

# World Journal of *Hepatology*

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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: A literature review

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### Abstract

Spontaneous bacterial (SBP) and spontaneous fungal peritonitis (SFP) can be a life-threatening infection in patients with liver cirrhosis (LC) and ascites. One of the possible mechanisms of developing SBP is bacterial

translocation. Although the number of polymorphonuclear cells in the culture of ascitic fluid is diagnostic for SBP, secondary bacterial peritonitis is necessary to exclude. The severity of underlying liver dysfunction is predictive of developing SBP; moreover, renal impairment and infections caused by multidrug-resistant (MDR) organism are associated with a fatal prognosis of SBP. SBP is treated by antimicrobials, but initial empirical treatment may not succeed because of the presence of MDR organisms, particularly in nosocomial infections. Antibiotic prophylaxis is recommended for patients with LC at a high risk of developing SBP, gastrointestinal bleeding, or a previous episode of SBP, but the increase in the risk of developing an infection caused by MDR organisms is a serious concern globally. Less is known about SFP in patients with LC, but the severity of underlying liver dysfunction may increase the hospital mortality. SFP mortality has been reported to be higher than that of SBP partially because the difficulty of early differentiation between SFP and SBP induces delayed antifungal therapy for SFP.

**Key words:** Liver cirrhosis; Spontaneous bacterial peritonitis; Spontaneous fungal peritonitis; Bacterial infections

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**Core tip:** Spontaneous bacterial (SBP) and spontaneous fungal peritonitis (SFP) are infectious complications in patients with liver cirrhosis (LC). Renal impairment, severity of underlying liver dysfunction, and infections caused by multidrug-resistant (MDR) organisms are associated with a fatal prognosis in SBP. Antibiotic prophylaxis is recommended for patients with LC and with a high risk of developing SBP, gastrointestinal bleeding, or a previous episode of SBP, but the increase in the risk of infections caused by MDR organisms is of concern. Increased mortality of SFP compared with that of SBP may partially result from delayed diagnosis and

starting of antifungal therapy.

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## INTRODUCTION

Patients with liver cirrhosis (LC) are at a high risk of developing bacterial infections because of hypoactivity of phagocytic cells in the hepatic reticuloendothelial system, decreased production of complement, and bacterial influx into the general circulation through portacaval shunts<sup>[1]</sup>. The most common are spontaneous bacterial peritonitis (SBP), urinary tract infections, respiratory infections (pneumonia), soft tissue infections, and bacteremia<sup>[2]</sup>.

SBP can be a life-threatening LC complication, and the severity of underlying liver dysfunction and renal impairment such as hepatorenal syndrome (HRS), are associated with poor prognosis<sup>[3]</sup>. An increasing prevalence of multidrug-resistant (MDR) bacterial infections has been associated with failure of empirical antibiotic therapy, and the prognosis of SBP caused by MDR bacteria is poor<sup>[4]</sup>. Less is known about spontaneous fungal peritonitis (SFP) in patients with LC<sup>[5,6]</sup>, but the available case reports indicate that the mortality of SFP is worse than that of SBP.

This article reviews the published data on the incidence, diagnosis, causative organisms, treatment, prognosis, and prognostic factors of SBP and SFP in patients with LC.

## BACTERIAL INFECTIONS IN PATIENTS WITH LIVER CIRRHOSIS

### *Possible mechanisms underlying bacterial infections including SBP*

In cirrhosis with portal hypertension, the micro-circulation in the intestinal mucosa is disturbed, resulting in a reduction of mucosal blood flow, intestinal bacterial overgrowth, and impaired mucosal integrity<sup>[7,8]</sup>. Intestinal bacterial overgrowth, impairment in permeability of the intestinal mucosal barrier, and deficiencies in local host immune defenses are estimated to be the major mechanisms to promote bacterial translocation (BT or pathological BT) in LC<sup>[7,9]</sup>. BT may be involved in the onset or aggravation of bacterial infections such as SBP and or HRS in patients with LC<sup>[7,8,10]</sup>. Pijls *et al*<sup>[11]</sup> reported increased large and small intestine permeability in patients with LC, and BT has been reported to be associated with bacterial infections caused by aerobic Gram-negative bacteria in patients with LC and was found to be more frequent

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in experimental LC models with than in those without ascites<sup>[7]</sup>.

