Recognition and Management of Spontaneous Bacterial Peritonitis

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Module 3: Management of Cirrhosis-Related Complications
Lesson 2: Recognition and Management of Spontaneous Bacterial Peritonitis

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Background

Among persons with ascites who have been followed for a year, spontaneous bacterial peritonitis (SBP) develops in approximately 10 to 30% and has an estimated in-hospital mortality rate of 20%.\[1,2,3\] The prevalence of SBP in outpatients with cirrhosis is 1.5 to 3.5% compared to 10% among inpatients with cirrhosis. In most instances, SBP results from translocation of bacteria from the intestinal lumen.\[4,5,6\] Less often, SBP results from bacteremia that originates at a distant site, such as a urinary tract infection. The majority of cases of SBP are caused by gram-negative enteric organisms, such as *Escherichia coli* and *Klebsiella pneumoniae*, but in recent years the proportion of SBP caused by gram-positive cocci, such as *Streptococcus pneumoniae*, *Staphylococcus* species, and *Enterococcus* species, has increased significantly.\[1,7,8\] Risk factors associated with the development of SBP include cirrhosis, ascitic fluid total protein less than 1 g/dL, total serum bilirubin greater than 2.5 mg/dL, variceal hemorrhage, and a previous episode of SBP.\[9,10,11,12\] The use of proton pump inhibitors may slightly increase the risk of developing SBP in persons with cirrhosis and ascites; therefore, in this setting, proton pump inhibitors should be prescribed only in persons who have a clear indication.\[13\]
Diagnosis of Spontaneous Bacterial Peritonitis

Indications for Testing

In a person with ascites, the presence of new-onset fever (temperature greater than 37.8°C or 100°F), abdominal pain, hepatic encephalopathy, metabolic acidosis, renal failure, hypotension, diarrhea, paralytic ileus, hypothermia, leukocytosis, or other signs or symptoms of infection should prompt a diagnostic paracentesis for ascitic fluid analysis and culture. Approximately 13% of individuals with SBP present without any symptoms. For persons with cirrhosis and ascites who are admitted to the hospital, approximately 10 to 15% have evidence of SBP. Thus, all persons with cirrhosis and ascites should undergo a diagnostic paracentesis at the time of hospital admission. In addition, paracentesis should be repeated in persons who develop signs or symptoms of infection. There is no need for transfusion of plasma or platelets prior to a diagnostic paracentesis, given the extremely low risk of hemorrhagic complications, except in the setting of disseminated intravascular coagulation or clinically apparent fibrinolysis.

Diagnostic Criteria and Classification of SBP

Spontaneous bacterial peritonitis refers to infection of the ascitic fluid, as evidenced by an ascitic fluid absolute polymorphonuclear leukocyte (PMN) count of at least 250 cells/mm$^3$ (0.25 x 10$^9$/L), with or without a positive ascitic fluid culture, in the absence of an intra-abdominal surgically treatable source of infection. Culture-negative neutrocytic ascites refers to individuals who have an ascitic fluid PMN count of at least 250 cells/mm$^3$ (0.25 x 10$^9$/L) in combination with a negative bacterial culture—in the absence of another explanation for an elevated PMN count (e.g. pancreatitis, peritoneal carcinomatosis, or peritoneal tuberculosis) or recent receipt of antimicrobial therapy. Obtaining ascitic fluid for diagnostic testing should be performed before treatment is initiated as even a single dose of broad-spectrum antibiotics can lead to no growth on bacterial culture in 86% of cases. Approximately 1 mL of ascitic fluid should be injected directly into a purple-top EDTA tube for the cell count and differential analysis. In the case of a traumatic paracentesis, with the entry of blood into the ascitic fluid (typically ascitic red cells greater than 10,000 cells/mm$^3$) the PMN count should be corrected by subtracting one PMN from the absolute PMN count for every 250 red cells/mm$^3$.

Bacterial Culture

Prior to administering antibiotics, ascitic fluid (at least 10 mL) should be obtained and then directly inoculated into a blood culture bottle at the bedside, instead of sending the fluid to the laboratory in a syringe or container, since immediate inoculation improves the yield on bacterial culture from approximately 65 to 90%, when the ascitic fluid cell count is at least 250 cells/mm$^3$ (0.25 x 10$^9$/L). Separate and simultaneous blood cultures should also be obtained, as up to 50% of patients with SBP have concomitant bacteremia.

