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Spontaneous bacterial peritonitis: Recent data on incidence and treatment

■ ABSTRACT

Recent studies have shown that spontaneous bacterial peritonitis (SBP) is more common than previously thought among patients admitted to the hospital with cirrhotic ascites. Other recent studies have clarified which antibiotic regimens are most successful for treatment and prevention, often shortening the duration of treatment. Still, the prognosis is poor and recurrence of SBP is common.

■ KEY POINTS

More than 92% of all cases are monomicrobial. Aerobic gram-negative bacilli (*Escherichia coli*, *Klebsiella* sp) are responsible for more than two thirds of all cases.

The diagnosis is based on testing of the ascitic fluid obtained by paracentesis. A polymorphonuclear cell count of more than 250 cells/mm³ of ascitic fluid is considered diagnostic and warrants immediate antibiotic treatment.

Several studies have since confirmed the effectiveness of cefotaxime in patients with SBP. A short course of cefotaxime is often as effective as a long course in these patients. Treatment with albumin, in addition to antibiotics, has been shown to improve survival.

Antibiotic prophylaxis to prevent a recurrence of SBP is recommended in selected patients, but with caution so as not to promote the development of resistance.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

CIRRHOTIC PATIENTS WITH ASCITES are particularly susceptible to spontaneous bacterial peritonitis (SBP) due to altered gut permeability, suppression of the reticuloendothelial system, and bacterial overgrowth. When SBP is discovered, something must be done quickly. Even then, the long-term outlook is not good, and recurrence is common.

An increased willingness to perform paracentesis to confirm SBP has led to the detection of more cases, and clinical trials have added to our knowledge of how to prevent or minimize recurrences. We present an overview of the diagnosis, treatment, and prevention of SBP.

■ WHAT IS SBP?

In 1971, Conn and Fessel described a syndrome of infected ascitic fluid in patients with hepatic cirrhosis, which they named SBP.[1] SBP is by definition an infection of previously sterile ascitic fluid, without any apparent intra-abdominal source of infection.[2] The infecting organisms are usually those found among the normal intestinal flora.

■ HOW DOES SBP DEVELOP?

The pathophysiology of SBP is not completely understood, but evidence suggests that bacteria translocate from the intestinal lumen to the systemic circulation, causing bacteremia and subsequent colonization of the ascitic fluid (**FIGURE 1**).[3–6] Bacteremia from the urine or the respiratory tract can also lead to infection of the ascitic fluid and SBP, and SBP may also be iatrogenic,[7–9] such as after endoscopic treatment of esophageal or gastric varices.

Proposed pathophysiology of SBP

Enteric bacteria

Altered gut permeability
Bacterial overgrowth
Bacterial translocation

Other sources
(skin, urine, respiratory tract)