Studies of BT and bacterial DNA (bact DNA) translocation are limited in humans<sup>[7]</sup>, but acute-phase proteins such as C-reactive protein (CRP) or procalcitonin have been used as BT biomarker<sup>[7]</sup>, and detection of bact DNA by polymerase chain reaction (PCR) in biologic fluid has been proposed as a useful surrogate biomarker of BT in patients with advanced LC<sup>[7]</sup>. The presence of bact DNA in ascites increases the risk of developing SBP and HRS<sup>[12]</sup> and is an indicator of poor prognosis<sup>[7,13]</sup>. Assay of bact DNA by PCR has low diagnostic accuracy for SBP because of possible contamination and has poor sensitivity<sup>[14]</sup>. *In situ* hybridization of bact DNA in leukocytes recovered from the ascitic fluid in patients with LC has high sensitivity and specificity even in patients with culture-negative SBP<sup>[14,15]</sup>. Proinflammatory cytokines or oxidative stress may be involved in the pathogenesis of BT, and anti-tumor necrosis factor (TNF) has been reported to be an effective treatment in an animal model of LC<sup>[8]</sup>. In addition to the severity of liver dysfunction, the genetic diversity and virulence of causative bacteria also may influence the development of BT<sup>[16]</sup>. Genetic variation of superoxide dismutase 1 may involve the development of SBP<sup>[17]</sup>. Bacterial metabolites that reach the liver through portal system activate toll-like receptors (TLRs)<sup>[18]</sup>, and the genetic polymorphism of TLR and nucleotide-binding oligomerization domain 2 genes may also be involved in the pathogenesis of BT, thus increasing the risk of infection in patients with LC by altering TLR binding to lipopolysaccharides or endotoxins<sup>[13,16]</sup>. Finally, intestinal colonization and translocation of drug-resistant bacteria may induce MDR SBP infections<sup>[19,20]</sup>.

### *Bacterial infections in patients with liver cirrhosis*

It is estimated that 30%-60% of inpatients with LC will develop a bacterial infection<sup>[1,21]</sup>, and that the occurrence of these infections is four to five times higher in patients with LC than that in the general population<sup>[21]</sup>. Bacterial infections can trigger rapid deterioration of liver function and are a common precipitating factor of acute-on-chronic liver failure in cirrhosis patients<sup>[10,16]</sup>.

Mortality and the incidence of LC-related complications are both significantly higher in patients with than without bacterial infections<sup>[22]</sup>.

Karvellas *et al*<sup>[23]</sup> reported that septic shock secondary to SBP has a high mortality rate of approximately 80% in patients with LC, and bloodstream infections occur in 4%-21% of patients with LC, which is 10-fold higher than the rate in noncirrhotic patients<sup>[24]</sup>. The mortality of bloodstream infections in patients with LC ranges from 23% to 58%<sup>[25]</sup>.

The incidence of bacterial infections in patients with LC is significantly correlated with the severity of the underlying liver dysfunction<sup>[10,22,26,27]</sup>. However, a recent study by Dionigi *et al*<sup>[27]</sup> found that patients with LC who become infected had an increased risk of death



independent of the severity of the underlying liver disease, even if they survived the acute infection. In patients with LC, infections caused by MDR bacteria are associated with a higher risk of mortality compared with those infections caused by susceptible bacteria<sup>[28,29]</sup>. An increased risk of MDR infections is a serious concern, is closely related to failure of antimicrobial therapy<sup>[29,30]</sup>, and may induce deterioration of liver function<sup>[29]</sup>. MDR bacteria are resistant to at least three widely used antibiotic families<sup>[22]</sup>. These include the resistant bacteria that produce extended-spectrum  $\beta$ -lactamase (ESBL), such as *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus* (MRSA)<sup>[31,32]</sup>. Recently, extensively drug-resistant (XDR) bacteria such as carbapenemase-producing *Klebsiella pneumoniae* and vancomycin-resistant *Enterococci* have been isolated from patients with LC<sup>[31]</sup>. The development of MDR infections is associated with suboptimal antibiotic use including antibiotic prophylaxis, nosocomial infection, recent infection with an MDR organism, current or recent hospitalization, exposure while receiving health care, and upper gastrointestinal bleeding in LC<sup>[33,34]</sup>. In a large prospective study, MDR bacteria were isolated in 4% of community-acquired infections, 14% of health care-associated infections, and 35% of nosocomial infections<sup>[33]</sup>. In two series of patients with LC evaluated in 2005-2007 and 2011-2012, Fernández *et al*<sup>[33]</sup> reported that MDR bacteria were more common in nosocomial infections and were associated with higher in-hospital mortality than in infections caused by antibiotic-susceptible bacteria. Pouriki *et al*<sup>[20]</sup> reported drug-resistant bacteria in intestinal cultures from 44% of uninfected patients with decompensated LC. Recent reports have found that asymptomatic intestinal colonization with MDR or XDR bacteria was an increased mortality risk in patients with LC in part because of BT of circulation of bacterial components<sup>[20]</sup>.

## SPONTANEOUS BACTERIAL PERITONITIS

### Diagnosis

The development of ascites in patients with LC is a marker of poor prognosis and has been associated with high liver transplantation-free mortality ranging from 15% to 20% in 1 year and 40% to 60% in 5 year from the first onset<sup>[35]</sup>.

