

# Spontaneous bacterial peritonitis in patients with cirrhosis: incidence, outcomes, and treatment strategies

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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:** bacterial infections, acute-on-chronic liver failure, drug resistance, antibiotic prophylaxis, acute kidney injury

## Introduction

Bacterial infections constitute a major complication of cirrhosis.<sup>1</sup> They account for 25%–46% of hospitalizations due to acute decompensation events in patients with cirrhosis and are associated with high morbidity and mortality.<sup>2</sup> Bacterial infections increase fourfold the probability of death of patients with decompensated cirrhosis, reaching a 30% mortality rate after the first month and 63% after the first year of follow-up.<sup>2</sup>

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.<sup>5,6</sup> 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.<sup>1,6,7</sup> 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.<sup>5</sup> 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


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index of suspicion is usually necessary for early diagnosis and treatment, which is associated with better outcomes.<sup>3</sup>

### Clinical aspects and bacteriology

The occurrence of spontaneous bacterial peritonitis varies according to the studied population. It is estimated that the incidence reaches 3.5% at 1 year in outpatients with decompensated cirrhosis and varies between 7% and 30% in hospitalized patients with cirrhosis and ascites.<sup>4,6-8</sup> In a recent multicenter intercontinental study, Piano et al reported a prevalence of spontaneous bacterial peritonitis of 27% over 1,302 inpatients with cirrhosis and bacterial infections.<sup>5</sup>

Spontaneous bacterial peritonitis is associated with poor prognosis.<sup>9-13</sup> Survival after the first episode is estimated to be 40% at 1 year.<sup>14</sup> Acute kidney injury occurs in as much as 54% of the patients, and acute-on-chronic liver failure occurs in 35%–60% of the patients, despite appropriate treatment.<sup>15-18</sup> In Table 1, the incidence of death and acute kidney injury in patients with spontaneous bacterial peritonitis is detailed.

Additionally, spontaneous bacterial peritonitis recurrence can be as high as 70% if no prophylaxis is implemented.<sup>7,19</sup> For this reason, as will be discussed later, universal secondary antibiotic prophylaxis is recommended, since it reduces the probability of recurrence to 20% and improves survival.<sup>20,21</sup>

Historically, gram-negative bacteria were the main causative agents of spontaneous bacterial peritonitis, with *Escherichia coli* and *Klebsiella* spp. being the most frequently isolated organisms.<sup>22-25</sup> However, major changes in the bacteriology of infections in patients with cirrhosis occurred over the last few decades with an increasing prevalence of gram-positive, quinolone-resistant, and multidrug-resistant bacteria.<sup>1,22,26</sup> A rising prevalence of gram-positive bacteria was reported over the past years in North America, South America, and Europe representing at present 48%–62% of the isolated organisms.<sup>4,27,28,54</sup> The most frequent gram-positive isolates are *Streptococcus* spp., *Enterococcus* spp., and *Staphylococcus* spp.<sup>4,27</sup> The main isolated microorganisms in patients with spontaneous bacterial peritonitis are shown in Table 2.

There has also been a shift in the prevalence of quinolone-resistant bacteria: as much as 70% of isolated bacteria in patients with spontaneous bacterial peritonitis are quinolone-resistant according to recent studies.<sup>26,29,30</sup> This is particularly worrisome, since norfloxacin remains the antibiotic of choice for spontaneous bacterial peritonitis prophylaxis.

Regarding multidrug-resistant organisms, these are found predominantly in nosocomial spontaneous bacterial peritonitis, being reported in 20%–35% of the episodes.<sup>22</sup> However, 4%–16% of community-acquired spontaneous

**Table 1** Summary of studies reporting incidence of death and acute kidney injury in patients with spontaneous bacterial peritonitis