Distinguishing Spontaneous from Secondary Bacterial Peritonitis

Secondary peritonitis refers to infection of the ascitic fluid caused by an intraabdominal surgically treatable source and can present similar to SBP. It is important to distinguish SBP from secondary bacterial peritonitis because of the critical need to determine whether surgical intervention is needed. Specifically, mortality approaches 100% in patients with secondary bacterial peritonitis who receive treatment with antibiotics alone (without surgery); mortality is approximately 80% in persons with cirrhosis and SBP who undergo an unnecessary exploratory laparotomy. Diagnostic tests may help distinguish SBP from secondary bacterial peritonitis due to a perforated viscus or a loculated abscess. Characteristically, with secondary bacterial peritonitis, the fluid PMN count is at least 250 cells/mm$^3$ (usually greater than several thousand) and multiple organisms, including fungi, are identified on Gram’s stain and isolated in culture. Laboratory diagnostic criteria for secondary bacterial peritonitis includes at least two of the following: ascitic fluid protein greater than 1 g/dL, lactate dehydrogenase higher than the upper limit of normal for serum, or glucose less than 50 mg/dL. In addition, ascitic fluid carcinoembryonic antigen greater than 5 ng/mL and
alkaline phosphatase greater than 240 U/L have been shown to be associated with gut perforation. After 48 hours of appropriate antibiotic therapy, the ascitic fluid PMN count should decrease with SBP (typically below the pretreatment level), but with secondary bacterial peritonitis the PMN count may increase. In addition, persistent signs and symptoms despite appropriate therapy for SBP should prompt an evaluation for secondary bacterial peritonitis. Individuals who meet criteria for secondary bacterial peritonitis—or in whom there is a high suspicion for secondary bacterial peritonitis—should undergo immediate abdominal imaging, and emergent laparotomy should be considered if perforation or a surgically treatable site of infection is identified or strongly suspected.

**Other Diagnostic Tests on Ascitic Fluid**

For an initial diagnostic paracentesis, other tests should be performed as clinically warranted on the remaining ascitic fluid. These tests can be submitted to the laboratory using a red top tube and may include albumin, total protein, glucose, lactate dehydrogenase, amylase, and bilirubin. A serum-ascites albumin gradient (SAAG) of 1.1 g/dL or greater is consistent with portal hypertension. A total protein level of less than 1.0 g/dL is associated with an increased risk of spontaneous bacterial peritonitis. Elevated total protein, low glucose concentration, and elevated lactate dehydrogenase ascitic values are seen in the setting of secondary bacterial peritonitis. Elevated ascitic amylase can occur in persons who have pancreatitis and in those with gut perforation. Biliary leakage into the peritoneum can be associated with increased ascitic fluid bilirubin concentration. For persons with a prior paracentesis, especially a recent paracentesis, most of these additional diagnostic tests will not need repeating.
Treatment of Spontaneous Bacterial Peritonitis

Criteria for Treatment

Individuals with suspected spontaneous bacterial peritonitis (SBP) and ascitic fluid PMN greater than or equal to 250 cells/mm$^3$ (0.25 × 10$^9$/L) should promptly receive empiric antibiotic therapy. Further, persons with culture-negative neutrocytic ascites have similar mortality rates as patients with culture-positive spontaneous bacterial peritonitis and benefit from antibiotic treatment, which should not be delayed while awaiting bacterial culture results (Figure 2).[14,18] Antimicrobial therapy should be given as soon as ascitic fluid has been obtained for culture and should not be delayed while awaiting culture results.

Empiric Therapy

An asymptomatic patient with bacterascites (normal ascitic PMN count defined as less than 250 cells/mm$^3$ and positive ascitic fluid culture) does not require immediate antibiotic treatment since bacterascites may represent transient colonization. In this situation, when the culture growth is discovered, the person should undergo a follow-up paracentesis after 48 hours (or if they develop symptoms) to repeat the cell count and culture results to ensure that bacterascites has not progressed to true SBP. Any cirrhotic patient with a positive ascitic fluid culture who has concerning signs or symptoms that may indicate infection, such as fever (temperature greater than 37.8°C or 100°F), abdominal pain, or unexplained hepatic encephalopathy, should receive empiric antibiotic treatment for spontaneous bacterial peritonitis, regardless of ascitic fluid PMN count.