SBP is as bacterial infection of the ascitic fluid with no apparent intraabdominal source of infection or malignancy<sup>[23]</sup>. A polymorphonuclear cell (PMN) count of  $\geq 250$  cells/mm<sup>3</sup> in the ascitic fluid, regardless of the isolation of bacteria from the fluid<sup>[36]</sup>, is diagnostic for SBP. PMN cell count is routinely performed by using the manual laboratory counting which is time-consuming and costly<sup>[37]</sup>. Some studies have reported that the manual and the automated counting methods have a good agreement in the determination of PMN in the ascitic fluid, and automated methods have the potential to replace the manual counting method<sup>[37,38]</sup>. Culture-

negative SBP, also known as culture-negative neutrocytic ascites (CNNA), should be treated in the same way as culture-positive SBP<sup>[39]</sup>. Estimates of the mortality of culture-positive SBP and CNNA are conflicting. Some report a lower mortality for CNNA compared with culture-positive SBP<sup>[40]</sup>; others report comparable rates<sup>[41]</sup>. Bacterascites has also been diagnosed in patients with positive microbiological culture of ascites and a PMN count  $< 250$  cells/mm<sup>3</sup><sup>[36,42]</sup>. The incidence of bacterascites in inpatients with LC has been estimated at 3%-4%<sup>[42]</sup>. Most reports on bacterascites were published in the 1980s and early 1990s; very few are recent<sup>[43]</sup>. The diagnosis of SBP is necessary to distinguish from the cases with secondary bacterial peritonitis, partially because surgical treatments should be considered in secondary bacterial peritonitis but never in SBP<sup>[44,45]</sup>. Secondary bacterial peritonitis consists of ascitic fluid infection due to intraabdominal infections, for example, perforation of gastrointestinal tract or abscess<sup>[44,45]</sup>. It is much less frequent but has still high mortality rate compared with SBP in patients with LC<sup>[44,45]</sup>.

### Causative organisms

Ascitic fluid is culture positive in 35%-65% of patients with SBP<sup>[35,46-49]</sup>. The positive ascitic fluid bacterial cultures have been reported to increase by placement of the fluid directly into blood culture flasks at the bedside immediately after collection for a diagnosis of SBP<sup>[46,50]</sup>. BT from the intestinal tract is believed to be involved, as enterobacteria account for a relatively large percentage of the causative bacteria<sup>[8]</sup>. However, some reviews report a recent shift in the bacterial spectrum to include a high prevalence of Gram-positive bacteria (16.6%-68.3%) globally<sup>[32,51,52]</sup>. The change in etiology may have resulted from increases in the use of quinolones for bacterial prophylaxis and instrumentation in patients with LC<sup>[32]</sup>. The most frequently cultured organism in the ascitic fluid of patients with LC and SBP is *Escherichia coli*<sup>[18,30,52-56]</sup>, followed by Gram-negative *Klebsiella* spp., *Streptococcus* spp., *Staphylococcus* spp., and *Enterococci* are frequently isolated Gram-positive bacteria<sup>[30,53-56]</sup>. Kalvandi *et al*<sup>[57]</sup> reported *E. coli*, and Preto-Zamperlini *et al*<sup>[58]</sup> reported *Streptococcus pneumoniae* as the most frequent isolate in the ascitic fluid of children with SBP.

The incidence of recurrent SBP has decreased in parallel with the use of norfloxacin<sup>[59,60]</sup>, but the increased prevalence of MDR bacteria in patients with SBP may be related to the use of long-term antibiotic prophylaxis or invasive procedures such as catheterization and ablation of hepatocellular carcinoma<sup>[61]</sup>. MDR bacteria are found frequently in nosocomial SBP (20%-35%)<sup>[61,62]</sup>, but also occur in community-acquired SBP (4%-16%)<sup>[18]</sup>. Nosocomial SBP is also more likely to be antibiotic resistant. Balaraju *et al*<sup>[63]</sup> reported that up to 48% of the *E. coli* in patients with nosocomial SBP were resistant to third-generation cephalosporins. Li *et al*<sup>[62]</sup> found higher frequencies of ESBL-producing *E. coli* and *Klebsiella* spp. in cases of nosocomial compared with

non-nosocomial SBP.

### Diagnostic markers

The gold standard for a diagnosis of SBP is the PMN count in the ascitic fluid<sup>[36]</sup>, but paracentesis is not always possible. Laboratory markers are useful for early diagnosis of SBP and early prediction of the response to initial treatment because a lack of response is a predictor of SBP mortality<sup>[64-66]</sup>. TNF- $\alpha$  and interleukin-6 are significantly higher in the ascitic fluid of patients with SBP than in those with sterile ascites<sup>[67,68]</sup>, and increases of those proinflammatory cytokines have been associated with renal impairment complicated by SBP and with mortality<sup>[67,69]</sup>. The lactoferrin concentration is also higher in patients with SBP than in those with sterile ascites<sup>[70-72]</sup>, and the lactoferrin level in ascitic fluid has shown high sensitivity and specificity for the diagnosis of SBP<sup>[39]</sup>. The optimal timing of lactoferrin assays is not yet clear, and diagnostic assay kits are not commercially available<sup>[39]</sup>.

