STATE-OF-THE-ART CLINICAL ARTICLE

Spontaneous Bacterial Peritonitis

José Such and Bruce A. Runyon

From the Hospital General Universitario, Alicante, Spain; and Transplantation Institute, Loma Linda University Medical Center, Loma Linda, California, USA

Spontaneous bacterial peritonitis (SBP) is probably the best-characterized infectious complication that develops in patients with cirrhosis and ascites [1, 2]. Since its first description in 1964, a large body of knowledge has accumulated regarding the clinical presentation, diagnosis, pathogenesis, treatment, and prevention of SBP, and the prognosis of patients who develop this infection [1–3]. Although SBP has been described as occurring in different clinical settings, such as nephrotic syndrome or heart failure, most SBP episodes develop in patients with advanced cirrhosis as a manifestation of severe derangement of hepatic function. Therefore, an episode of ascitic fluid (AF) infection has been proposed as an indication for liver transplantation, in the absence of contraindications.

Variants of AF Infection

Several variants of AF infection have been described (table 1).

SBP. SBP has been defined as an AF infection associated with a positive bacterial culture and an AF polymorphonuclear (PMN) cell count of $\geq 250/mm^3$, in the absence of a surgically treatable intraabdominal source of infection. SBP was the first AF infection described and is probably the most common variant. In a large series of AF infectious episodes, 67.8% met the above criteria for SBP. Because this infection is almost always monomicrobial, growth of more than one organism should raise a suspicion of secondary peritonitis (see below).

Culture-negative neutrocytic ascites (CNNA). This variant is diagnosed when cultures of AF are negative, a PMN cell count is $\geq 250/mm^3$, and when there is no surgically treatable intraabdominal source of infection [4]. Other possible causes of neutrocytic ascites such as peritoneal carcinomatosis, pancreatitis, and tuberculous peritonitis must be ruled out. The clinical, prognostic, and therapeutic characteristics of CNNA are similar to that of SBP, and CNNA, therefore, is treated in a similar fashion.

Monomicrobial nonneutrocytic bacterascites (MNB). This variant is characterized by the isolation of bacteria in cultures of AF and a PMN cell count of $<250/mm^3$. The clinical course of MNB is dependent on the presence or absence of associated clinical symptoms. For patients who present with MNB and with clinical signs or symptoms suggestive of infection, the morbidity and mortality rates are similar to those for patients with SBP or CNNA. In contrast, among patients with asymptomatic MNB the colonization is usually resolved without antibiotic therapy.

Secondary bacterial peritonitis. This entity is diagnosed in cases for which AF cultures are positive (usually polymicrobial), PMN cell counts are $\geq 250/mm^3$, and for which there is a surgically treatable intraabdominal source of infection. Clinical signs and symptoms do not distinguish secondary from spontaneous peritonitis; however, the AF analysis is helpful in this regard. The AF in secondary peritonitis usually meets at least two of the following criteria: a total protein content of >1 g/dL, a glucose concentration of <50 mg/dL, and a lactate dehydrogenase level of >225 U/mL (or higher than the upper limit of normal for serum). The diagnosis of secondary peritonitis must be made early in the course of illness, since death is the usual outcome in the absence of surgical correction.

Polymicrobial bacterascites. Polymicrobial bacterascites is diagnosed when gram staining or cultures of AF demonstrate multiple organisms and there is a PMN cell count of $<250/mm^3$. This variant usually occurs as a result of inadvertent puncture of the intestines during attempted paracentesis. Fortunately, this is a rare event, occurring in ~ 1 of 1,000 paracenteses. Ileus, the presence of multiple surgical scars, and inexperience of the operator are risk factors for this iatrogenic variant of AF infection. If the AF protein concentration is >1 g/dL and the osponic activity of the fluid is adequate, this colonization resolves spontaneously.

Flora

More than 60% of SBP episodes are caused by gram-negative enteric bacteria [5]. *Escherichia coli* and *Klebsiella pneu-*

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Reprints or correspondence: Dr. Bruce Runyon, Director of Hepatology and Medical Director of Liver Transplantation, Loma Linda University Medical Center, 11234 Anderson Street, Room 1405, P.O. Box 2000, Loma Linda, California 92354.

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Table 1. Classification of ascitic fluid infections.

