. Another important issue is the increasing incidence of extended-spectrum b-lactamase (ESBL)-producing bacteria as well as multiresistant Gram-positive bacteria (*Enterococcus faecium*) or methicillin-resistant *Staphylococcus aureus* (MRSA) in this setting. ESBLs cause resistance to various types of newer b-lactam antibiotics (third-generation cephalosporins, monobactams, quinolones, e.g.)<sup>[45,69,70]</sup>. In-hospital mortality and/or 30-day mortality have been shown to be increased in nosocomial SBP caused by multiresistant bacteria compared with common bacteria<sup>[71,72]</sup>. It is recommended that, in patients with cirrhosis who develop nosocomial SBP and present with risk factors for multiresistant bacteria, a more effective first-line empirical antibiotic therapy with a broader spectrum should be used, such as carbapenems<sup>[61,73,74]</sup>. Nevertheless, this regimen should be narrowed as soon as possible if microbiological results reveal non-resistant easily treatable causative microorganisms.

One of the most important predictor of death in SBP is renal function impairment that occurs in almost 30% to 40% of patients. The use of plasma volume expansion, such as albumin, decreases the risk of death from 30% to 10%<sup>[75-77]</sup>. The use of albumin is based on the theory that plasma volume expansion could attenuate the hemodynamic changes observed in those patients<sup>[78]</sup>. Albumin is the main circulating antioxidant system in the human body and nowadays it is known that cirrhotic patients have not only a decrease in the synthesis of albumin by the liver but also some degree of impairment in its function. Therefore, serum albumin in cirrhosis is not only reduced but also dysfunctional. Nevertheless, there are some evidences of the beneficial effect of albumin administration and it seems that it is mostly due to its non-oncotic properties<sup>[79]</sup>. In the setting of SBP, albumin, but not other plasma expanders such as hydroxyethyl starch (HES), succeeds in hemodynamic



improvement<sup>[80]</sup>. The first study that has evaluated the value of albumin infusion in SBP used a dosage of 1.5 g/kg of body weight within 6 hours of diagnosis, followed by 1 g/kg of body weight on day three and demonstrated a reduction in the incidence of renal failure and in-hospital and 3 months' mortality<sup>[81]</sup>. A recent meta-analysis of randomized trials considerably confirmed these points: albumin infusion prevents renal impairment and reduces mortality among patients with SBP<sup>[82]</sup>. Sigal and colleagues have demonstrated in one study that albumin should be given when the serum creatinine is > 1 mg/dL, blood urea nitrogen > 30 mg/dL, or total bilirubin > 4 mg/dL but it is not necessary in patients who do not meet these criteria<sup>[83]</sup>.

A follow-up ascitic fluid is recommended to document sterility of culture and dramatic decrease in PMN count if the setting, symptoms, ascitic fluid analysis, organism(s), or response to treatment are atypical. Lack of resolution of the infection raises the possibility of secondary peritonitis and should prompt further evaluation and surgical intervention when appropriate. Current guideline recommends changing treatment if PMN count has not decreased at least 25% from pretreatment level after 2 days of treatment<sup>[14,64]</sup>.

## PROPHYLAXIS

The recurrence rate after one year of the first episode of SBP has been demonstrated in 40% to 70% of patients with survival rates of 30% to 50% after 1 year and 25% to 30% at 2 years<sup>[62,84]</sup>. Therefore, the efficacy and role of prophylactic antibiotics is undeniable. Different situations, however, should be set apart.

First, are those patients who had already had a previous episode of SBP. In this group of patients, the recommendation of antibiotic prophylaxis is indisputable. For secondary prophylaxis the strongest evidence is for norfloxacin<sup>[85]</sup>. The mortality rates could be significantly reduced to 20% in patients submitted to the use of oral norfloxacin (400 mg/day) and the approach advised by the AASLD Guideline, recently published, seems to be cost effective<sup>[14]</sup>. Other choices had been studied such as the use of trimethoprim/sulfamethoxazole or ciprofloxacin that also appears to be cost-effective<sup>[86]</sup>. Some guidelines recommend the use of trimethoprim/sulfamethoxazole or oral ciprofloxacin as an alternative. However, there are some drawbacks for this strategy. In the first case, we have to take into account that the data of the use of trimethoprim/sulfamethoxazole are weak and it is even no longer recommended as the first line of treatment in urinary tract infection due to the higher risk of resistance. In the latter alternative use of intermittent ciprofloxacin has been associated with higher rate of quinolone-resistant organism, a fact that can be potentially dangerous<sup>[87]</sup>. Therefore, the use of weekly quinolones could not achieve this efficacy and the emergence of resistant pathogens seems to be an actual problem.