Procalcitonin, a prohormone of calcitonin synthesized in the C cells of the thyroid gland<sup>[73,74]</sup>, is an acute-phase reactant protein that has been studied in patients with SBP. Seven studies assayed serum procalcitonin<sup>[69,75-80]</sup>, three assayed procalcitonin in ascitic fluid<sup>[75,76,80]</sup>. Serum procalcitonin was significantly higher in SBP than in sterile ascites in six of the seven<sup>[69,75,76,78-80]</sup>, which supports use of serum procalcitonin as an SBP marker. In a review by Yang *et al*<sup>[81]</sup> of the available data from 339 patients with LC accompanied by SBP, it was concluded that serum procalcitonin was a relatively sensitive and specific marker for the diagnosis of SBP. It has been reported that serum procalcitonin was significantly higher in cirrhotic patients with culture-positive SBP than in those with CNNA<sup>[77,82]</sup>. Two of the three evaluations of procalcitonin in ascitic fluid found no significant differences in procalcitonin levels in patients with SBP and those with sterile ascites<sup>[76,80]</sup>. The usefulness of ascitic fluid procalcitonin to distinguish between SBP and sterile ascites has not been demonstrated.

Calprotectin is a calcium- and zinc-binding protein with antimicrobial and antiproliferative functions. It is almost exclusively expressed in neutrophils, and its level in body fluids is proportional to the influx of neutrophils<sup>[69,83]</sup>. Burri *et al*<sup>[83]</sup> reported that ascitic fluid calprotectin level was correlated with the PMN count and that it reliably predicted a count of  $\geq 250$  cells/mm<sup>3</sup>, which is the standard for a diagnosis of SBP. Subsequent studies found that ascites calprotectin is significantly higher in cirrhotic patients with SBP than in those without SBP<sup>[47,69]</sup>. Lutz *et al*<sup>[47]</sup> have shown that the ratio of calprotectin to total protein in ascitic fluid was a better diagnostic marker of SBP than calprotectin alone and that a high ratio was independently associated with 30-d mortality.

Leukocyte esterase activity, which can be assayed with commercially available reagent strips, may have diagnostic value<sup>[39]</sup>. Castellote *et al*<sup>[84]</sup> reported that the

use of reagent strips is a rapid and inexpensive tool for the diagnosis of ascitic fluid infection and it had a high negative predictive value (99%), indicating that a negative result may be useful as screening to exclude SBP. Oey *et al*<sup>[85]</sup> reviewed 23 studies of leukocyte esterase in patients with SBP published between 2002 and 2015 and concluded that it had poor sensitivity and positive predictive value for the diagnosis of SBP. They found that the sensitivity of the reagent strips for diagnosing SBP was variable, and a negative test result strongly suggested the absence of SBP<sup>[85]</sup>. In another review of 26 studies published from 2002 to 2010, Koulaouzidis<sup>[86]</sup> confirmed the poor sensitivity and poor positive predictive value of leukocyte esterase activity as well as the high 93%-100% negative predictive value. A negative test result may thus indicate a high probability of the absence of SBP<sup>[84-86]</sup>.

There is evidence for the diagnostic value of other markers including monocyte chemotactic protein-1 in serum<sup>[87]</sup> and ascitic fluid<sup>[88,89]</sup>, lipopolysaccharide-binding protein in serum<sup>[90]</sup> and ascitic fluid<sup>[91]</sup>, macrophage inflammatory protein type-1 beta in ascitic fluid<sup>[76]</sup>, interferon- $\gamma$ -induced protein-10 in serum<sup>[92]</sup> and ascitic fluid<sup>[92]</sup>, triggering receptor expressed on myeloid cells-1 in ascitic fluid<sup>[93]</sup>, high-sensitivity CRP in serum<sup>[94]</sup> and ascitic fluid<sup>[55]</sup>, and neutrophil gelatinase-associated lipocalin in ascitic fluid<sup>[95]</sup>. Further study is needed to validate the diagnostic usefulness of these candidate markers.

### Incidence

The incidence of SBP in LC with ascitic fluid has been estimated as 7%-30% in hospital inpatients<sup>[52,56]</sup> compared with 1.5%-3.5%<sup>[56,96,97]</sup> in outpatients with LC. The annual recurrence rate is approximately 70%<sup>[98]</sup>, and the 1-year survival after recovery from the first episode of SBP is 30%-40%<sup>[99]</sup>.

### Prediction of incidence

Factors associated with the incidence of SBP in patients with LC and ascites include age, history of SBP<sup>[100]</sup>, gastrointestinal bleeding<sup>[61,100]</sup>, and endoscopic intervention for varix control<sup>[101]</sup>. Severity of liver dysfunction<sup>[42,54,56,61,102]</sup> including the Child-Pugh score or model for end-stage liver disease (MELD) score has been reported as a predictive factor, but few studies have not found an association of MELD score and the incidence of SBP<sup>[103]</sup> in patients with LC and refractory ascites. The MELD score does not include some clinical variables that are evaluated in the Child-Pugh score<sup>[104,105]</sup>. A PMN count<sup>[42,102]</sup> and a low protein concentration ( $< 1.5$  g/dL) in the ascitic fluid, which may be related to decreased opsonic activity in the ascitic fluid<sup>[26,54,56]</sup>, have also been reported as predictive factors, but the evidence for ascitic fluid protein is not conflicting<sup>[106]</sup>. The severity of liver dysfunction and serum and ascitic albumin levels have also been reported as risk factors for the recurrence of SBP<sup>[39]</sup>.