Type of infection	PMN cell count (/mm^3)	Bacterial culture result
Spontaneous bacterial peritonitis	≥250	Positive (usually 1 organism)
Culture-negative neutrocytic ascites	≥250	Negative
Monomicrobial nonneutrocytic bacterascites	<250	Positive (1 organism)
Secondary bacterial peritonitis	≥250	Positive (polymicrobial)
Polymicrobial bacterascites	<250	Positive (polymicrobial)

NOTE. PMN = polymorphonuclear.

moniae are the organisms isolated most frequently. Gram-positive cocci account for ~25% of episodes; streptococcal species are isolated most frequently. Although the flora of the colon is predominantly anaerobic, isolation of an anaerobic organism as the cause of SBP is an infrequent event, probably because of the high oxygen content of the intestinal wall and surrounding tissues and because of the relative inability of anaerobes to translocate across the intestinal mucosa (see below). This pattern of bacterial prevalence may differ for patients who are receiving selective intestinal decontamination (SID), usually with fluorinated quinolones, to suppress the gram-negative intestinal flora and reduce the incidence of SBP. SID reduces the number of episodes caused by gram-negative bacteria, but can increase the frequency of gram-positive SBP episodes.

Pathogenesis

Figure 1 schematizes our current knowledge concerning the pathogenesis of SBP [3, 6].

Intestinal bacterial overgrowth (IBO). Among cirrhotic patients, 30% to 48% have colonization of the upper bowel with colonic bacteria; patients with more advanced liver disease have higher rates of colonization. Bacterial translocation is the process by which intestinal bacteria exit the intestinal lumen, cross the intestinal wall, and colonize intestinal and/or mesenteric lymph nodes. IBO has been shown to be a prerequisite for the development of bacterial translocation in experimental animals (figure 1). Possible explanations for IBO among patients with cirrhosis include an altered local IgA immune response and delayed intestinal transit.

Intestinal permeability. Intestinal structural abnormalities characterized by vascular congestion and edema, as well as an increased interepithelial cell space, are evident in patients with cirrhosis. These abnormalities probably increase intestinal permeability and facilitate bacterial translocation.

Bacterial translocation. Once intestinal bacteria translocate across the mucosa and escape the intestines, they can then spread to other tissues including the bloodstream. The presence of ascites appears to be an important risk factor for the development of bacterial translocation in cirrhotic rats. Bacterial translocation has also been observed in humans at the time of laparotomy. In healthy individuals, bacteria that colonize lymph nodes are killed by local immune defenses. However, in the setting of cirrhosis, several forms of immune deficiency (see figure 1 and below) favor the spread of bacteria to the bloodstream.

Alterations in the systemic immune system. Bacteria that enter the bloodstream of a healthy host are rapidly coated by IgG and/or complement components and then engulfed and killed by circulating neutrophils [2]. However, in the setting of cirrhosis, several abnormalities have been described in the humoral and cellular bactericidal systems including decreased serum levels of complement factors, impaired chemotaxis, poor function and phagocytic activity of neutrophils, and decreased function of Fc-γ-receptors in macrophages.

Reticuloendothelial system phagocytic activity. The stationary macrophages, such as the Kupffer cells of the liver,