Source	Design	Outcomes	Findings
Follo et al (1994) <sup>17</sup>	Retrospective cohort study	Acute kidney injury and death	Incidence of in-hospital acute kidney injury and death: 33% and 24%, respectively
Sort et al (1999) <sup>90</sup>	Clinical trial	Acute kidney injury and death	Three-month incidence of acute kidney injury and death: 10% for both outcomes (in patients treated with antibiotics plus albumin)
Marciano et al (2018) <sup>15</sup>	Retrospective cohort study	Acute kidney injury and death	Three-month incidence of acute kidney injury and death: 54% and 38%, respectively
Oliveira et al (2016) <sup>7</sup>	Retrospective cohort study	Hepatorenal syndrome and death	Thirty-day incidence of hepatorenal syndrome and death: 30% and 41%, respectively
Tandon and Garcia-Tsao (2011) <sup>18</sup>	Systematic review	Death	In-hospital/30-day incidence of death: 29%
Poca et al (2015) <sup>9,94</sup>	Retrospective cohort study	Death	In-hospital incidence of death: 28% (included only patients with high-risk spontaneous bacterial peritonitis)
Tandon et al (2013) <sup>10</sup>	Retrospective cohort study	Death	One-month incidence of death: 27%
Tsung et al (2013) <sup>11</sup>	Retrospective cohort study	Death	Six-month incidence of death: 44%
Bal et al (2016) <sup>12</sup>	Retrospective cohort study	Death	Fifty-day incidence of death: 43%
Cheong et al (2009) <sup>13</sup>	Retrospective cohort study	Death	Thirty-day incidence of death: 49%

**Notes:** Acute kidney injury definition and treatment of patients with spontaneous bacterial peritonitis differs among studies.

**Table 2** Isolated bacteria from ascitic fluid in patients with spontaneous bacterial peritonitis

Microorganism	Prevalence (%)
<b>Gram-negative bacteria</b>	48–59
<i>Escherichia coli</i>	25–33
<i>Klebsiella</i> spp.	8–13
<i>Pseudomonas aeruginosa</i>	1–10
Other gram-negative bacilli	3–6
<b>Gram-positive bacteria</b>	48–62
<i>Enterococcus</i> spp.	9–24
<i>Staphylococcus coagulase negative</i>	27
<i>Streptococcus viridans</i>	10–15
<i>Staphylococcus</i> spp.	13–19
<i>Streptococcus pneumoniae</i>	3
<i>Staphylococcus aureus</i>	5–13
<b>Multidrug-resistant bacteria</b>	27–34

Note: Data from references 8–10,19,48,66,67,75.

bacterial peritonitis are also caused by multidrug-resistant organisms.<sup>4,6,22,31–33</sup> In the aforementioned multicenter intercontinental study conducted by the International Club of Ascites, the reported prevalence of multidrug-resistant organisms in patients with cirrhosis and bacterial infections reached 35%.<sup>5</sup> Several independent risk factors were reported, such as infections occurring in Asia or South America, the use of antibiotics in the 3 months prior to the infection, and nosocomial- or healthcare-associated infections.<sup>5</sup> Extended-spectrum beta-lactamase-producing gram-negative bacteria, such as *Enterobacteriaceae*, were the most common multidrug-resistant organisms (34%) followed by carbapenem-resistant *Enterobacteriaceae* (27%).<sup>5</sup> Surprisingly, in this study and in a recent study by Moreau et al, the use of norfloxacin was not associated with higher prevalence of multidrug-resistant bacteria, which is in contrast to prior studies that did report an association.<sup>5,34</sup>

Possible explanations for the previously mentioned changes in the bacteriology of spontaneous bacterial peritonitis include the extensive use of quinolones for prophylaxis, the increasing use of invasive procedures, the rising prescription of broad-spectrum antibiotics, and the broadening criteria for admission in intensive care units, among others.<sup>5,28,35</sup> With the advent of these microbiological variations, it is essential to perform a local bacteriological surveillance to adjust prophylactic and therapeutic antibiotic use.<sup>36</sup>

## Spontaneous fungal peritonitis

Patients with cirrhosis are, also, at an increased risk of fungal infections.<sup>6,37</sup> Spontaneous fungal peritonitis is defined as a fungal infection of ascitic fluid with no apparent intraabdominal source of infection or malignancy. In a recent retrospective study, Hwang et al analyzed the clinical characteristics

and the prognosis of 416 patients with spontaneous peritonitis, 3.6% of whom presented spontaneous fungal peritonitis.<sup>38</sup> In these patients, the most frequent isolate was *Candida albicans*, followed by *Candida glabrata*, *Candida krusei*, *Cryptococcus* spp., and *Aspergillus* spp.<sup>6,39</sup> Early differentiation of spontaneous fungal peritonitis is usually difficult due to the late rescue of fungi in ascitic fluid cultures, the lack of suspicion and clinical signs, which leads to a delay in the specific antifungal treatment and higher mortality of these patients.<sup>39</sup> Even though prognosis in patients with spontaneous fungal peritonitis has not been reported in depth, fungal infections in patients with cirrhosis are known to be associated with dismal prognosis.<sup>37,40</sup>