Long-term use of proton pump inhibitors (PPIs) may increase the risk of SBP<sup>[107-110]</sup> because of facilitation of intestinal BT, but the association is controversial<sup>[26,111,112]</sup>. Multivariate analysis has identified the use of PPIs by patients with LC as an independent risk factor for the development of SBP<sup>[108,109]</sup>, and Kwon *et al*<sup>[107]</sup> reported that PPI use was associated with the development of SBP and increased mortality, but other studies have not found a significant association of PPIs and development of SBP in patients with LC<sup>[112,113]</sup>. A recent meta-analysis by Yu *et al*<sup>[114]</sup> of 10 case-control and six cohort studies involving 8145 patients and published between 2008 and 2014 concluded that it is not possible to establish causality between PPI use and increased risk of SBP. A similar analysis by Khan *et al*<sup>[115]</sup> of six case-control and eight cohort studies concluded that there was a statistically significant association between PPI use and increased incidence of SBP, but that the difference in incidence was small. Kim *et al*<sup>[116]</sup> reported that PPI use was not associated with risk or SBP recurrence. PPI use may be associated with slightly increased risk for SBP<sup>[117]</sup>, but the significance of the association has not been confirmed.

### Mortality

SBP mortality has decreased in the four decades since it was first described as a result of early diagnosis and prompt treatment<sup>[56]</sup> and treatment by liver transplantation<sup>[103]</sup>. Hospital mortality is estimated as 10%-50% for the first episode and 31%-93% for the second or subsequent episodes<sup>[53,118]</sup>. Recent studies have estimated 1-mo mortality at > 20%<sup>[52,102]</sup>, inpatient mortality at > 30%<sup>[61]</sup>, and 1- and 2-year mortality following an SBP episode as 50%-70% and 70%-75%, respectively<sup>[23,39]</sup>. A recent nationwide cohort study in Taiwan reported that SBP mortality was 24.2% at 1 mo and 66.5% at 3 year<sup>[119]</sup>.

### Prediction of mortality

Predictors of mortality in SBP include severe underlying liver disease with a high Child-Pugh<sup>[48,52,64,96,100,102,104,105,120-122]</sup> or MELD score<sup>[47,48,52,104,121-123]</sup>, renal impairment<sup>[16,52,54,64,65,96,100,124,125]</sup> such as HRS, and onset of severe sepsis<sup>[96]</sup>. Some studies did not find differences in the mortality of nosocomial and community-acquired SBP<sup>[63]</sup>; others have reported increased mortality in nosocomial compared with community-acquired SBP, which was correlated with the involvement of drug-resistant bacteria<sup>[4,21,63,65]</sup>. Other predictors of SBP mortality include old age<sup>[16,102]</sup>, gastrointestinal bleeding<sup>[4,52]</sup>, complications of shock<sup>[65]</sup>, rapid deterioration of liver function<sup>[64]</sup>, positive ascitic fluid culture<sup>[16,48]</sup>, elevated blood leukocyte level<sup>[47,104,123]</sup>, low serum sodium<sup>[63,102]</sup>, complications of hepatic encephalopathy<sup>[52,63,122]</sup>, presence of hepatocellular carcinoma<sup>[54]</sup>, and complications of other infections, such as pneumonia<sup>[122]</sup>. Tandon *et al*<sup>[123]</sup> reported that peripheral blood leukocyte count  $\geq 11 \times 10^9$  cells/L and MELD score  $\geq 22$  were independent predictors of 30-d mortality in patients with LC and SBP.

Renal impairment develops in 30%-40% of patients with LC and SBP<sup>[16]</sup> and is a significant prognostic factor in patients with LC and SBP. The available evidence strongly associates renal impairment with SBP mortality<sup>[16,52,54,64,65,96,100,124,125]</sup>, but Lim *et al*<sup>[97]</sup> exceptionally reported that renal impairment, including HRS, was not predictive of mortality possibly because of early and effective treatment of SBP. Tandon *et al*<sup>[121]</sup> reported 67% mortality in patients with SBP and renal failure, but only 11% in patients with SBP and normal renal function. Some clinical studies indicated the use of intravenous albumin in addition to antibiotics for treatment of SBP<sup>[70,126-130]</sup>. Possible mechanisms of albumin use for improvement of SBP include its oncotic properties, immunomodulatory and antioxidant effects, and its endothelium stabilization capacity<sup>[131]</sup>. Dosage and duration of intravenous albumin in previous studies were as follows: (1) 1.5 g/kg body weight at the time of diagnosis and 1 g/kg body weight on day 3<sup>[126-128,130]</sup>; and (2) 20% 50 mL every day for 3 d<sup>[70]</sup>. Moreover, some clinical studies indicated that the use of intravenous albumin and antibiotics can reduce the incidence of renal impairment and mortality in patients with LC and SBP<sup>[126,129,130]</sup>. The efficacy of albumin treatment in patients with LC and other types of bacterial infection remains unknown. Thévenot *et al*<sup>[132]</sup> reported that albumin did not improve renal function or survival at 3 mo in patients with LC and non-SBP bacterial infections.