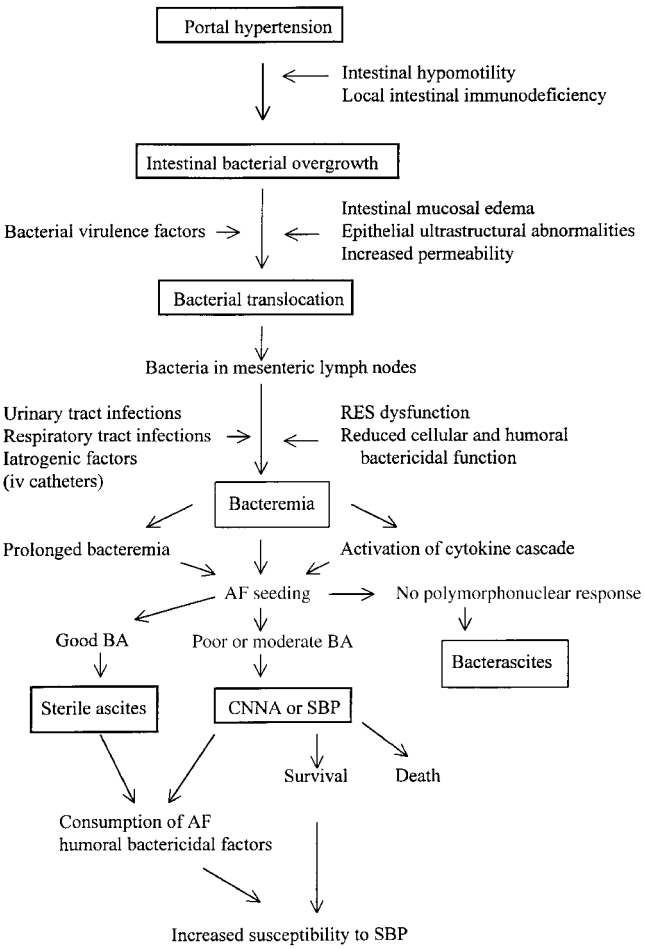

Figure 1. Mechanisms that may be involved in the pathogenesis of spontaneous bacterial peritonitis. AF = ascitic fluid; BA = bactericidal activity; CNNA = culture-negative neutrocytic ascites; RES = reticuloendothelial system; SBP = spontaneous bacterial peritonitis.

Table 2. Predisposing factors for the development of AF infection in patients with cirrhosis and ascites.

1. Severity of liver disease: Child-Pugh class C patients
2. AF total protein level <1 g/dL and/or AF C3 level <13 mg/dL
3. Gastrointestinal bleeding
4. Urinary tract infection
5. Intestinal bacterial overgrowth
6. Iatrogenic factors: urinary bladder and intravascular catheters
7. Previous spontaneous bacterial peritonitis episode(s)

NOTE. AF = ascitic fluid; C3 = third component complement.

assist the circulating neutrophils in the extraction and killing of particulate matter (e.g., bacteria) from the systemic circulation. These cells, and perhaps others, comprise the reticuloendothelial system. The function of this essential bactericidal system may be severely impaired in the setting of cirrhosis. Patients with the most severe dysfunction of this system have the highest risk of bacteremia and concomitant shortened survival, due to sepsis. The presence of intrahepatic and extrahepatic portosystemic shunts as a consequence of portal hypertension, prevent circulating bacteria from encountering Kupffer cells. The final consequence of these abnormalities is the prolongation of bacteremia and eventual seeding of other sites, including AF.

AF defense mechanisms. The arrival of bacteria to the AF does not guarantee that infection will develop. In fact, cirrhotic AF is capable of humoral self-defense, mainly on the basis of the effectiveness of the complement system. Patients with adequate activity of this vital bactericidal system usually do not develop AF bacterial infections [3]. However, it has been demonstrated that among those with an AF third component (C3) of complement level of <13 mg/dL and/or a protein level of <1 g/dL, there is a predisposition to this infection [3, 7]. The complement levels may be deficient because of increased consumption of these components or because of impaired synthesis. Most of the bacteria that colonize AF are intestinal gram-negative bacteria. The presence of lipopolysaccharides in their cell wall activates the alternative pathway of complement. If the complement levels are adequate to effectively kill the bacteria, infection will not develop. However, if complement levels are consumed and depleted, killing may be ineffective. It is of interest to note that SID with norfloxacin reduces the gram-negative intestinal flora and presumably reduces the colonization of AF, and the agent has been shown to increase the C3 complement levels in AF [7]. In summary, the frequent colonization of AF by bacteria decreases its antimicrobial ability and can eventually lead to the development of infection (figure 1).

Predisposing Factors

Factors that predispose to AF infection are outlined in table 2. The severity of the liver disease is probably the most important factor. Almost 70% of patients who develop SBP are Child-Pugh class C, with the remainder being class B. A serum total bilirubin level of >2.5 mg/dL is an independent predictive factor of SBP [6]. Deficient AF bactericidal activity is the main intraperitoneal predisposing factor for the development of AF infection. A direct correlation between total protein level, complement components, and opsonic activity explains why an AF total protein level of <1 g/dL is a risk factor for the development of AF infection [3].

Among cirrhotic patients with acute gastrointestinal bleeding, 20% have AF infection at the time of admission to the hospital, and another 30% to 40% may develop bacterial infections (including extraperitoneal infection) during hospitalization. In an experimental model of cirrhosis, hemorrhagic shock has been shown to increase bacterial translocation and intestinal permeability, and to decrease the effectiveness of the reticuloendothelial system.