Portal vein
Mesenteric lymph nodes

Reticuloendothelial system
depression

Systemic circulation

Leukocyte dysfunction

Bacteremia

Bacterial infection of ascitic fluid

Altered ascitic fluid defenses

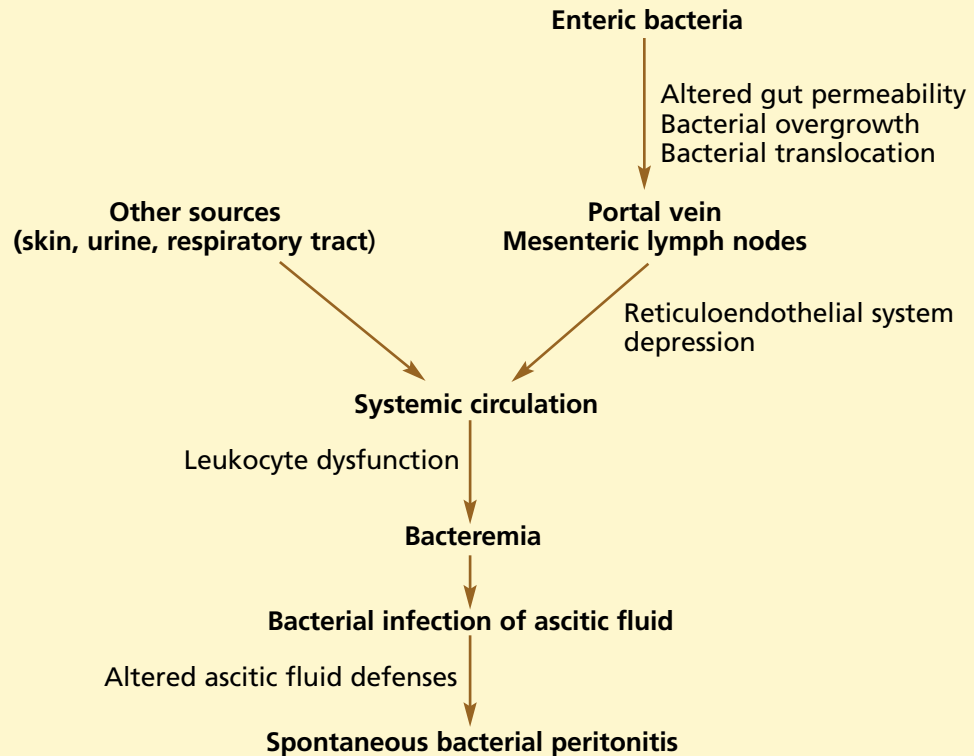**Spontaneous bacterial peritonitis**

FIGURE 1. Altered gut permeability and bacterial overgrowth in cirrhotic patients lead to translocation of intestinal bacteria to the systemic circulation and bacteremia. Seeding of bacteria to the ascitic fluid leads to spontaneous bacterial peritonitis. Leukocyte dysfunction and decreased ascitic fluid defense mechanisms facilitate this process. Reprinted from reference 2, with permission from Elsevier.

Even with intensive treatment, in-hospital mortality is 10% to 30%

■ A PREVALENT AND DEADLY DISEASE

Studies from the 1970s reported that the prevalence of SBP was 5% to 10% in cirrhotic patients with ascites.[10–12] Recent studies using newer diagnostic criteria and improved culture techniques have estimated a prevalence of 10% to 30% in cirrhotic patients with ascites admitted to hospitals.[6,13,14]

Factors contributing to mortality
SBP is deadly. In reports from the 1970s, the mortality rate exceeded 90%.[15,16] Today, even with intensive treatment, the in-hospital mortality is still between 10% and 30%.[17] Factors associated with poor outcome include several indicators of poor liver function: eg, the development of renal failure, hepatic encephalopathy, high levels of serum bilirubin, and upper gastrointestinal bleeding.[18–20]

The development of renal impairment after the diagnosis of SBP is probably the strongest independent predictor of death. In a study by Follo et al,[21] in 252 consecutive episodes of SBP, the mortality rate was 100% when associated with progressive renal impairment, 31% when associated with steady renal impairment, and only 7% in those without renal impairment.[21]

■ MANAGEMENT

Presentation depends on stage
The clinical presentation of SBP depends on the stage at which the infection is diagnosed.[2] In the early stages, most patients are asymptomatic. As the disease progresses, patients show signs and symptoms of peritoneal infection.

Fever is the most common presenting symptom and is present in as many as two thirds of patients at the time of diagnosis. Approximately half of patients present with abdominal pain or altered mental status, and about one third present with diarrhea or paralytic ileus. Hypotension or hypothermia is found in fewer than 20% of patients.[22]

Because the presentation depends on the stage of the disease, and because the signs and symptoms are nonspecific, the diagnosis relies on laboratory and microbiological tests. Currently, paracentesis with laboratory testing of the ascitic fluid is the only way to confirm or rule out SBP in patients with cirrhosis. **Diagnostic paracentesis** should therefore be performed in:

• Any patient with new-onset ascites, including patients with congestive heart failure or Budd-Chiari syndrome
• Any cirrhotic patient with ascites who develops symptoms such as unexplained encephalopathy or renal failure
• Any patient with stable cirrhosis and ascites whose condition deteriorates suddenly.[17,23]

If SBP is suspected in a patient with clinically undetectable ascites, ultrasonography is indicated to identify the ascites and to perform guided paracentesis.

Cell counts in ascitic fluid

A polymorphonuclear cell count of more than $250/mm^3$ in ascitic fluid is currently considered diagnostic of SBP and warrants the prompt start of antibiotic treatment.[24] In patients with hemorrhagic ascites or in those with traumatic paracentesis, an adjustment of the cell count should be made to account for the presence of blood in the ascitic fluid. This is done by subtracting one polymorphonuclear cell for every 250 red blood cells in the ascitic fluid.[24] For instance, if the red blood cell count in the ascitic fluid is $50,000/mm^3$ and the polymorphonuclear cell count is $350/mm^3$, the adjusted polymorphonuclear cell count will be $150/mm^3$.