## Pathophysiology

The interaction between changes in intestinal microbiota, altered intestinal permeability, bacterial translocation, and systemic immune dysfunction represent the fundamental pillars for the development of spontaneous bacterial peritonitis.<sup>41</sup> These series of events facilitate bacterial translocation from intestinal lumen to mesenteric lymph nodes, and subsequently to portal and systemic circulation, from where eventually ascitic fluid will be colonized and, under proper conditions, infection will develop.

## Role of gut microbiota, intestinal bacterial overgrowth, and bacterial translocation

Alterations in the gut microbiome can occur as quantitative (intestinal bacterial overgrowth) or qualitative (dysbiosis) changes.<sup>42</sup> The pathophysiology of dysbiosis in patients with cirrhosis is not fully understood. It has been proposed that changes in bile acid composition secreted into the gut might favor pathogenic bacterial growth.<sup>43</sup> In patients with cirrhosis and portal hypertension, intestinal mucosa's microcirculation is altered in part by a reduction in mucosal blood flow, which promotes intestinal bacterial overgrowth and alters its integrity, ultimately favoring bacterial translocation.<sup>22,43,44</sup> Additionally, intestinal dysmotility characterizes patients with cirrhosis, which contributes to the pathogenesis of spontaneous bacteremia and spontaneous bacterial peritonitis.<sup>45,46</sup> Even though translocation is possible for all bacterial and fungal species, *E. coli*, *Klebsiella* spp., and *Streptococcus* spp. are the most frequently implicated pathogens.

## Role of immune dysfunction

Immune dysfunction in patients with cirrhosis constitutes a complex state of immunosuppression in parallel with a persistent proinflammatory state.<sup>47</sup> On one hand, cirrhosis leads to a reduced number of circulating immune cells

as well as a decreased hepatic synthesis of immune molecules, such as the complement system;<sup>48,49</sup> on the other hand, there is an excessive synthesis of proinflammatory cytokines, which are in part mediated by the continuous and subclinical translocation of bacteria and antigens.<sup>50</sup> When this dynamic balance between pro- and anti-inflammatory states favors the latter, patients are particularly prone to bacterial infections.<sup>41</sup>

## Risk factors for spontaneous bacterial peritonitis

There are several known risk factors for spontaneous bacterial peritonitis in patients with cirrhosis and ascites, including upper gastrointestinal bleeding, low ascitic protein concentration (<1.5 g/dL), and a history of prior episodes of spontaneous bacterial peritonitis. The current recommendations of antibiotic prophylaxis are shown in Table 3.<sup>3,20,53,58,59</sup>

Upper gastrointestinal bleeding increases the risk of spontaneous bacterial peritonitis and other infections during or after the bleeding episode, occurring in up to 50% of the patients.<sup>3</sup> Additionally, spontaneous bacterial peritonitis might trigger acute variceal bleeding in as much as 20% of the patients.<sup>51–53</sup> The relationship between gastrointestinal bleeding and bacterial infections in patients with cirrhosis has been well established, although not well understood.<sup>54</sup> The fact that use of prophylactic antibiotics during gastrointestinal bleeding decreases the rate of bacterial infections, the risk of early rebleeding, and increases survival favors this hypothesis.<sup>52,55</sup> Therefore, short-term primary antibiotic prophylaxis is considered a standard practice in all patients with cirrhosis and upper gastrointestinal bleeding.<sup>56</sup> Prophylaxis should be initiated as soon as possible and continued for up to 7 days. Intravenous ceftriaxone at a dose of 1 g per day is the preferred antibiotic prophylaxis in patients with advanced cirrhosis, mainly in regions with high prevalence of quinolone-resistant bacterial infections and in patients already receiving prophylaxis

with quinolones.<sup>53,57</sup> Alternatively, oral quinolones like norfloxacin administered at a dose of 400 mg twice a day for 7 days can be used in patients who were not hospitalized at the time of the gastrointestinal bleeding, who have early stage liver disease, and in areas with low prevalence of infections caused by quinolone resistant bacteria.<sup>3,58</sup> However, individual patient risk characteristics and local antimicrobial susceptibility patterns at each center should be considered when determining appropriate antimicrobial prophylaxis.<sup>3,52,53</sup>