A meta-analysis of studies published between 2002 and 2011 identified a four-fold increased risk of mortality of patients with LC and SBP caused by MDR bacteria<sup>[133]</sup>, and a retrospective multicenter study in Korea found that SBP caused by ESBL-producing bacteria was an independent prognostic factor of high in-hospital mortality<sup>[54,108]</sup>. Chon *et al*<sup>[4]</sup> reported that both in-hospital mortality and follow-up mortality after recovery from SBP were significantly higher in nosocomial SBP than in community-acquired SBP. Alexopoulou *et al*<sup>[31]</sup> did not find significant differences in the 30-d mortality of infections caused by MDR bacteria and nonresistant bacteria in 60 cases of culture-positive SBP and 70 cases of bacteremia without SBP.

However, 30-d mortality from infections caused by XDR bacteria was significantly higher than that of infections caused by MDR or nonresistant bacteria<sup>[31]</sup>. In another study, an overall 20% 30-d survival of nosocomial SBP was related to inadequate empirical antibiotic treatment<sup>[32]</sup>.

### Antibiotic prophylaxis

Antibiotic prophylaxis is effective, but long-term antibiotic administration leads to the emergence of MDR, which is a serious concern worldwide<sup>[33,134-136]</sup>. The current practice guidelines of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommendations<sup>[26]</sup> limit its recommended use to patients who are at the highest risk of developing a bacterial infection. However, some studies have reported significant decreases

in the incidence of SBP in patients with antibiotic prophylaxis<sup>[18,137]</sup>. Patients with LC and low ascites protein concentrations of  $< 1.5$  g/dL are at risk of developing a first episode of SBP<sup>[26,138]</sup>. Primary antibiotic prophylaxis is recommended in patients with LC and no history of SBP and low ascites protein plus other predisposing factors, such as severe liver failure (Child-Pugh score  $> 9$ ), impaired renal function (serum creatinine  $> 1.2$  g/dL or blood urea nitrogen  $> 25$  mg/dL), or hyponatremia ( $\leq 130$  mEq/L), are present<sup>[23,26,102]</sup>. Primary prophylaxis is also recommended in patients with LC and acute gastrointestinal bleeding<sup>[138]</sup> or to reduce the incidence of SBP after gastrointestinal bleeding<sup>[134]</sup>. Antibiotic prophylaxis has also been associated with reduced rebleeding within 7 d and to lower 28-d mortality<sup>[18,134]</sup>. The standard therapy in patients with LC and acute gastrointestinal bleeding is oral norfloxacin<sup>[18]</sup>, but Fernández *et al*<sup>[139]</sup> reported that intravenous ceftriaxone is more effective than oral norfloxacin. A randomized, controlled trial demonstrated that primary prophylaxis with trimethoprim/sulfamethoxazole also decreased the risk of SBP<sup>[140]</sup>. Recurrence rates as high as 70% have been reported in patients with LC who have recovered from a previous episode of SBP without secondary antibiotic prophylaxis<sup>[61]</sup>. Secondary prophylaxis is indicated for patients with a previous episode of SBP<sup>[26,53]</sup>. Norfloxacin was shown to decrease overall recurrence from 68% to 20%<sup>[26]</sup> and recurrence with a Gram-negative microorganism from 60% to 3% in the first year<sup>[61]</sup>. However, studies published between 2010 and 2016 reported that the frequency of recurrence with bacteria resistant to quinolones was 30%-33%<sup>[52]</sup>. The efficacy and safety of rifaximin for primary prophylaxis for SBP and for prophylaxis of recurrent SBP have been studied<sup>[141-145]</sup>. A study of primary prophylaxis by Assem *et al*<sup>[141]</sup> demonstrated that alternating norfloxacin and rifaximin as combination therapy was remarkably more effective compared with norfloxacin monotherapy in part because of an increased incidence of quinolone-resistant and Gram-positive SBP. Mostafa *et al*<sup>[142]</sup> showed that rifaximin prophylaxis was more effective than norfloxacin in patients with LC and at least one previous episode of SBP. A randomized, controlled trial of secondary prophylaxis by Elfert *et al*<sup>[143]</sup> demonstrated that SBP recurrence and mortality were significantly lower with rifaximin than with norfloxacin.

A systematic review by Goel *et al*<sup>[144]</sup> concluded that rifaximin was as effective for both primary and secondary prophylaxis as other systemically absorbed antibiotic. Rifaximin might be considered, particularly in cases involving quinolone-resistant bacteria<sup>[18]</sup>. The optimal duration of prophylaxis is currently unclear<sup>[26]</sup>, but secondary prophylaxis should be continued until the ascites is resolved or liver transplantation can be performed<sup>[3]</sup>.