Culturing ascitic fluid

The ascitic fluid obtained from paracentesis should also be sent for Gram-staining and culture. Studies have shown that bedside inocu-lation of the ascitic fluid into blood culture bottles significantly increases the detection rate for the responsible microorganism.[25–27] Compared with conventional culturing techniques, bedside inoculation also provides quicker identification of the culprit organisms.[25] Optimal sensitivity is achieved when at least 10 mL of ascitic fluid is inoculated into the blood culture bottles.[25] The sensitivity of this culture technique decreases sharply when lower volumes of ascitic fluid are used.

In patients with SBP, studies based on quantitative cultures of ascitic fluid have shown a median bacterial concentration of one organism (one bacterium) per milliliter of ascitic fluid.[25] This low concentration explains the low sensitivity of conventional culture techniques for detection of the responsible microorganism, and it explains the low sensitivity of Gram-staining for SBP (approximately 10%).

Bacteria isolated from the ascitic fluid in patients with SBP are usually those of the normal intestinal flora. More than 92% of all cases of SBP are monomicrobial, with aerobic gram-negative bacilli being responsible for more than two thirds of all cases. *Escherichia coli* accounts for nearly half of these cases, followed by *Klebsiella* species and other gram-negative bacteria. Almost 25% of cases are caused by gram-positive organisms, with streptococcal species being the most common.

SBP is only rarely caused by anaerobic organisms or by more than one type of bacteria, so their presence in ascitic fluid should raise suspicion of bacterial peritonitis due to some other cause.[23] In these cases, evaluation for perforation of the gut or other hollow organs is indicated. Imaging with upright abdominal radiography, abdominal computed tomography, or water-soluble gut contrast studies may help in determining the diagnosis. In some of these cases, surgical intervention may be necessary and life-saving.

■ TREATMENT

Starting empiric antibiotic therapy immediately improves survival in SBP,[28] although the mortality rate is still about 10% to 30%, and those who survive are at high risk of a recurrence.[23] Empiric antibiotic treatment[24] should

The only way to confirm SBP is by paracentesis with lab testing

TABLE 1

Options for empiric antibiotic therapy of SBP

DRUG	DOSE*	ROUTE	DURATION	STUDY
Cefotaxime	2 g every 12 hours	Intravenous (IV)	5 days	29,30
Ceftriaxone	2 g every 24 hours	IV	5 days	31–34
Amoxicillin plus clavulanic acid	1 g/0.2 g every 6–8 hours; 500 mg/125 mg every 8 hours	IV; oral	2 days; 6–12 days	37,38
Ofloxacin†	400 mg every 12 hours	Oral	8 days	39

*Dose may need to be adjusted according to renal function
†Only in patients without complications (ie, sepsis, ileus, gastrointestinal bleeding, encephalopathy, or serum creatinine concentration > 3 mg/dL) who have not received a quinolone prophylactically.

be started once the polymorphonuclear cell count in ascitic fluid exceeds 250/mm³.

Since gram-negative aerobic Enterobacteriaceae and non-enterococcal streptococci are the most common organisms to cause SBP, initial empiric antibiotic therapy should cover these bacteria. It should also achieve high concentrations in ascitic fluid.

Antibiotic regimens in evolution

Initially, the regimen most often used to treat SBP was a beta-lactam such as ampicillin or cephalotin, and an aminoglycoside such as gentamycin or tobramycin. However, in the first randomized comparative study of two different regimens for SBP, cefotaxime was superior to ampicillin plus tobramycin for resolving SBP.[29] In that study, ampicillin plus tobramycin was also associated with nephrotoxicity or superinfections in approximately 10% of patients. Several studies have since confirmed the effectiveness of cefotaxime in patients with SBP.

Duration of therapy

Ten to 14 days of intravenous (IV) antibiotics used to be the standard treatment. A study by Runyon and colleagues,[30] however, showed no difference in rates of infection or hospital-related mortality, bacteriologic cure, or recurrence of infection in cirrhotic patients with SBP treated for 10 days vs those treated for 5 days with IV cefotaxime.[30] A short course of cefotaxime is therefore as effective as a long course in these patients.