Bacteriuria is common among patients with cirrhosis, particularly among females, and it appears to be a predisposing factor for the development of SBP. Screening for and treatment of urinary tract infections, even in the absence of symptoms, may be helpful in preventing AF infections. Urinary bladder catheters should be avoided if possible in patients with cirrhosis.

Intravascular catheters are commonly used in patients with cirrhosis, especially in the intensive care unit (ICU). Among these patients, between 4% and 20% of bacteremic episodes may be caused by intravascular catheters, and their use should be minimized in this population.

Infections of AF that occur after episodes of variceal bleeding appear to be related more to the bleeding itself, rather than to therapeutic or diagnostic endoscopic procedures. Prophylactic antibiotics have been shown to be unnecessary for these procedures, unless the patient has other risk factors for endocarditis.

Finally, those patients who survive an episode of SBP are at high risk of recurrence: 43% at 6 months, 69% at 1 year, and 74% at 2 years.

Prevalence and the Clinical Picture

In the past, SBP was considered an infrequent complication of cirrhosis, probably because of the infrequency of paracentesis (because of unfounded fear of complications), and the low diagnostic efficacy of bacterial cultures (resulting from the insensitivity of older methods). In reality, AF infection is the most frequent infectious complication among patients with cirrhosis and those with ascites, comprising 31% of all bacterial infections.

The symptoms observed most frequently are fever (69%) and abdominal pain (59%). Contrary to popular belief, a rigid abdomen does not occur in patients with infected ascites, even if there is free perforation of the intestine into the fluid. The presence of large-volume ascites prevents contact of the visceral and parietal peritoneal surfaces that is sufficient to elicit the spinal reflex that causes rigidity. Other signs and symptoms

Table 3. When to perform a paracentesis.

New-onset ascites
At the time of each admission to the hospital
When deterioration of the clinical status or laboratory test values is evident
When the patient develops an associated complication, such as hepatic encephalopathy or gastrointestinal bleeding

include hepatic encephalopathy (54%), abdominal tenderness (49%), diarrhea (32%), ileus (30%), shock (21%), and hypothermia (17%). Among patients with SBP, ~10% have no signs or symptoms. Because of this lack of specificity and sensitivity of clinical signs and symptoms, instances of unexplained deterioration in patients with cirrhosis should lead to a diagnostic paracentesis. Prompt diagnosis and treatment maximize survival among patients with AF infections.

Diagnosis

Suspicion of infection is based on the clinical setting. However, the diagnosis of AF infection is based on AF analysis, and to obtain fluid an abdominal paracentesis must be performed. Paracentesis has been shown to be safe despite the predictable coagulopathy in these patients; there is an ~1% chance of significant abdominal-wall hematoma, .01% chance of hemoperitoneum, and .01% chance of iatrogenic infection related to paracentesis. Indications for paracentesis are outlined in table 3. Paracentesis should be avoided only in instances of clinically evident fibrinolysis or disseminated intravascular coagulation.

Table 4 details some of the diagnostic tests that can be ordered on AF. A cell count and differential should be ordered for every specimen, even when a therapeutic paracentesis is performed. The diagnosis of SBP is suspected when the AF PMN cell count reaches 250/mm^3. Patients with neutrocytic ascites (i.e., PMN count, $\geq$250/mm^3) should receive prompt empiric antibiotic treatment (see below), without waiting for the results of the AF culture, given that SBP and CNNA share common clinical, prognostic, and therapeutic characteristics, and a delay in antibiotic treatment may result in a significant and potentially fatal deterioration in the clinical status of the patient.

Serum and AF albumin levels should be obtained for calculation of the serum-ascites albumin gradient [8]. A serum-ascites albumin gradient of $\geq$1.1 g/dL is nearly 100% accurate in detecting the presence of portal hypertension. This test need be performed only on the first specimen from a given patient.

AF should be inoculated into blood-culture bottles at the bedside [5]. The volume of fluid used for cultures varies according to the manufacturer's specifications; however, application of a 10-mL inoculum into each bottle has been shown to optimize results in standard 100-mL bottles. Use of blood-culture bottles yields bacterial growth in ~80% of episodes of neutrocytic ascites, compared to <50% for the conventional technique [5].