Treatment Regimens

Broad-spectrum antibiotic therapy is recommended for treatment of proven or suspected SBP and may be narrowed when susceptibility results become available.[1,14] Studies have demonstrated resistance rates of approximately 30% in gram-negative infections to fluoroquinolones and trimethoprim-sulfamethoxazole, with particularly high rates in patients who have received fluoroquinolone prophylaxis; on the other hand, more than 90% of isolates in persons who have received fluoroquinolone prophylaxis still remain susceptible to cefotaxime. Extended-spectrum antibiotics, such as carbapenems, may even be considered in nosocomial cases. The choice of treatment will depend on location of acquisition (community versus nosocomial), local resistance patterns, and culture sensitivity results when available. The following summarizes recommended and commonly used antimicrobial regimens to treat SBP (Figure 3).[14]

- **Cefotaxime**: Intravenous cefotaxime administered 2 grams every 8 hours (or similar third-generation cephalosporin) for a total course of 5 days is the treatment of choice for SBP, as it covers the most common causative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*. Cefotaxime has been shown to be successful in treating SBP in 77 to 98% of cases.[26,27,28,29]
- **Ceftriaxone**: Intravenous ceftriaxone 1 gram every 12 hours or 2 grams every 24 hours for 5 days can be used in place of cefotaxime.[30,31,32,33]
- **Ciprofloxacin**: In a randomized trial involving patients who did not receive a fluoroquinolone for SBP prophylaxis, intravenous ciprofloxacin 200 mg every 12 hours for 2 days, followed by oral ciprofloxacin (500 mg PO every 12 hours for 5 days) was effective and more cost-effective than intravenous ceftazidime. [34] Fluoroquinolones should not be used to treat SBP in patients taking a fluoroquinolone for SBP prophylaxis.
- **Ofloxacin**: Oral ofloxacin 400 mg orally twice a day for an average of 8 days was shown in one randomized, controlled trial to be as effective as intravenous cefotaxime for hospitalized patients with SBP who do not have vomiting, shock, grade II or greater hepatic encephalopathy, or serum creatinine greater than 3 mg/dL.[28] Fluoroquinolones should not be used to treat SBP in patients taking a fluoroquinolone for SBP prophylaxis.
- **Beta-Lactam Hypersensitivity**: Intravenous ciprofloxacin 400 mg every 12 hours or intravenous...
levofloxacin 750 mg every 24 hours can be used in patients who have a beta-lactam allergy, but should be avoided in patients who have been receiving a fluoroquinolone for SBP prophylaxis.\[^{35}\]

**Adjunctive Intravenous Albumin**

In a randomized, controlled study involving cirrhotic patients with SBP, the use of intravenous albumin (1.5 g/kg given within 6 hours of enrollment and repeated as a 1.0 g/kg dose on day 3) as an adjunctive to cefotaxime was shown to decrease in-hospital mortality when compared with use of cefotaxime alone (29% versus 10%).\[^{36}\] In addition, those treated with albumin had a reduction in the development of renal impairment (10% versus 33%) (Figure 4). Intravenous albumin should be given for patients who have any of the following: a serum creatinine greater than 1 mg/dL, blood urea nitrogen greater than 30 mg/dL, or total bilirubin greater than 4 mg/dL.\[^{37}\]

**Follow-up Diagnostic Paracentesis**

Follow-up ascitic fluid analysis is not necessary following treatment of SBP, unless something is unusual about the patient’s symptoms, fluid analysis, organism, or clinical course (e.g. lack of clinical improvement).\[^{14}\] If the ascitic fluid PMN count has not declined by at least 25% after two days of antibiotic therapy, then the antibiotic coverage needs to be broadened to cover resistant organisms and secondary bacterial peritonitis needs to be considered. Patients with secondary bacterial peritonitis should undergo surgical intervention of the perforated vixcus or drainage of the abscess and should be treated with broad-spectrum antibiotics, such as third-generation cephalosporins, with the addition of an antimicrobial agent that has good anaerobic coverage, such as metronidazole.
Indications for Spontaneous Bacterial Peritonitis Prophylaxis

Most episodes of SBP are thought to result from bacterial translocation from the gut.\textsuperscript{4,5,6} Given the risk of resistance and alteration of gut flora, this long-term antibiotic prophylaxis should be reserved for high-risk patients only. Identified risk factors for the development of SBP include ascitic fluid total protein less than 1 g/dL, gastrointestinal hemorrhage, and a previous history of SBP.