Other IV antibiotic regimens shown to be as effective as cefotaxime in these patients are ceftriaxone, ceftizoxime, ceftazidime, and the combination of amoxicillin plus clavulanic acid.[31–38] Dosages are shown in **TABLE 1**.[29–34,37–39]

Route of administration

Although IV therapy for SBP has been the standard, a trial investigating the effectiveness of oral ofloxacin found it to be as effective as IV cefotaxime in cirrhotic patients with SBP.[39] All patients enrolled in this randomized trial had uncomplicated SBP (exclusion criteria included shock, ileus, gastrointestinal hemorrhage, profound hepatic encephalopathy, or serum creatinine concentration > 3mg/dL). This regimen can therefore be used in patients with uncomplicated SBP who are in relatively good clinical condition.

Patients receiving quinolone to prevent SBP

Currently, in patients taking quinolones to prevent a second episode of SBP, the infection is commonly caused by gram-positive cocci or quinolone-resistant gram-negative bacilli.[40,41] Oral treatment with ofloxacin, which is a quinolone antibiotic, should therefore be avoided in such patients. IV cefotaxime or ceftriaxone is an effective alternative.[41,42]

Assessing treatment response

Paracentesis should be repeated after at least 2 days of antibiotic therapy to assess the response to treatment.[18,24,43] A decrease in the polymorphonuclear cell count of less than 25% of the

In less severe SBP, oral ofloxacin was as effective as IV cefotaxime

pre-treatment value indicates failure of antibiotic treatment.[24] In these cases, antibiotic therapy should be modified on the basis of bacterial susceptibility (in culture-positive SBP) or empirically (in culture-negative cases). These patients also require evaluation regarding the possibility of secondary peritonitis.

Other treatments

In addition to antibiotics, treatment with albumin has been associated with improved survival in cirrhotic patients with SBP in a randomized trial.[44] This trial demonstrated that, in patients with SBP, treatment with IV albumin plus an antibiotic reduces the incidence of renal impairment (defined as more than a 50% increase from baseline in blood urea nitrogen or creatinine) and in-hospital mortality. In this study, 126 patients with SBP were randomly assigned to treatment with cefotaxime alone or cefotaxime plus IV albumin, given at a dose of 1.5 g per kilogram of body weight during the first 6 hours after randomization, with the infusion repeated at a dose of 1 g/kg 3 days later. Renal impairment developed in 33% of patients receiving cefotaxime, but in only 10% of those receiving cefotaxime plus albumin. The in-hospital death rates were 28% and 6%, respectively, and at 3 months the death rates were 41% and 22%, respectively.

Although the above findings need to be confirmed in additional controlled studies, based on the available data, it is appropriate to give IV albumin as part of the treatment of SBP because of the proven survival advantage.

■ PROPHYLAXIS

As SBP is associated with high rates of illness and death in cirrhotic patients, it seems reasonable to consider measures to prevent it. Since aerobic gram-negative bacteria of intestinal origin are the most frequent cause of SBP,[45–47] selective intestinal decontamination has been suggested as a way to prevent it by inhibiting gram-negative flora of the gut while preserving the remaining flora, especially anaerobic bacteria.[47] Preserving the anaerobic bacteria is important in maintaining resistance against intestinal colonization,

overgrowth, and extraintestinal spread of pathogenic bacteria.[45] However, antibiotics should be used judiciously for this purpose, so as not to encourage the development of resistant strains.

Three specific groups of cirrhotic patients known to benefit from SBP prophylaxis include:
- Those with gastrointestinal bleeding
- Those with ascites who are recovering from a prior episode of SBP
- Those with an ascitic albumin concentration of less than 1 g/dL.

Cirrhotic patients with gastrointestinal bleeding

Bacterial infections are common in cirrhotic patients with gastrointestinal bleeding. Up to 20% of cirrhotic patients with bleeding have a bacterial infection upon hospital admission, and another 50% develop a bacterial infection while hospitalized, compared with 5% to 7% in the general hospital population.[46–48] Furthermore, bacterial infections are associated with fivefold to sixfold increased in-hospital death rates for these patients.[45,49]

Factors contributing to infection. Gastrointestinal bleeding favors the development of bacterial infections by several potential mechanisms, including an increase in bacterial translocation and an alteration of intestinal permeability.[45,50] A retrospective evaluation of risk factors for infections in patients with cirrhosis and gastrointestinal bleeding[48] showed a strong association with bacterial infections such as sepsis and SBP. These results were replicated in a prospective study showing that gastrointestinal bleeding was by far the most common risk factor for the development of bacterial infections among cirrhotic patients.[46]

