

## Spontaneous fungal peritonitis: Epidemiology, current evidence and future prospective

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### Abstract

Spontaneous bacterial peritonitis is a complication of ascitic patients with end-stage liver disease (ESLD);

spontaneous fungal peritonitis (SFP) is a complication of ESLD less known and described. ESLD is associated to immunodepression and the resulting increased susceptibility to infections. Recent perspectives of the management of the critically ill patient with ESLD do not specify the rate of isolation of fungi in critically ill patients, not even the antifungals used for the prophylaxis, neither optimal treatment. We reviewed, in order to focus the epidemiology, characteristics, and, considering the high mortality rate of SFP, the use of optimal empirical antifungal therapy the current literature.

**Key words:** Cirrhosis; Critically ill patient; Spontaneous fungal peritonitis; Life-threatening infections; Fungal ascitis; Nosocomial spontaneous peritonitis

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**Core tip:** Spontaneous bacterial peritonitis (SBP) occurs in patients with end-stage liver disease (ESLD); spontaneous fungal peritonitis (SFP) is a complication of ESLD less known and described. Patients with SFP had a significantly worse prognosis than those with SBP. The incidence accounts from 0% to 13% of patients with ESLD and spontaneous peritonitis. Data are conflicting regarding fungi distribution between nosocomial and non-nosocomial infections. *Candida* spp. are the most frequent fungal infectious agent isolated. Previous SBP antibiotic prophylaxis, hepatorenal syndrome, low ascitic fluid protein (< 1 g/dL), elevated acute physiology and chronic health evaluation II and serum lactate also significantly adversely impact hospital mortality.

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## INTRODUCTION

Spontaneous bacterial peritonitis (SBP) occurs in patients with end-stage liver disease (ESLD); however, spontaneous fungal peritonitis (SFP) is a complication of ESLD less known and described. A diagnosis of SFP is based on large numbers of neutrophil granulocytes (> 250 cells/mL) of ascitic fluid and diagnostic investigation to exclude other causes of intra-abdominal infection<sup>[1]</sup>, whereas we define fungal ascitis as fungal culture positive in ascitic fluid in the presence of ascitic neutrophil counts lower than 250 neutrophils/mL. Hospital-acquired (HA) spontaneous peritonitis (SP), both HA-SBP and HA-SFP, is peritonitis that occurs 48-72 h after hospitalization in the absence of signs of infection at hospital admission.

## EPIDEMIOLOGY

### Asia

Hwang *et al*<sup>[1]</sup> evaluated ESLD patients with SP between 2000 and 2005 in a Korean tertiary care center: 401 patients with SBP and 15 with SFP (3.6%); eleven of the 15 SFP was polymicrobial (Table 1). SFP was more common in nosocomial SP and in patients with higher Child-Turcotte-Pugh (CTP). The most commonly fungus found was *Candida* spp (8 patients *C. albicans*; 1 patient *C. tropicalis*; 1 patient *C. glabrata*), followed by *Cryptococcus neoformans* (5 patients). More than two-thirds of patients (11 patients, 73.3%) with fungal infection died within the first month after diagnosis of SP. All 10 patients showed no improvement with empirical antimicrobial therapy and died within a month. Of 5 patients who showed improvement with empirical antimicrobial therapy, only one died in the first month for gastrointestinal bleeding; the remaining four patients survived. HA-SBP and community-acquired SBP (CA-SBP) occurred in 151 and 265 patients, respectively. Distribution of fungi between HA-SFP vs CA-SFP was 12 vs 3, respectively. The mean value of CTP score was  $12.5 \pm 2.0$  in the SFP cohort and  $11.1 \pm 1.7$  in the SBP cohort<sup>[1]</sup>.

In another retrospective study conducted in Korea, between January 1<sup>st</sup> 2003 and December 1<sup>st</sup> 2010, ninety-five ESLD patients with SP were included. Among the forty-seven pathogens isolated, one (2.2%) was a *Candida* spp. The patient with *Candida* spp in ascitic fluid had hepatocellular carcinoma and died of liver failure shortly after admission<sup>[2]</sup>.

Cheong *et al*<sup>[3]</sup> evaluated the clinical difference between SP acquired in the hospital or in the community in patients with ESLD between 2000 and 2007 in a Korean tertiary care center: HA-SBP occurred in 126 and CA-SBP occurred in 110 patients. Distribution of fungi between HA-SFP vs CA-SFP was 2.4% (3 patients) vs 0%.