Another recognized risk factor for spontaneous bacterial peritonitis is the presence of low ascitic protein concentration (<1.5 g/dL) when combined with any of the following characteristics: Child-Pugh score ≥9, serum bilirubin level ≥3 mg/dL, impaired renal function (creatinine ≥1.2 mg/dL or blood urea nitrogen level ≥25 mg/dL), or hyponatremia (≤130 mEq/L).<sup>59–63</sup> In these patients, norfloxacin 400 mg per day is recommended as primary prophylaxis and should be indicated lifelong or until liver transplantation.<sup>3</sup> However, some experts suggest that prophylaxis interruption might be considered if patients present sustained clinical improvement and resolution of ascites.<sup>62</sup> In patient with a low ascitic protein concentration without other risk factors, the incidence of spontaneous bacterial peritonitis is relatively low, and therefore, antibiotic prophylaxis is not recommended.<sup>1</sup>

The 1-year cumulative incidence of spontaneous bacterial peritonitis recurrence after the first episode is as high as 70% if no prophylaxis is indicated.<sup>64</sup> It was Ginés et al who demonstrated in a randomized, double-blind, placebo-controlled trial that the use of norfloxacin at a dose of 400 mg per day was associated with a reduction of the risk of spontaneous bacterial peritonitis recurrence to 20%.<sup>20</sup> For this reason, current guidelines recommend secondary prophylaxis with norfloxacin at a dose of 400 mg per day in all patients who survived an episode of spontaneous bacterial peritonitis.<sup>3</sup> Although the duration of prophylaxis is not well established,

**Table 3** Antibiotic prophylaxis of spontaneous bacterial peritonitis

Indication	Antibiotic and dose	Duration
Patients with at least one previous episode of spontaneous bacterial peritonitis	Norfloxacin 400 mg per day	Until death or liver transplant
Patients with high risk of spontaneous bacterial peritonitis <sup>a</sup>	Norfloxacin 400 mg per day	Until death or liver transplant <sup>b</sup>
Patients with upper gastrointestinal bleeding	Ceftriaxone 1 g per day or norfloxacin 400 mg twice a day <sup>c</sup>	For 7 days

**Notes:** <sup>a</sup>Patients with cirrhosis and low ascitic protein concentration (<1.5 g/dL) and at least one among the following: Child-Pugh score ≥9, serum bilirubin level ≥3 mg/dL, impaired renal function and hyponatremia (≤130 mEq/L). <sup>b</sup>Some experts suggest that prophylaxis interruption might be considered if patients present sustained clinical improvement and resolution of ascites. <sup>c</sup>Norfloxacin can be used in patients who were not hospitalized at the time of the gastrointestinal bleeding, who have early stage liver disease, and in areas with low prevalence of infections caused by quinolone resistant bacteria. Data from references 3, 20, 53, 58, and 59.

it is recommended that it be maintained until death or liver transplantation.<sup>3</sup>

Despite the advantages of antibiotic prophylaxis in patients with cirrhosis, its use might be associated with the development of bacterial resistance.<sup>20,57,59,65</sup> For this reason, it would be of great value to identify patients at higher risk of recurrence to avoid prophylaxis overuse. In a cohort study published by Titó et al, spontaneous bacterial peritonitis recurrence was higher in patients with Child-Pugh score  $\geq 9$ , Model of End-Stage Liver Disease (MELD) score  $>20$ , serum bilirubin level  $>4$  mg/dL, and prothrombin time  $\leq 45\%$ .<sup>21</sup> More recently, Huang et al also reported serum albumin levels as an important risk factor for spontaneous bacterial peritonitis recurrence.<sup>66</sup> However, the evidence is still insufficient to stratify patients with high or low risk of spontaneous bacterial peritonitis recurrence, and therefore, universal secondary prophylaxis is still recommended.<sup>3</sup>