Secondary Prophylaxis of Spontaneous Bacterial Peritonitis

After a primary episode of SBP, the recurrence rate at one year is approximately 70%, with a 1-year overall survival rate of 30 to 50% in patients who do not receive antibiotic prophylaxis. Secondary antibiotic prophylaxis in a cirrhotic patient with a prior history of SBP reduces the risk of SBP recurrence from 68% to 20%. Accordingly, most experts recommend daily long-term antimicrobial prophylaxis for patients with a history of one or more episodes of SBP (Figure 5).\textsuperscript{14}

Primary Prophylaxis of Spontaneous Bacterial Peritonitis

Cirrhotic patients with low-protein ascites (less than 1.0 g/dL) and either impaired renal or liver function are at increased risk of developing SBP.\textsuperscript{14} Although controversy exists regarding the use of prophylactic antibiotics in patients who have never had SBP (primary prophylaxis), in one randomized trial, daily oral norfloxacin in patients with more advanced liver disease prevented the development of spontaneous bacterial peritonitis and hepatorenal syndrome and improved survival at 3 months when compared with those who received placebo.\textsuperscript{38} The American Association for the Study of Liver Diseases (AASLD) guidelines suggest using long-term antibiotic prophylaxis in patients who have ascitic fluid total protein less than 1.5 g/dL and at least one of the following: impaired renal function (serum creatinine greater than or equal to 1.2 mg/dL, blood urea nitrogen greater than or equal to 25 mg/dL, or serum sodium less than or equal to 130 mEq/L), or liver failure (Child-Turcotte-Pugh greater than or equal to 9 points and total bilirubin greater than or equal to 3 mg/dL).\textsuperscript{14}

Gastrointestinal Hemorrhage

Between 25% and 65% of cirrhotic patients with gastrointestinal bleeding develop bacterial infection, including spontaneous bacterial peritonitis.\textsuperscript{39} Antibiotic prophylaxis in this setting has been shown to decrease the risk of bacterial infections, the risk of re-bleeding, and overall mortality. In one meta-analysis of five trials, antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding demonstrated a 9% increase in survival.\textsuperscript{40} Indeed, the use of prophylactic antibiotics in this setting is thought to have contributed significantly to the reduced mortality in patients with variceal bleeding (from 43% to 15%) over the past two decades.\textsuperscript{41} In this situation, the AASLD guidelines recommend using a 7-day course of prophylactic antimicrobials.\textsuperscript{14}
Regimens for Spontaneous Bacterial Peritonitis Prophylaxis

Primary and Secondary Spontaneous Bacterial Peritonitis Prophylaxis

Several studies have shown that oral norfloxacin 400 mg daily prevents SBP in persons with low-protein ascites and those with previous history of SBP. Alternative regimens that have been studied include oral double-strength trimethoprim-sulfamethoxazole 5 doses per week or oral ciprofloxacin 750 mg once a week. Prolonged use antibiotic prophylaxis in this setting has led to the development of gram-negative bacterial resistance (to fluoroquinolones and trimethoprim-sulfamethoxazole), as well as an increased likelihood of developing gram-positive infections. Therefore, prophylaxis should be reserved for patients at high risk of developing SBP and daily dosing regimens are preferred. Daily long-term dosing with norfloxacin has proved superior to hospital-only administration of norfloxacin in the prevention of the first episode of SBP in persons with cirrhosis who have a serum total bilirubin greater than 2.5 mg/dL or ascitic fluid protein less than or equal to 1.5 g/dL. The preferred prophylaxis regimen is norfloxacin 400 mg daily; since norfloxacin is no longer available in the United States, most experts recommend substituting ciprofloxacin for norfloxacin. If norfloxacin cannot be used, reasonable alternatives include trimethoprim-sulfamethoxazole one double-strength tablet daily, ciprofloxacin 500 mg PO daily, or levofloxacin 250 mg PO daily (Figure 6).