The ''optional'' tests (table 4) are ordered when there is suspicion for something other than sterile, cirrhotic ascites, and the ''unusual'' tests are ordered only when the pretest probability of peritoneal tuberculosis or carcinomatosis, etc., is high enough to justify their use. The utility of other tests, such as those for pH, lactate dehydrogenase, cholesterol, fibronectin, α-1 antitrypsin, glycosaminoglycans, etc., has not been proven, and these tests are not recommended.

Treatment

Many years ago, the usual treatment for patients with SBP was the combination of a β-lactam plus an aminoglycoside. However, patients with SBP are very sensitive to the nephrotoxicity associated with use of aminoglycosides, and even if toxic levels are avoided, fatal renal failure is common. In 1985, results of a randomized trial demonstrated that cefotaxime, a third-generation cephalosporin, achieved cures in SBP episodes for 85% of patients, compared to 56% of patients who received ampicillin plus tobramycin [9]. More importantly, neither renal impairment nor side effects were reported in association with cefotaxime. Since then, cefotaxime has become the empiric antibiotic of choice for the treatment of SBP. More recent studies have demonstrated that dosing regimens and duration of treatment can be reduced with continued excellent results. An intravenous dosage of 2 g of cefotaxime every 8 hours for 5 days is enough, even in patients with bacteremia. The dosage need not be altered for cases of hepatic or renal failure. Despite many years of use, 72% to 96% of AF SBP isolates remain susceptible to cefotaxime.

Other antibiotics have been tested in the treatment of SBP, such as ceftriaxone, aztreonam, cefonicid and, recently, amoxicillin/clavulanate. Although some of them, e.g., ceftriaxone or amoxicillin/clavulanate, seem promising, more studies are needed before their use can be recommended. Parenteral amoxicillin/clavulanate is not available in the United States.

A novel approach for the treatment of SBP has been the use of oral ofloxacin. A randomized trial compared the efficacy of oral ofloxacin with that of intravenous cefotaxime in a selected group of cirrhotic patients with SBP in the absence of septic shock, hepatic encephalopthy, azotemia, gastrointestinal bleed-

Table 4. Tests performed for analysis of ascitic fluid.

Routine tests	Optional tests	Unusual tests
WBC count and differential	Total protein levels	Tuberculosis smear and culture
Albumin levels	Glucose levels	Cytology
Cultures in blood-culture bottles	Lactate dehydrogenase levels	Triglyceride levels
	Gram staining	Bilirubin levels
	Amylase levels	

ing, or ileus. The infection resolution rate was 84% in the ofloxacin group and 85% in the cefotaxime group, with a hospital survival rate of 81% in both groups. The results of this study point to the possibility of outpatient treatment of uncomplicated SBP. However, other issues, such as patient compliance and duration of therapy must be closely evaluated before this option can become routine.

Repeated paracenteses for follow-up of patients with SBP are considered. However, this procedure does not appear to be necessary if the clinical response to treatment is dramatic, the setting is typical, and the infection is monomicrobial. Repeated paracentesis is recommended if the first AF analysis has the following characteristics: (1) polymicrobial infection and (2) two or more of these factors—total protein level, >1 g/dL; glucose level, <50 mg/dL; or lactate dehydrogenase level greater than the upper limit of normal for serum. Patients with these characteristics frequently have secondary bacterial peritonitis; these patients should undergo an emergency radiological evaluation to determine a surgical source for their peritonitis followed by surgical intervention when appropriate.

Bacterascites represents the colonization of AF with bacteria without a neutrocytic response. It has been shown that the outcome of bacterascites is different in patients who are symptomatic vs. those without signs or symptoms of infection. Patients with signs or symptoms of infection are more prone to progress to SBP and therefore should receive empiric antibiotic treatment as detailed above for SBP. Therefore, treatment should be initiated if there is new abdominal pain and/or temperature ⩾100°F. In general, there is no growth demonstrated in cultures for 12–48 hours. Therefore, at time of the paracentesis it is not known whether the cultures will yield bacteria and treatment is initiated on the basis of clinical judgement. If neither AF nor blood nor urine cultures yield bacteria by 48 hours, the antibiotic can be discontinued. In contrast to patients with symptomatic bacterascites, only 15% of asymptomatic patients with bacterascites progress to SBP. Therefore, it is recommended that the paracentesis be repeated as soon as the first culture yields bacteria. Antibiotics are initiated only if signs or symptoms of infection develop or if the second paracentesis demonstrates neutrocytic ascites.