Other studies evaluated the efficacy of rifaximin for spontaneous bacterial peritonitis prophylaxis. Rifaximin is an attractive alternative to norfloxacin since it has the potential advantage of preventing bacterial overgrowth and translocation without the possible side effects of systemic antibiotics.<sup>67</sup> A systematic review and meta-analysis by Goel et al showed that rifaximin might be effective for secondary spontaneous bacterial peritonitis prophylaxis compared to systemically absorbed antibiotics and compared to no intervention.<sup>68</sup> However, at present the evidence is considered insufficient, and therefore, current guidelines do not recommend the use of rifaximin for spontaneous bacterial peritonitis prophylaxis.<sup>3</sup>

Other less characterized risk factors for spontaneous bacterial peritonitis are: age, endoscopic management of esophageal varices, and the use proton pump inhibitors.<sup>6,33,69</sup> The role of proton pump inhibitors as a risk factor for spontaneous bacterial peritonitis is controversial. It has been proposed that the increase in gastric pH might impair the natural host defense against ingested bacteria, and thus predisposes to modifications of the intestinal flora.<sup>70,71</sup> Some studies demonstrated that long-term use of proton pump inhibitors might increase the risk of spontaneous bacterial peritonitis by facilitating intestinal bacterial translocation.<sup>6,74,75</sup> In multivariate analysis, the use of proton pump inhibitors was associated with the development of spontaneous bacterial peritonitis and increased mortality in several studies.<sup>70,76,77</sup> However, a large multicenter prospective study demonstrated that proton pump inhibitors were not associated with a higher risk of spontaneous bacterial peritonitis.<sup>78</sup> Therefore, it is not possible at present to establish a recommendation regarding the use of proton pump

inhibitors in patients with decompensated cirrhosis, so that its use should be restricted to those with a clear indication.<sup>3</sup>

## Diagnosis of spontaneous bacterial peritonitis

Patients with spontaneous bacterial peritonitis might present with or without symptoms. Fever, abdominal pain, ileus, diarrhea, acute variceal bleeding, and development or worsening of encephalopathy or ascites might occur at presentation or during follow-up.<sup>3,22,70,71</sup> Alternatively, suspicion of spontaneous bacterial peritonitis might arise from abnormalities in the laboratory, such as acute kidney injury, leukocytosis, and hyperbilirubinemia among others.<sup>1,4,6</sup> It should be noted that a relative increase in white blood cell count could be an indirect sign of spontaneous bacterial peritonitis, since patients with hypersplenism might not develop leukocytosis even under severe inflammatory conditions.<sup>3,70,71</sup> A high index of suspicion in all patients with ascites that are evaluated at the emergency department, general wards, and intensive care units is the key for early diagnosis. A diagnostic paracentesis should be performed without delay, ideally within 6 hours of patient's admission or deterioration, and before starting antibiotics.<sup>3</sup>

One-half of the episodes of spontaneous bacterial peritonitis are present at the time of hospital admission, whereas the rest are acquired during hospitalization.<sup>1,64</sup> Diagnosis is based on paracentesis with a polymorphonuclear leukocyte count  $\geq 250/\text{mm}^3$  in ascitic fluid, with or without positive ascitic culture, in the absence of other cause of peritonitis.<sup>4,22</sup> Ascitic fluid cultures are positive in 35%–65% of spontaneous bacterial peritonitis episodes, with isolation of a single microorganism.<sup>6</sup>

Bacterascites, which is defined as positive ascitic culture with polymorphonuclear count  $<250/\text{mm}^3$ , represents a transient and potentially reversible ascitic fluid colonization.<sup>3</sup> Since a significant proportion of patients with bacterascites will spontaneously resolve the infection, if patients are asymptomatic treatment is not mandatory.<sup>3,70,71</sup> This group of patients might undergo a follow-up paracentesis after 48 hours, and if the polymorphonuclear leukocyte count remains at  $\leq 250/\text{mm}^3$  and the culture is negative, the episode is considered resolved. Alternatively, if the polymorphonuclear count is  $\geq 250/\text{mm}^3$  and/or ascitic culture is persistently positive, antibiotic treatment should be started.<sup>3</sup>