Infection Prophylaxis after Gastrointestinal Hemorrhage

Oral norfloxacin 400 mg twice daily for 7 days has been shown to prevent infection in persons with cirrhosis following gastrointestinal hemorrhage. In addition, intravenous ceftriaxone 1 gram daily for 7 days was shown to be superior to norfloxacin for SBP prophylaxis in a randomized trial that enrolled patients with gastrointestinal hemorrhage and advanced cirrhosis, as defined by two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin greater than 3 mg/dL. In persons with cirrhosis and gastrointestinal hemorrhage, the AASLD guidelines recommend using a 7-day course of prophylactic antimicrobials with either intravenous ceftriaxone 1 g daily or norfloxacin 400 mg twice daily. Since oral antimicrobial therapy is not generally used in persons with active acute gastrointestinal hemorrhage, the AASLD guidelines suggest initiating therapy with intravenous ceftriaxone, with the option to switch to oral therapy once bleeding stops and the person has resumed oral intake. Since norfloxacin is no longer available in the United States, many experts substitute oral ciprofloxacin 500 mg twice daily for oral norfloxacin 400 mg twice daily in this setting. If intravenous ceftriaxone cannot be used due to a severe beta-lactam allergy, intravenous ciprofloxacin 400 mg every 12 hours could be used as the initial prophylaxis regimen during active bleeding.
Summary Points

- New onset fever, abdominal pain, confusion, or other signs or symptoms of infection in a person with cirrhosis should prompt an evaluation of the ascitic fluid for SBP.

- Individuals with cirrhosis and ascites who are admitted to the hospital should undergo diagnostic paracentesis to evaluate for SBP, even in the absence of signs or symptoms of infection.

- For a diagnostic paracentesis, ascitic fluid should be sent for cell count and differential analysis and should be directly inoculated into blood culture bottles at the bedside.

- Individuals with ascitic fluid PMN count greater than or equal to 250 cells/mm$^3$ meet criteria for a presumptive diagnosis of SBP and should be treated with antibiotic therapy.

- Any person with cirrhosis and ascites who has signs or symptoms concerning for SBP should be treated with antibiotic therapy regardless of ascitic fluid PMN count.

- Recommended therapy for SBP consists of intravenous cefotaxime 2 grams every 8 to 12 hours (or a similar third-generation cephalosporin) for a minimal duration of 5 days.

- Antibiotic prophylaxis for SBP should be given to persons with cirrhosis with a prior history of either SBP or acute gastrointestinal bleeding, and should be considered in persons without history of SBP if the ascitic fluid total protein is less than 1.5 g/dL.

- Recommended regimens for primary and secondary SBP prophylaxis consist of oral ciprofloxacin 500 mg daily or trimethoprim-sulfamethoxazole one double-strength tablet daily. Daily dosing is preferred over intermittent dosing due to the increased risk of developing antimicrobial resistance with intermittent dosing.

- For persons with cirrhosis and acute gastrointestinal hemorrhage, intravenous ceftriaxone 1 gram daily is recommended for a total duration of 7 days. Alternatively, after control of bleeding and resumption of oral intake, the ceftriaxone can be transitioned to oral ciprofloxacin 500 mg twice daily to complete the 7-day course.
Citations


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Figures

Figure 1 Indications for Performing Diagnostic Paracentesis

**Figure 2 Approach to the Diagnosis and Treatment of Spontaneous Bacterial Peritonitis (SBP)**

This algorithm provides a general approach to the diagnosis and management of patients with possible spontaneous bacterial peritonitis. The clinician should suspect secondary bacterial peritonitis with any of the following: (1) the patient has an inadequate response to antibiotics, (2) more than one organism is isolated from culture, or (3) at least two of the following ascitic fluid values are present—protein greater than 1 g/dL, LDH greater than ULN serum levels, and glucose less than 50 mg/dL. If secondary bacterial peritonitis is suspected, appropriate imaging should be obtained, antibiotic coverage broadened to include anaerobes, and laparotomy considered.

Figure 3 Therapy for Spontaneous Bacterial Peritonitis

This figure is adapted from recommendations in the 2012 AASLD Guidelines on the Management of Adult Patients with Ascites Due to Cirrhosis; the AASLD guidelines include the use of norfloxacin, but this medication is no longer available in the United States.

Figure 4 Treatment with IV Albumin plus Cefotaxime in Patients with Spontaneous Bacterial Peritonitis

This graphic shows that the addition of albumin to cefotaxime clearly prevented renal impairment and improved mortality when compared with cefotaxime alone. P values: renal impairment p=0.002, in-hospital mortality p=0.01, 3 month mortality p=0.03

Figure 5 Indications for Spontaneous Bacterial Peritonitis (SBP) Prophylaxis

Figure 6 Prophylaxis for Spontaneous Bacterial Peritonitis (SBP)

This table is adapted from recommendations in the 2012 AASLD Guidelines on the Management of Adult Patients with Ascites Due to Cirrhosis; the AASLD guidelines include the use of norfloxacin, but this medication is no longer available in the United States.