Li *et al*<sup>[4]</sup> evaluated the drug resistance profile of pathogens isolated by ascitic fluid of 288 Chinese patients with ESLD between 2011 and 2013. Three

hundred and six pathogens were isolated: 207 non-nosocomial and 99 nosocomial infections. Fungi were found in the ascitic fluid of nine patients (2.9%); there was significant difference regarding fungi distribution between nosocomial (7.1%, 7 patients) and non-nosocomial (0.9%, 2 patients) cases ( $P = 0.004$ ).

Jindal *et al*<sup>[5]</sup> recently evaluated the outcome of carbapenem- vs cephalosporin-regimen in Indian cirrhotic patients with SP. A total of 175 patients were enrolled, of these two patients (1.1%) had SFP (1 patient with *Candida* spp and 1 patient with *Aspergillus* spp) and were treated with success.

### Europe

Piano and Angeli reviewed microbiological data between 2007 and 2009 of a tertiary care center of northern Italy. Of sixty-nine culture positive SP, two (3%) were SFP. Fluconazole-susceptible *C. albicans* was isolated in the two cases<sup>[6]</sup>.

In an observational study conducted in 4 university hospitals in north-eastern France, between January 1<sup>st</sup> 2010 and December 31<sup>st</sup> 2011, one hundred and ninety ESLD patients had ascites (median age 61.5 years, 58.5% CTP C): 268 ascitic fluid positive culture were obtained. Of these 140 were bacterascites and 57 SBP. Fungi were found in 2.1% of patients with bacterascites and none of SP patients. Bacterascites seems to be considered a serious condition given the mortality rate (close to 20%). The authors concluded that bacterascites is probably a surrogate marker of advanced liver disease<sup>[7]</sup>.

In order to evaluate the different etiology between HA- and CA-SBP, ninety-five SP episodes were reviewed from a French Liver Unit. Seventy-eight microorganisms were found (39 isolates in each group) including 1 yeast (*C. albicans*). Distribution of *C. albicans* between HA-SFP vs CA-SFP was 0% vs 2.5% (1 patient)<sup>[8]</sup>.

Friedrich *et al*<sup>[9]</sup> evaluated the drug resistance profile of pathogens isolated from ascitic fluid of 311 ESLD patients (hospitalized in a German tertiary care center) with their first episode of SP between 2007 and 2013. A total of 138 pathogens were isolated (49 non-nosocomial and 89 nosocomial). Fungal infections, *Candida* spp, were found in 10 patients (7.2%); *C. albicans* (3.6%) is the most frequent fungal infectious agent isolated. Interestingly, there was no significant difference regarding *Candida* spp distribution between nosocomial (9.0%, 8 patients) and non-nosocomial (4.1%, 2 patients) cases ( $P = 0.287$ ).

Reuken *et al*<sup>[10]</sup> reviewed retrospectively 244 positive ascitic fluid culture isolated from ESLD patients between 2000 and 2011 in a German tertiary hospital, of these 90 were documented as monomicrobial SP. Fungal infections, *Candida* spp, were found in 3 patients (3.3%) of the ninety with SP.

Umgelter *et al*<sup>[11]</sup> analyzed prospectively 41 positive ascitic fluid culture isolated from ESLD patients between 2000 and 2011 in a German university medical center.

**Table 1 Polymicrobial infections**

Ref.	HA-SBP definition	Study design	Data provided by the author	Setting	Patients with polymicrobial infections	Fungal polymicrobial infections
Friedrich <i>et al</i> <sup>[9]</sup> , 2015	PMN > 250 > 48 h of hospitalization	Retrospective cohort	No	University Hospital	24/138	N/A
Li <i>et al</i> <sup>[4]</sup> , 2015	PMN > 250 > 48 h of hospitalization	Retrospective cohort	No	University Hospital	16/306	N/A
Hwang <i>et al</i> <sup>[11]</sup> , 2014	PMN > 250 > 72 h of hospitalization	Retrospective cohort	No	University Hospital	N/A	11/15
Ariza <i>et al</i> <sup>[12]</sup> , 2012	PMN > 250 > 48 h of hospitalization	Retrospective cohort	No	University Hospital	15/261	N/A
Umgelter <i>et al</i> <sup>[11]</sup> , 2009	PMN > 50 > 48 h of hospitalization	Prospective cohort	Yes	University Hospital	4/41	2/2
Bert <i>et al</i> <sup>[8]</sup> , 2003	PMN > 250 > 48 h of hospitalization	Retrospective cohort	No	University Hospital	7/78	N/A

HA: Hospital-acquired; SBP: Spontaneous bacterial peritonitis; PMN: Polymorphonuclear; N/A: Not available.