Studies in portal hypertensive rats have shown that hemorrhagic shock is followed by increased bacterial translocation to mesenteric lymph nodes due to changed permeability of the intestinal mucosa. In this respect, gastrointestinal bleeding with shock is more likely to lead to SBP than gastrointestinal bleeding without shock.[51–53] However, cirrhotic patients with gastrointestinal bleeding without shock are still at higher risk for SBP than cirrhotic patients without gastrointesti-

Prophylaxis is advised in those with GI bleeding, a prior episode of SBP, or low ascitic albumin

TABLE 2

Recommended antibiotic regimens for the prevention of SBP

DRUG	DOSING	DURATION
In cirrhotic patients with gastrointestinal bleeding, with or without ascites		
Norfloxacin	400 mg orally every 12 hours	7 days
In cirrhotic patients with ascites and prior SBP		
Norfloxacin	400 mg orally every 24 hours	All three regimens should be given
Ciprofloxacin	750 mg orally every week	indefinitely, or until transplantation
Trimethoprim/ sulfamethoxazole	160/800 mg (one DS tablet) daily, 5 days a week	or resolution of ascites
In cirrhotic patients with an ascitic albumin concentration below 1 g/dL		
Norfloxacin	400 mg orally every 24 hours	All three regimens should be given
Ciprofloxacin	750 mg orally every week	only during hospitalization
Trimethoprim/ sulfamethoxazole	160/800 mg (one DS tablet) daily, 5 days a week	

nal bleeding. This has been attributed to temporary impairment in reticuloendothelial system function, to breach of the mucous membranes that usually function as barriers to bacterial entrance to the body, and also to endoscopic procedures in bleeding patients.[54,55]

Recommended treatment. In cirrhotic patients admitted for gastrointestinal bleeding, regardless of whether they have ascites, a 7-day course of an antibiotic such as norfloxacin is shown to improve survival and is thus recommended[24] (**TABLE 2**). In patients who cannot take oral antibiotics, IV antibiotics such as ciprofloxacin can be given.

Cirrhotic patients with ascites and prior episode of SBP
In patients who have recovered from an episode of SBP, recurrence of SBP is common, estimated to be 43% at 6 months and 69% at 1 year.[56]

Decreasing the risk of recurrence. Selective intestinal decontamination, by elimination of gram-negative bacilli from the intestinal flora, has been shown to decrease the risk of a recurrence of SBP. In a double-blind, placebo-controlled study of oral norfloxacin 400 mg/day,[57] the overall probability of recurrence was 20% in the norfloxacin group vs 68% in the placebo group (P = .0063). Even more significant, the chance of a recurrence caused by gram-negative organisms

Recurrence is common: 43% at 6 months, 69% at 1 year

was 3% in the norfloxacin group vs 60% in the placebo group (P = .0013).

Preventive therapy recommended. Patients who have recovered from one or more episodes of SBP should receive long-term prophylaxis with antibiotics.[17,24] Antibiotic prophylaxis should continue until the disappearance of ascites, or until transplantation (**TABLE 2**).

Cirrhotic patients with low-protein ascitic fluid
A low concentration of ascitic fluid protein is associated with an increased risk of SBP in cirrhotic patients with ascites.[58–60] A study of 127 cirrhotic patients with ascites[58] found five variables associated with an increased risk of SBP, but only an ascitic fluid protein concentration less than 1 g/dL showed an independent predictive value. Two later studies[59,60] also showed this association.

The endogenous antimicrobial activity (opsonic activity) of human ascitic fluid has been shown to correlate directly with the protein concentration of the ascitic fluid,[61] and patients with deficient opsonic activity in the ascitic fluid have been shown to be predisposed to SBP.[62]

Recommended treatment. Prolonged use of oral antibiotics leads to selection of resistant organisms in the gut flora. Therefore, only hospitalized patients with low-protein

ascites (ascitic fluid albumin concentration of less than 1g/dL) should undergo prophylactic antibiotic therapy, and therapy should be discontinued at the time of discharge. A randomized trial[63] indicated that this strategy may be the best compromise for preventing ascitic fluid infection without selecting resistant organisms.[64]

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