The second situation is called primary prophylaxis, and is indicated when the patient had never had an episode of SBP but has risk factor for it. The risk of developing SBP in this group of patients is 13% to 45% in one-year period and the recommendation of primary prophylaxis is not as well defined as the two other cases. The increase in Gram-positive resistance organisms in those who use prolonged antibiotic prophylaxis has been considered a problem to recommend it and some authors disagree with this strategy, limiting the antibiotic employment to in-hospital period<sup>[88]</sup>. Factors that have been associated with increased SBP incidence are: low protein ascitic fluid (< 1.5 g/dL), impaired renal function (Cr > 1.2 mg/dL; BUN > 25 mg/dL or serum Na < 130 meq/L) or liver failure (Child score > 9

and bilirubin > 3)<sup>[64,84,85]</sup>. In this highly selected 'high-risk' group of patients with cirrhosis, norfloxacin reduced the 1-year probability of SBP from 61% to 7% ( $p < 0.001$ ) and improved the 1-year survival probability from 48% to 60% ( $p < 0.05$ )<sup>[88]</sup>. Nonetheless, guidelines state very cautiously that the long-term use of norfloxacin can be justified or should be considered in these selected patients.

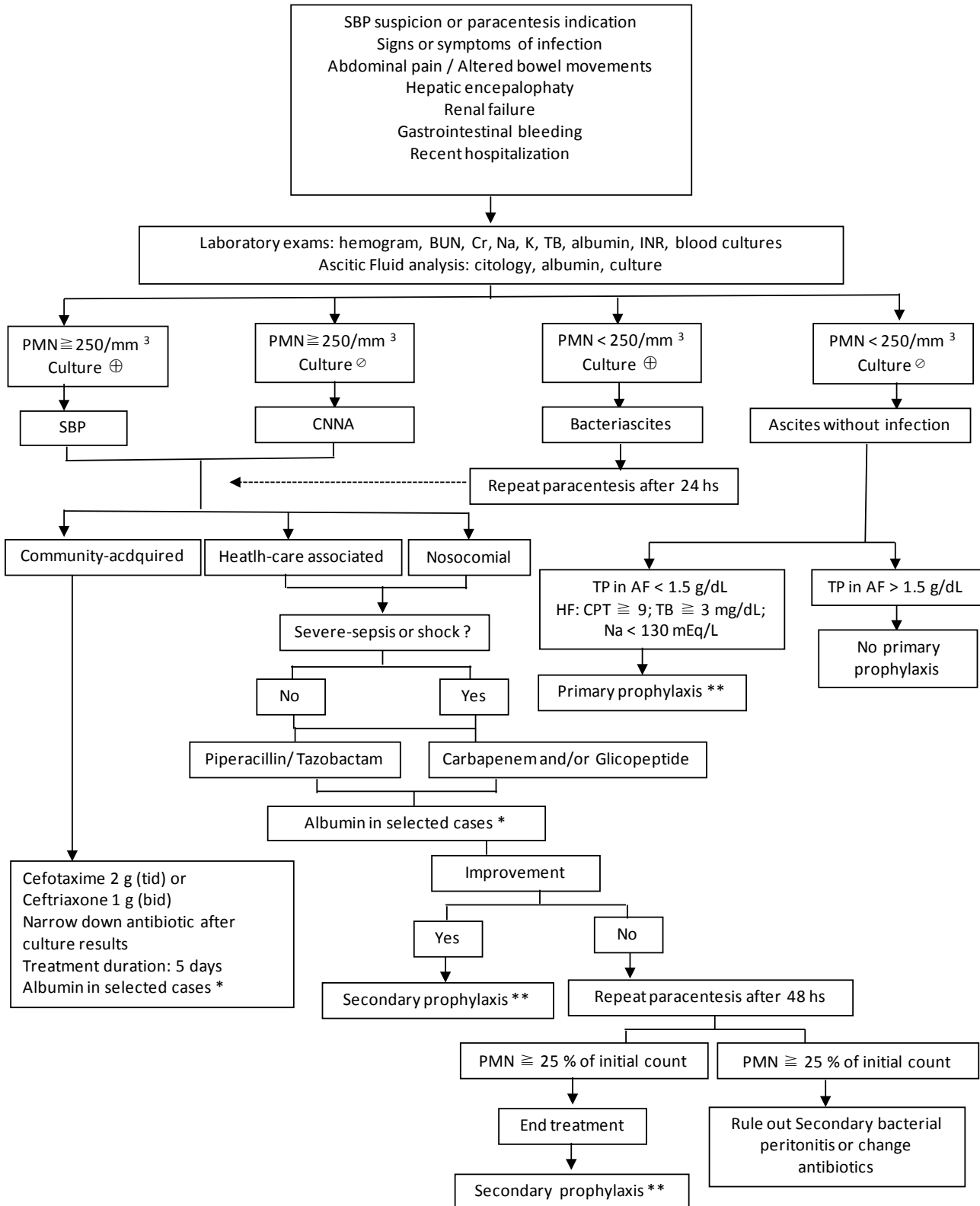
The third setting is the role of SBP prophylaxis in patients with acute gastrointestinal bleeding that is renownd. A meta-analysis evaluated the use of antibiotic prophylaxis for patients with gastrointestinal hemorrhage and reports a significant reduction in the incidence of infections (32%) and an improvement in short-term survival (9%) was also demonstrated<sup>[89]</sup>. The decrease in the rate of variceal rebleeding could be observed in another study<sup>[90]</sup>. Although quinolones are frequently used in this scenario, in patients demanding invasive procedures, infections are increasingly caused by Gram-positive bacteria and an intravenous route could be more appropriate. Ceftriaxone intravenously 1 g/d for 7 days has been shown to be superior to oral norfloxacin, mostly in patients with advanced cirrhosis<sup>[69]</sup>. A French group demonstrated a reduction in hospitalization mortality for patients with variceal hemorrhage from 43% 20 years ago to 15% recently; much of the reduced mortality was attributed to use of antibiotics to prevent infections<sup>[91]</sup>. The increased emergence of multiresistant pathogens, mostly quinolone-resistant bacteria, has demanded the search for alternative ways of SBP prophylaxis. Other antibiotics such as amoxicillin-clavulanate and trimethoprim/sulfamethoxazole are proved to be efficient<sup>[92]</sup>. In addition, the use of cisapride and propranolol were evaluated in order to increase the intestinal motility and consequently decrease the bacterial translocation<sup>[93]</sup>. The studies in animal models reveal the efficacy of such drugs, but their use in humans needs to be demonstrated. Ultimately, the rational use of proton pump inhibitors is also an important issue because these drugs have also been associated with an increased rate of SBP<sup>[94-97]</sup>.