*C. albicans* was found in 2 patients (4.8%) both in association with bacterial infections (Table 1). All *C. albicans* were susceptible to fluconazole.

In a retrospective observational study on a cohort of cirrhotic patients with SP conducted in a Spanish teaching hospital, between 2001 and 2009, 261 ascitic fluid culture positive SP were evaluated. The authors excluded from the analysis 15 cultures because polymicrobial, so SFP in this cohort could be underestimated. Distribution of *C. albicans* between HA-SFP vs CA-SFP was 0% vs 0.005% (1 patient)<sup>[12]</sup>.

### Africa

In a prospective study carried out in an Egyptian intensive care unit (ICU) from January to August 2013, 46 patients with ESLD were enrolled. Three patients had a polymorphonuclear (PMN) cell count greater than 250 cells/mL in ascitic fluid, of these 3 patients 1 patient had ascitic and blood culture negative, 2 patients (4.3%) had fungal growth in ascitic fluid: 1 patient had ascitic and blood culture positive for *A. niger* and 1 patient had ascitic culture positive for *C. albicans* and blood culture positive for *C. albicans* and *C. tropicalis*. Three (6.5%) patients had a PMN cell count lower than 250 cells/mL in ascitic fluid, of these 1 had ascitic and blood culture positive for *C. albicans*, 1 had ascitic culture positive for *C. albicans* and blood culture negative, 1 had ascitic culture positive for *A. niger* and blood culture negative. Of these 6 patients only 1 patient who had ascitic and blood culture negative died. Independent risk factors for a fungal infection were found to be previous antibiotic prophylaxis for SBP, hepatorenal syndrome and low protein ascites with total protein concentration of less than 1 g per deciliter. Patients with SFP presented worse prognosis than patients with SBP<sup>[13]</sup>.

### North America/miscellaneous

Karvellas *et al*<sup>[14]</sup> conducted a retrospective cohort study involving cirrhotic patients with SBP from 28 hospitals of Canada, United States and Saudi Arabia between 1996 and 2011 presenting with septic shock: a positive culture (blood or ascitic fluid) was found in 86 (68%) of 126 patients enrolled (53 HA-SFP vs 73 CA-SFP), the most common pathogens isolated were *Escherichia coli* (27.3%) followed by *Candida* spp (11.1%): 9 *C. albicans* and 2 *C. glabrata/tropicalis*. No one of these 11 patients survived to hospital discharge. SP-associated septic shock has a poor prognosis (mortality 80%). Appropriate antimicrobial therapy should be given as soon as possible: non-administration corresponds to an increase of 1.86 times hospital mortality per hour. Others hospital mortality risk factors are elevated acute physiology and chronic health evaluation II (APACHE II) and serum lactate.

## CURRENT EVIDENCE

Fungi are common saprophytes of the human organism, being ubiquitously on skin and mucous membranes. Antibiotics (used for the prevention of SBP in patients with ascites) acting on the intestinal bacterial flora produce an excessive growth of fungi especially of the intestinal tract<sup>[15]</sup> with subsequent "translocation" from the gut lumen across the mucosa into the peritoneal cavity. Immunosuppression and malnutrition, common in ESLD patients, promote this process.

Differences between SBP and SFP: compared with SBP patients, the CTP score seems to be higher in SFP patients<sup>[1]</sup>. Patients with SFP had significantly higher mortality than the patients with SBP<sup>[1,13]</sup>. Patients who do not respond to empiric antimicrobial therapy

(if this does not cover the fungus) have a very poor prognosis (mortality 100%)<sup>[1]</sup>. Data are conflicting regarding fungi distribution between nosocomial and non-nosocomial infections, cases of fungal peritonitis is not clearly more common in HA-<sup>[1,4]</sup> than CA-SP<sup>[9]</sup>. The number of isolates is so low that any analysis is underpowered so a meta-analysis of observational studies could clarify the fungi distribution between nosocomial and non-nosocomial infections.