### **Empirical antibiotic treatment for spontaneous bacterial peritonitis**

Empirical antibiotic treatment must be initiated immediately after the diagnosis of SBP<sup>[53]</sup>. If the

ascites neutrophil count decreases to  $< 25\%$  of the pretreatment value after 2 d of antibiotic treatment, then there is an increased probability of failure to respond to any treatment<sup>[66]</sup>. Third-generation cephalosporins have been the most frequently used antibiotics in the treatment of SBP since 1985<sup>[4]</sup> and were highly effective until about 10 year ago<sup>[64]</sup>. They are still effective for community-acquired infections in patients with LC, with resolution rates of around 80%<sup>[33]</sup>, but the development of resistance to third-generation cephalosporins is of great concern. Resistance can result in failure to respond to initial empiric therapy with a third-generation cephalosporin in 33%-75% of cases, and failure to respond is associated with reduced survival<sup>[148,49]</sup>. Recent studies indicate that third-generation cephalosporins are not appropriate for the treatment of nosocomial infections in patients with LC<sup>[34]</sup> because of effectiveness as low as 40% related to an increase in the prevalence of MDR bacteria in nosocomial infections<sup>[61,64]</sup>. SBP treatment recommendations distinguish between nosocomial and community-acquired infections<sup>[61]</sup> following evidence from studies like that by Lutz *et al*<sup>[146]</sup> who reported that approximately one third of health care-related and nosocomial SBP infections were resistant to third-generation cephalosporins. They also found that patients with health care-related SBP infections resistant to first-line treatment had worse survival than were those with infections susceptible to first-line treatment<sup>[146]</sup>. Moreover, Ariza *et al*<sup>[147]</sup> reported that resistance to third-generation cephalosporins occurred in 7.1% community-acquired SBP, 21.1% health care-related SBP, and 40.9% nosocomial SBP among 246 episodes in 200 patients with LC and SBP (2001-2009). Some studies recommend that third-generation cephalosporins not be used for empirical treatment of health care-related SBP<sup>[136,146]</sup>; Lutz *et al*<sup>[146]</sup> recommend piperacillin-tazobactam rather than third-generation cephalosporins. The most recent recommendations restrict third-generation cephalosporins to selected patients, primarily those with community-acquired SBP<sup>[21,32]</sup>.

Daptomycin is effective against Gram-positive *Enterococci* resistant to vancomycin and against MRSA. A recent randomized, controlled study reported that empirical treatment of nosocomial SBP with meropenem plus daptomycin was more effective in resolving SBP and had better 3-mo survival than did third-generation ceftazidime<sup>[31,64]</sup>. Piano *et al*<sup>[64]</sup> and European expert opinion<sup>[49]</sup> both recommend a combination regimen of meropenem and daptomycin for the management of nosocomial SBP. A randomized trial by Jindal *et al*<sup>[122]</sup> reported that cefepime, a fourth-generation cephalosporin with good activity against most nosocomial Gram-negative bacteria and Gram-positive cocci, was as effective as imipenem for resolution of SBP. Following evaluation of antibiotic susceptibility in 575 SBP cases, Shi *et al*<sup>[30]</sup> recommended cefoperazone/sulbactam or piperacillin/tazobactam for the empirical treatment of SBP.

## SPONTANEOUS FUNGAL PERITONITIS

Patients with LC are at an increased risk of fungal infection<sup>[138]</sup> because the antibiotics used for prevention of SBP can select for excessive growth of fungi in the intestinal flora with subsequent fungal translocation into peritoneal cavity and development of SFP<sup>[6]</sup>. Fungi are much larger than bacteria, which makes fungal translocation across the gut mucosa more difficult than BT, and may require higher intestinal permeability, which is more common in patients with advanced LC<sup>[148,149]</sup>. Fungal translocation may be facilitated by upper gastrointestinal bleeding, which is also common in patients with advanced LC<sup>[150]</sup>. Immunosuppression and malnutrition in LC patients also promote this fungal translocation<sup>[6]</sup>. Direct percutaneous inoculation of fungi is the proposed route of fungal infection in patients with refractory ascites and a history of paracentesis<sup>[150]</sup>.

There are few data on the characteristics of SFP in LC patients<sup>[5,6]</sup>, but case studies are available. Fungal colonization in ascitic fluid is not a rare complication in end-stage liver disease<sup>[5]</sup>, and studies of the clinical characteristics of SFP are becoming more frequent. SFP is defined as a fungal infection of ascitic fluid with no apparent intraabdominal source of infection or malignancy<sup>[148]</sup>. A PMN count of  $\geq 250$  cells/mm<sup>3</sup> in the ascitic fluid with a positive fungal culture regardless of co-colonization of bacteria is diagnostic of SFP<sup>[151]</sup>. A positive fungal culture with a PMN count of  $< 250$  cells/mm<sup>3</sup> is diagnosed as fungiascites or fungal ascites<sup>[151]</sup>. Fungal ascites has a higher mortality rate than does bacterascites<sup>[151]</sup>. Of spontaneous peritonitis cases, 0%-7.2% are culture positive for fungus<sup>[6,30,32,62,82,148,152-154]</sup>, and the most frequent isolate is *Candida albicans*<sup>[5,6,148,149,153-156]</sup>. Other causative fungi include *Candida glabrata*<sup>[30]</sup>, *Candida krusei*<sup>[153]</sup>, *Cryptococcus* spp.<sup>[148,157]</sup>, *Aspergillus* spp.<sup>[150,154]</sup>, and *Penicillium* spp.<sup>[154]</sup>. Polymicrobial infections, i.e., bacterial co-colonization, occurs in 32%-74% of SFP cases<sup>[148,149,153,154,156]</sup>, but early diagnosis by conventional microbial culture is difficult because of the time required for growth<sup>[155]</sup>, and the efficacy of PCR or assay of the fungal biomarker 1,3-beta-D-glucan in ascitic fluid has not been established<sup>[149,155]</sup>.