A small proportion of patients with cirrhosis might develop secondary bacterial peritonitis, which is crucial to differentiate from spontaneous bacterial peritonitis. Secondary peritonitis should be suspected in patients who have localized abdominal signs or symptoms, multiple organisms

on ascitic culture, high ascitic neutrophil count, or elevated ascitic protein concentration.<sup>3,22</sup> Additionally, it should be suspected in patients diagnosed with spontaneous bacterial peritonitis who present an inadequate treatment response. These patients require a different approach, including a rapid consultation with a surgical team.<sup>70,71,79</sup>

## Treatment of spontaneous bacterial peritonitis

The management of spontaneous bacterial peritonitis is based on three aspects. Firstly, a rapid diagnosis is crucial to start empiric antibiotic treatment taking into account the local bacteriology. Secondly, stratification of patients is key to identifying candidates that should receive intravenous albumin aimed to reduce the risk of acute kidney injury and death. Finally, as was discussed in the previous section, once resolution of the infection occurs, lifelong prophylaxis is mandatory.<sup>3</sup> All patients with spontaneous bacterial peritonitis should be evaluated for liver transplantation, unless an obvious major contraindication is present.<sup>3</sup>

## Empirical treatment

Empirical antibiotic treatment must be initiated immediately after the diagnosis of spontaneous bacterial peritonitis is made to reduce the development of complications and improve survival.<sup>64,80,81</sup> The choice of empirical antibiotic treatment should take into account the patient’s history of bacterial infections, including prior bacterial isolates and type of antibiotic used, the location where it is assumed that the infection was acquired (ambulatory, healthcare-associated or nosocomial), the severity of the infection, and the expected local bacterial resistance profile.<sup>22,82</sup>

Historically, third generation cephalosporins were the first-line treatment option of spontaneous bacterial peritonitis because of their superiority in randomized controlled trials with minimal nephrotoxicity when compared to other

antibiotics.<sup>83</sup> However, changes in the bacteriology of spontaneous bacterial peritonitis over the past years challenge this recommendation.<sup>36</sup> It should be noted that a universal recommendation would not fit all regions, and that each country or even single institutions should adapt global recommendations to its bacteriology. The European guidelines on antibiotic treatment of bacterial infections in patients with cirrhosis are shown in Table 4. Adherence to these recommendations was recently shown to be associated with better outcomes in patients with cirrhosis and bacterial infections.<sup>84</sup>

The current approach recommends third-generation cephalosporin (cefotaxime or ceftriaxone) or piperacillin-tazobactam as the first-line strategy for community-acquired spontaneous bacterial peritonitis; the latter is also to be considered for healthcare-associated and nosocomial spontaneous bacterial peritonitis in areas with low prevalence of infections by multidrug-resistant organisms.<sup>3</sup> Meropenem combined with glycopeptides or daptomycin has been suggested as the primary approach for healthcare-associated spontaneous bacterial peritonitis or in severe infections in areas with high prevalence of multidrug-resistant organisms, and for nosocomial spontaneous bacterial peritonitis in general.<sup>3,23</sup>

The increasing use of carbapenems facilitated the emergence of carbapenem-resistant bacteria. This implies a potential shift from multidrug-resistant organisms to extensively drug-resistant bacteria defined by a nonsusceptibility to at least one agent in all antimicrobial categories.<sup>85</sup> Recently, new antibiotics such as ceftolozane-tazobactam and ceftazidime-avibactam were developed and released. These antibiotics are promising for the treatment of carbapenem-resistant species, extended spectrum beta-lactamase producing gram-negative bacteria, multidrug-resistant *Pseudomonas aeruginosa*, and multidrug-resistant *Acinetobacter* spp.<sup>86</sup>

The results of a recent prospective cohort study serve as platform to propose a treatment algorithm according to the severity of infection.<sup>87</sup> Briefly, the authors state that

**Table 4** Summary of recommendations of empirical antibiotic treatment of spontaneous bacterial peritonitis according to the guidelines of the European Association for the Study of the Liver

Type of infection	Empirical antibiotic regimen
Community acquired <sup>a</sup>	Third-generation cephalosporin or piperacillin-tazobactam
Healthcare associated <sup>b</sup>	A) Piperacillin-tazobactam in patients without sepsis and in areas with low prevalence of multidrug resistant bacteria. B) Consider treatment as nosocomial if high prevalence of multidrug resistant bacteria or sepsis.
Nosocomial <sup>c</sup>	Carbapenems alone or with daptomycin, vancomycin, or linezolid if high prevalence of multidrug-resistant bacteria, gram-positive bacteria or sepsis