*C. albicans* is the most frequent fungal infectious agent isolated<sup>[1,2,9-11,14]</sup> following by *C. neoformans*<sup>[1]</sup> and *Aspergillus* spp<sup>[5,13]</sup>. Fungal infection is often polymicrobial (73.3%-100% of cases), on the contrary polymicrobial bacterial infections affecting 5.2%-17.4% of cases (Table 1).

Risk factors for hospital mortality in SFP are SBP antibacterial prophylaxis, hepatorenal syndrome, low protein ascites with total protein concentration of less than 1 g per deciliter<sup>[13]</sup>, elevated APACHE II and serum lactate<sup>[14]</sup>.

Bremmer *et al*<sup>[16]</sup> in an historic cohort study including 25 patients (21 liver transplanted and 4 not liver transplanted), with isolation of *Candida* spp in ascitic fluid, found that *C. albicans* (48%; 12 out of 25) is the commonest pathogen, less frequently *C. glabrata* (20%), *C. parapsilosis* (16%), *C. tropicalis* (12%) and *C. zeylanoides* (4%). In the study, 28-d mortality was significantly higher in patients with elevated Charlson Comorbidity Index, Model for End-Stage Liver Disease (MELD) and APACHE II scores. There was no significant difference regarding 28-d mortality between fungal ascitis and SFP; conversely there was significant difference regarding 28-d mortality between patients who do not underwent liver transplantation (14 out of 21) and patients who underwent liver transplantation (0 out of 4). This study suggests that antifungal therapy used to treat SFP, could be a "bridge" to liver transplantation.

Saludes *et al*<sup>[17]</sup> recently reported 7 episodes of *Candida* spp isolation in ascites of cirrhotic patients detected in a Spanish hospital during the past 15 years. *C. albicans* was isolated in 5 patients (71.4%) and *C. glabrata* in 2 patients (28.6%). All patients were CTP C, per year mortality was 100% and 3 patients died in the first 10 d of diagnosis.

Choi *et al*<sup>[18]</sup> reviewed the clinical and laboratory features of all cirrhotic patients whose ascites samples were positive for *Candida* spp. A total of 21 cirrhotic patients was identified. Patients were regarded as having peritonitis if they had 1 or more clinical symptom(s) or sign(s) in the absence of any other possible explanation. Ten patients (47.6%) were classified into the spontaneous *Candida*-related peritonitis group, and the remaining 11 patients (52.4%) were classified into asymptomatic fungal ascitis. Mortalities were higher in the spontaneous *Candida* peritonitis group at discharge (50.0% vs 27.3%), 6-mo (90% vs 45.5%) and 1-year (100% vs 54.5%) ( $P = 0.007$ ). Receiver-operating characteristic curve analysis revealed that the cut-off

value of ascitic fluid PMN cell count of 315 cells/mL had the highest diagnostic accuracy with both sensitivity and specificity.

## FUTURE PROSPETIVES

The available data suggest that the SFP could affect negatively the prognosis of patients with SP, therefore new diagnostic and therapeutic strategies are required. *Candida* spp. Is associated with a severe outcome when manifested with peritonitis<sup>[18]</sup>. In a recent clinical trial, fluconazole was added in patients with HA-SBP with no response to meropenem and daptomycin. In this study, never previously proposed, the authors added empiric antifungal therapy in a therapeutic HA-SBP protocol<sup>[19]</sup>, although in the latest guidelines no mention is made about the use of antifungals in ESLD patients<sup>[20,21]</sup>. Actually start antifungal therapy as soon as possible improves prognosis in patients with invasive candidiasis<sup>[22,23]</sup>.

Mortality from SFP is increased in case of severe underlying diseases and/or if initial antimicrobial therapy is inappropriate<sup>[14,24-26]</sup>. Karvellas *et al*<sup>[14]</sup> state that non-administration of an appropriate antimicrobial therapy corresponds to an increase of 1.86 times hospital mortality per hour. Unfortunately, it is not possible to extrapolate from this study the subgroup of SFP, but we can assume that septic shock has a worse outcome.