High Child-Pugh or MELD scores increase the risk of SFP in patients with LC<sup>[5,6,148]</sup>, and a retrospective case-control study by Gravito-Soares *et al.*<sup>[153]</sup> found no significant difference in the Child-Pugh or MELD scores of patients with SFP and SBP. The risk of SFP is increased in patients with LC who undergo invasive procedures<sup>[153]</sup> and increases with the length of the hospital stay<sup>[153,156]</sup>. Some studies have reported that a significantly greater proportion of SFP infections than SBP infections were nosocomial<sup>[148,156]</sup>, but the data are conflicting<sup>[6]</sup>. In previous studies of spontaneous peritonitis with ascitic culture-positive diagnosed between 2003 and 2016, nosocomial SFP was confirmed in 7.7% (53/689) of nosocomial spontaneous peritonitis, and non-nosocomial SFP was confirmed in 1.7% (17/1018) of non-nosocomial spontaneous peritonitis<sup>[156]</sup>.

Risk factors associated with hospital mortality in SFP include severe underlying liver disease<sup>[148]</sup>, Child-Pugh score<sup>[155]</sup>, MELD score<sup>[149]</sup>, antibacterial prophylaxis<sup>[6]</sup>, incidence of HRS<sup>[6]</sup>, low ascites protein concentration<sup>[6]</sup>, Acute Physiology And Chronic Health Evaluation II score<sup>[149]</sup>, and sepsis shock<sup>[153]</sup>. SFP mortality is estimated to be 56%-90%<sup>[5,148,149,151,153]</sup>, and 1-mo mortality may<sup>[148,153]</sup> or may not be significantly higher than SBP mortality<sup>[149,157]</sup>. Hwang *et al.*<sup>[148]</sup> reported a high SFP mortality that was related to unresponsiveness to initial empirical treatment for suspected SBP. The condition of nearly all the patients with SFP worsened after initial empirical treatment, and they died during the early stage of peritonitis regardless of undergoing antifungal treatment<sup>[148]</sup>. Some patients with SFP improved after receiving the initial empirical treatment without any antifungal agents<sup>[148]</sup>. Those patients may have had SBP and colonization by innocent fungi<sup>[148]</sup>, as it was not possible to distinguish fungal colonization from true SFP in the clinical setting<sup>[148]</sup>. SFP is usually diagnosed after the identification of fungi in cultures of ascitic fluid. The mortality is high because of delayed diagnosis, lack of clinical signs, lack of suspicion of SFP, and delay in treatment with antifungal therapy<sup>[5,6,148,155,156,158]</sup>. Fungal resistance to empirical specific antifungal therapy together with delayed diagnosis and treatment is related to poor prognosis of SFP<sup>[153]</sup>.

Recent treatment guidelines on management of infections in LC do not include antifungals for prophylaxis or optimum treatment but do include recommendations for fungal infections<sup>[138]</sup>. Echinocandins are recommended as first-line treatment for patients with LC and nosocomial SFP or critically ill patients with LC and community-acquired SFP<sup>[148]</sup>. Fluconazole is recommended for less severe infections<sup>[6,138,152]</sup>. De-escalation from echinocandins to fluconazole is advised in critically ill patients with LC and SFP when their condition is stable and sensitivity tests are available<sup>[6,152]</sup>. However, directed antifungal therapy may not improve the outcomes of some patients with SFP<sup>[149,156]</sup> because of lack of response to the administration of empirical treatment and delay in starting antifungal therapy<sup>[156]</sup>.

Although early differentiation between SFP and SBP may be difficult partially because identification of fungi in cultures of ascitic fluid is time-consuming, clinician is able to suspect SFP or SBP due to MDR if spontaneous peritonitis is not improved after 48 h empirical antibiotic treatment<sup>[151]</sup>. Therefore, new cultures in ascitic fluid and blood may be performed in these patients<sup>[151]</sup>. Moreover, additional administration of antifungal agents or administration of antifungal agents and alternation of antibiotics may be considered in these patients<sup>[151,159]</sup>.

## CONCLUSION

The evidence of previous studies confirms that SBP and SFP in patients with LC is often life-threatening. The severity of liver dysfunction, the presence of renal impairment, and the emergence of MDR bacteria have



a clinically significant influence on the prognosis of SBP. The efficacy of the recommended antibiotic therapy for SBP may be decreased in nosocomial infections because of increases in the prevalence of MDR bacteria. In SFP, mortality is associated not only with the severity of the underlying liver disease but also with delay in diagnosis and initiation of antifungal therapy. Further research is needed to better our understanding of the nature of SFP and improve the response to treatment with the available antifungal agents.

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