**Notes:** Data from European Association for the Study of the Liver.<sup>3</sup> <sup>a</sup>Infection diagnosed at the time of admission or in the first 48 hours in patients who do not meet criteria for healthcare-associated infection. <sup>b</sup>Infection diagnosed at the time of admission or in the first 48 hours in patients that in the previous 90 days had contact with the hospital (dialysis, paracentesis, endoscopy, etc) or that they live in a residence. <sup>c</sup>Infection diagnosed in hospitalized patients after 48 hours, or infection diagnosed at admission or in the first 48 hours in patients who have been hospitalized for at least 2 days in the past 90 days.

empirical treatment of infections should consider patient's Quick Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE II) scores, and in those with greater risk, a more aggressive empirical treatment should be indicated.<sup>3,22,87</sup>

If proper antibiotic treatment is implemented, spontaneous bacterial peritonitis resolves in ~90% of patients.<sup>88</sup> In general lines, a 5–7-day treatment course is recommended, which has proven to be as effective as longer treatments.<sup>3,88</sup> The adequate response of spontaneous bacterial peritonitis should be demonstrated by means of a follow-up paracentesis after 48 hours of initiation of empiric antibiotic treatment showing a reduction in neutrophil count of at least 25% and a negative ascitic culture.<sup>3</sup> Additionally, treatment failure should be suspected if the patient's condition deteriorates. Under these circumstances, infection by resistant bacteria or secondary bacterial peritonitis should be suspected and new therapeutic strategies should be considered.<sup>31,64</sup>

Recent treatment guidelines on management of infections in patients with cirrhosis do not include recommendations for the treatment of spontaneous fungal peritonitis. In most case reports and case series, echinocandins are suggested as the first-line treatment for these patients.<sup>37,38</sup>

## Use of albumin in spontaneous bacterial peritonitis

Despite proper and early antibiotic treatment, spontaneous bacterial peritonitis is associated with a high risk of acute kidney injury, hepatorenal syndrome, and death.<sup>89</sup> The study by Sort et al was the first to demonstrate that with the use of intravenous albumin, the risk of both hepatorenal syndrome and death was significantly reduced.<sup>90</sup> The beneficial effect of albumin was observed particularly in patients with basal serum bilirubin  $\geq 4$  mg/dL or  $\geq 68$   $\mu$ mol/L, or serum creatinine  $\geq 1$  mg/dL or  $\geq 88$   $\mu$ mol/L. To date, other plasma expanders have not consistently proved to be as effective as albumin, and therefore, albumin continues to be the standard of care.<sup>91</sup>

## Other recommendations

Diuretics as well as other potentially nephrotoxic drugs should be discontinued in patients with spontaneous bacterial peritonitis.<sup>92</sup>

Mandorfer et al reported that the use of nonselective  $\beta$ -blockers in patients with spontaneous bacterial peritonitis increased the risk for hepatorenal syndrome and acute kidney injury, the time of hospitalization, and reduced transplant-free survival. Thus, in patients with spontaneous bacterial

peritonitis, the use of nonselective  $\beta$ -blockers should be used with caution and most experts favor its discontinuation.<sup>93</sup>

## Conclusion

Spontaneous bacterial peritonitis continues to be one of the main complications in patients with cirrhosis. Early antibiotic treatment and intravascular expansion with albumin are key strategies to improving prognosis in these patients. However, acute kidney injury, acute-on-chronic liver failure, and death are frequent midterm complications that might arise in spite of adequate patient management. Primary and secondary spontaneous bacterial peritonitis prophylaxis have proven to be effective, but should be used with caution to reduce the risk of bacterial resistance development. In fact, it is alarming that quinolone-resistant and multidrug-resistant organisms cause more than one-half and one-third of the infections in patients with cirrhosis, respectively. In daily practice, physicians are challenged to adequately treat and prevent spontaneous bacterial peritonitis, but at the same time, there is a need to avoid antibiotic overuse. The balance between these forces is difficult to find, but a key element to improving antibiotic use is to perform periodic epidemiological and bacteriological surveillance to adapt treatment recommendations.

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## Disclosure

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