Prophylaxis

Several groups of patients with cirrhosis who are at high risk for SBP have been identified: those with gastrointestinal bleeding, those with AF protein levels of <1 g/dL, and those who have survived a previous episode of SBP [10–12]. Prophylactic measures that are directed at decreasing the risk of infection have been studied in these groups of patients (table 5).

Table 5. Prevention of ascitic fluid infection.

Selective intestinal decontamination should be initiated in the following groups of cirrhotic patients with ascites:
- Patients with gastrointestinal bleeding: norfloxacin, 400 mg b.i.d. per os or via nasogastric tube for 7 days
- Patients with ascitic fluid protein levels of <1 g/dL: norfloxacin, 400 mg q.d. per os during hospitalization
- Patients who have recovered from a previous episode of spontaneous bacterial peritonitis: norfloxacin, 400 mg q.d. per os indefinitely

General Measures

Long-term measures include abstinence from alcohol, improvement in nutrition and the general status of the patient, and aggressive treatment and eradication of localized infections before dissemination occurs. Measures directed at reducing the risk of gastrointestinal bleeding or the development of ascites, such as surgical portacaval shunts or trans-jugular intrahepatic portasystemic stent-shunts, may help prevent SBP. Diuretic therapy decreases the AF volume and has been shown to significantly increase the AF opsonic activity, theoretically helping to prevent the development of SBP.

SID

Low-protein AF. Because most SBP episodes are caused by intestinal gram-negative flora, attempts have been made to reduce this bacterial population. Norfloxacin is a poorly absorbed quinolone that selectively inhibits the gram-negative flora without affecting the anaerobic population. The presence of anaerobes is required to maintain the stability of the intestinal flora and to prevent overgrowth of problem organisms. SID by use of norfloxacin, 400 mg q.d., during hospitalization has proven useful in reducing the incidence of SBP as well as the incidence of extraperitoneal infections in patients with low-protein AF.

Gastrointestinal bleeding. Cirrhotic patients with gastrointestinal bleeding are at increased risk for developing SBP. Among those patients admitted to the hospital with gastrointestinal bleeding, 22% are already infected and 30% to 40% may develop infection during hospitalization. Norfloxacin has been shown to be valuable in reducing bacterial translocation due to gram-negative bacteria in cirrhotic rats exposed to hemorrhagic shock. Results of a randomized trial demonstrate that norfloxacin, 400 mg orally b.i.d. for 7 days, significantly reduced the incidence of infectious episodes caused by gram-negative bacteria in cirrhotic patients with gastrointestinal bleeding. Other therapeutic alternatives have been considered, such as amoxicillin/clavulanic acid, trimethoprim-sulfamethoxazole, and parenteral antibiotics.

Survivors of a previous episode of SBP. Results of a randomized trial demonstrate that the administration of oral norfloxacin, 400 mg per day, to survivors of a previous episode of SBP significantly reduced the rate of recurrence from 68% to 20%.

Adverse Effects of SID

The development of quinolone-resistant strains of gram-negative bacteria has been observed in patients receiving norfloxacin for primary or secondary prophylaxis; however, the clinical consequences remain to be determined. In a recent study, 9 of 10 patients who had undergone continuous SID for 43 weeks developed bacterial infections due to quinolone-resistant bacteria. Shorter periods of SID, however, do not appear to be associated with this problem. Therefore, long-term SID must be used with caution. Fortunately, no cross-resistance has been observed between cefotaxime and the quinolones. Therefore, the clinical outcome of bacterial infections caused by quinolone-resistant bacteria that are treated with cefotaxime is similar to that of infections that are caused by susceptible bacteria. Another advantage of SID is that it has been reported to reduce health care costs, in part, by preventing the need for hospitalizations for treatment of SBP.

Prognosis

During the early 1970s, the mortality associated with hospitalization for SBP reached 80% to 90%. Since that time, the widespread use of paracentesis; the higher index of suspicion of infection; and the clarification of diagnostic criteria, together with use of better and safer antibiotics, has significantly improved the short-term prognosis of these patients. Currently, there are essentially no deaths as a result of this infection, provided it is detected and treated before the development of shock or renal failure. Unfortunately, the long-term prognosis remains extremely poor among survivors of an episode of SBP, a manifestation of severe impairment of liver function. Probabilities of survival of 1 and 2 years are in the range of 30% and 20%, respectively. Therefore, liver transplantation should be considered for patients who survive an episode of SBP.

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