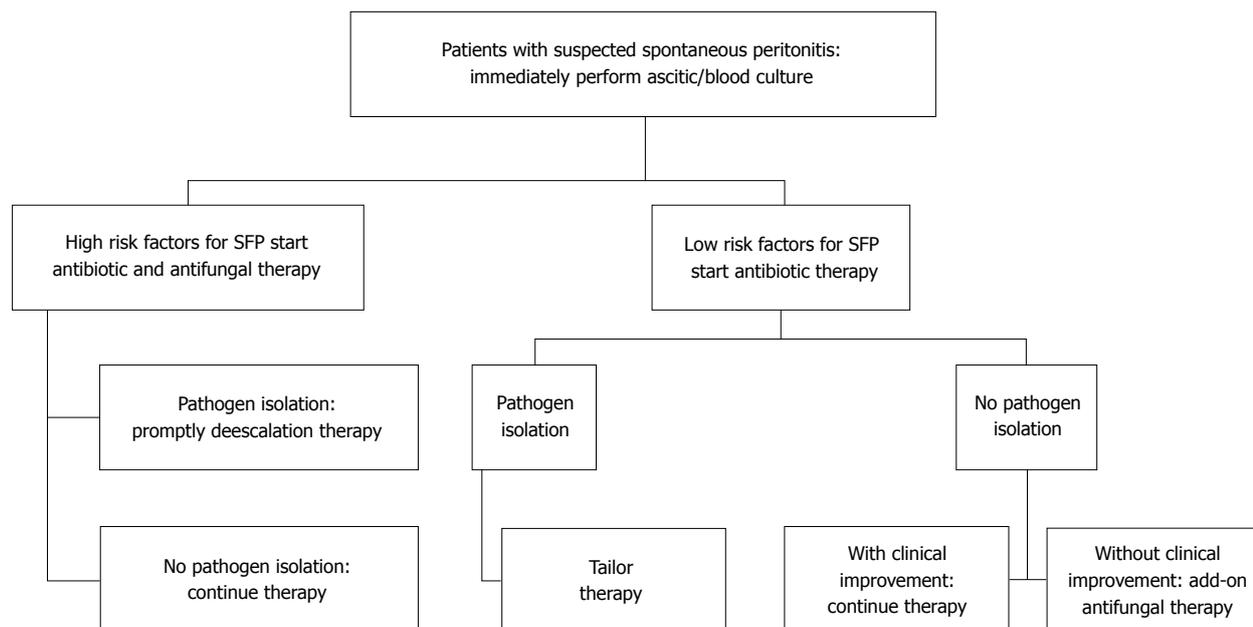
Area of uncertainty that remains for clinicians is the management of fungal ascitis: studies report no differences in mortality rates among patients with ascitic cell count upper or lower 250 cells/mL<sup>[16]</sup>, or higher mortality in the SFP group but with a fungal ascitis mortality ranging from 27.3% at discharge to 54.5% after 1 year of discharge<sup>[18]</sup>, conversely bacterascites show lower mortality rates than SBP<sup>[7]</sup>.

As we recently proposed, given the low incidence of the SFP, a prophylaxis would be unuseful<sup>[27]</sup>. Treatment should be considered in absence of a positive culture in patients with a higher Charlson Comorbidity Index, MELD and APACHE II scores. Patients with a positive fungal culture of the ascitic fluid independently of PMN count should be treated.

Echinocandins are recommended for patients with HA-SFP or patients with CA-SFP and severe underlying illness given the poor prognosis of inappropriate antimicrobial therapy<sup>[28]</sup>. De-escalation to fluconazole is recommended when sensitivity tests are available<sup>[29]</sup>.

Echinocandins should be considered as empirical or preemptive systemic antifungal therapy for patients with suspected SFP. The de-escalation to fluconazole reduces pharmaceutical costs and emerging of resistant microorganisms<sup>[30]</sup>.

Micafungin in a different setting of patients with ESLD (liver transplant patients with a MELD score  $\geq 20$ ) showed non inferiority to standard antifungal prophylaxis, although renal function showed a better performance in micafungin group<sup>[31]</sup>. In conclusion



**Figure 1 Spontaneous fungal peritonitis management algorithm.** Risk factors for fungal diseases<sup>[32]</sup>: Surgery, total parenteral nutrition, fungal colonisation, renal replacement therapy, infection and/or sepsis, mechanical ventilation, diabetes, and APACHE II or III score; Add-on: consider adding empiric antifungal therapy. APACHE: Acute physiology and chronic health evaluation.

an algorithm should be proposed for the treatment of patients with suspected SFP (Figure 1).

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