Actually, the importance of this life-threatening condition is being widely studied and the early diagnosis associated with better treatments with drugs that have less nephrotoxicity have dramatically changed the current scenario of SBP. The widespread use of broad-spectrum antibiotics needs to be stopped and further studies on alternatives forms of SBP prophylaxis are expected for the optimal management of such hazardous cirrhosis complication.

The figure 1 tries to propose an algorithm about the evaluation and management of patients with SBP suspicion.

## CONCLUSION

SBP is the commonest and life-threatening infection in patients with end-stage liver disease requiring prompt recognition and treatment. Traditionally, it is defined by the presence of >250 polymorphonuclear/mm<sup>3</sup> in ascites in the absence of an intra-abdominal source of infection or malignancy. Diagnostic paracentesis should be performed on all patients with ascites at hospital admission because the classical signs of SBP are often absent and in any patient with cirrhosis and renal dysfunction or hepatic encephalopathy. Better and faster diagnostic tools are necessary for the prompt diagnosis of SBP. Timely treatment is both crucial and different depending on the clinical setting. Patients with community-acquired infections must receive recommended first-line antibiotics (i.e. cefotaxime or ceftriaxone) while those with nosocomial infections will require broader spectrum antibiotics (e.g. carbapenems). Patients with SBP must be stratified in low risk and high risk based on renal function and jaundice. Intravenous albumin may reduce the mortality on high-



SBP: spontaneous bacterial peritonitis; CNNA: culture negative neutrocytic ascites; TB: total bilirubin; BUN: urea nitrogen; Cr: creatinin; Na: sodium; K: potassium; INR: international normalization rate; PMN: polymorphonuclear; AF: ascitic fluid; HF: hepatic failure; TP: total protein; CPT: Child-Pugh-Turcotte classification

\* Albumin: selected case: TB > 4 mg/dL; Cr > 1 mg/dL; BUN > 30 mg/dL. Dose: First day: 1.5 mg/kg/day; Third day: 1 g/kg/day

\*\* Primary and Secondary prophylaxis: Norfloxacin 400 mg/day

Figure 1 Proposed Algorithm for Ascitic Fluid Management.

risk patients. Prophylaxis is of critical relevance for trying to improve prognosis. Thus, identification of risk factors and particularization of timing and selection of prophylactic measures are the key to success while attenuating the bacterial resistance to multiple antibiotics.

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- Peer reviewer:** Chun Gao, MD, Department of Gastroenterology, China-Japan Friendship Hospital, Ministry of Health, No.2 Yinghua East Road, Beijing 100029, PR China.