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Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites

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Abstract:

Background: Spontaneous bacterial peritonitis (SBP) is a severe and life-threatening complication in patients with liver cirrhosis and ascites, resulting from spontaneous infection of ascitic fluid without an identifiable intra-abdominal source. It affects approximately 10–30% of hospitalized cirrhotic patients and is associated with significant morbidity and mortality. The pathogenesis is primarily related to bacterial translocation due to increased intestinal permeability, small intestinal bacterial overgrowth, and impaired immune defenses. Despite advances in diagnostic and therapeutic strategies, SBP remains a major clinical challenge, particularly in the era of rising antimicrobial resistance. Recent epidemiological shifts have demonstrated an increasing prevalence of Gram-positive and multidrug-resistant organisms, especially in nosocomial settings, which complicates empirical antibiotic selection. Clinical presentation may be subtle or atypical, emphasizing the importance of routine diagnostic paracentesis in all cirrhotic patients with ascites. Diagnosis is mainly based on an ascitic fluid polymorphonuclear leukocyte count ≥250 cells/mm³, regardless of culture results. Early initiation of appropriate antibiotic therapy and adjunctive albumin administration significantly improves outcomes.

Keywords: Spontaneous bacterial peritonitis; Liver cirrhosis; Ascites; Bacterial translocation; Multidrug-resistant organisms; Paracentesis; Ascitic fluid analysis; Antibiotic therapy; Albumin.

Introduction:

Spontaneous Bacterial Peritonitis (SBP) is a severe and potentially life-threatening complication that occurs in patients with liver cirrhosis and ascites, characterized by spontaneous infection of the ascitic fluid without any evident intra-abdominal source of contamination. SBP represents a significant clinical burden, affecting approximately 10-30% of hospitalized cirrhotic patients with ascites. The pathogenesis is strongly linked to bacterial translocation from the gut to the peritoneal cavity, primarily due to immune dysfunction and alterations in intestinal permeability. If left untreated, SBP carries a high mortality rate, making prompt recognition and empirical treatment a cornerstone in the management of cirrhotic patients with ascites **(1)**.

SBP was first described in the 1960s and has since been extensively studied, especially regarding its diagnosis and management in the modern era of antimicrobial resistance. Recent guidelines emphasize the importance of diagnostic paracentesis for all cirrhotic patients admitted with ascites, even in the absence of overt symptoms, to allow for early detection and treatment **(2).**

Despite advances in understanding the disease, morbidity and mortality remain considerable, particularly among patients with acute-on-chronic liver failure **(3).**

Pathophysiology

The development of Spontaneous Bacterial Peritonitis (SBP) is intricately linked to the concept of bacterial translocation, which refers to the migration of enteric bacteria from the intestinal lumen through the

mucosal barrier to mesenteric lymph nodes and eventually into the peritoneal cavity. This process is significantly enhanced in patients with cirrhosis due to a combination of structural and immunological changes in the gastrointestinal tract **(4).**

Several key mechanisms contribute to the pathogenesis of SBP:

- Increased intestinal permeability: Portal hypertension and mucosal congestion lead to structural alterations in the gut epithelium, facilitating the passage of bacteria and endotoxins across the intestinal wall **(5).**

Small intestinal bacterial overgrowth (SIBO): Altered bile flow, delayed intestinal motility, and decreased gastric acid secretion in cirrhosis promote bacterial colonization in the upper gut, which increases the risk of translocation **(5)**.

- Impaired immune defenses: Cirrhotic patients exhibit decreased function of Kupffer cells and neutrophils, as well as reduced levels of complement proteins Taken together, these factors create a permissive environment for the spontaneous seeding of ascitic fluid with bacteria, leading to SBP. The likelihood of SBP increases in parallel with the severity of liver dysfunction, particularly in those with advanced Child-Pugh or MELD scores **(6).**

Hematogenous seeding of ascites fluid:

50% of SBP episodes are accompanied by bacteremia with the same organism isolated from the ascitic fluid. The causative organism can sometimes be cultured from urine or sputum**(7).**

Epidemiology and Microbiology

Spontaneous Bacterial Peritonitis (SBP) is a common and serious complication in patients with cirrhosis and ascites. The prevalence of SBP among hospitalized cirrhotic patients with ascitic fluid ranges from 10% to 30%, depending on the population and setting (e.g., community vs. hospital-acquired). The incidence increases significantly among patients with low ascitic protein levels (<1.5 g/dL), gastrointestinal bleeding, or advanced liver disease **(8).**

Historically, Gram-negative bacilli, especially Escherichia coli and Klebsiella pneumoniae, have been the predominant pathogens. However, over the past decade, there has been a marked shift in the microbiological profile of SBP pathogens. This change is attributed to widespread antibiotic use, increased hospital exposure, and the emergence of multidrug-resistant (MDR) organisms **(9).**

Recent studies have shown a rising prevalence of Gram-positive organisms, including Staphylococcus aureus (both MSSA and MRSA), Enterococcus faecalis, and Streptococcus species. Moreover, MDR strains such as extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant organisms, and vancomycin-resistant enterococci (VRE) are increasingly isolated, particularly in nosocomial and healthcare-associated SBP **(10).**

These changes have significant implications for empirical therapy, as the traditional use of third-generation cephalosporins may be insufficient in many hospital settings. Tailoring antibiotic strategies based on local microbiological patterns and resistance data is now considered essential to optimize outcomes **(11).**

Clinical Presentation

The clinical manifestations of Spontaneous Bacterial Peritonitis (SBP) can vary significantly, ranging from subtle symptoms to overt signs of systemic infection or organ failure. This variability in presentation makes clinical suspicion and routine diagnostic paracentesis essential in all cirrhotic patients with ascites who are actually ill **(12).**

The development of SBP occurs almost exclusively in patients with cirrhosis complicated by ascites. About 10 – 13% of patients with SBP have no identifiable signs or symptoms, requiring a higher degree of awareness from clinicians to make the diagnosis **(13).**

The most common findings in symptomatic patients include fever (69%), abdominal pain (59%), changes in mental status (54%), abdominal tenderness (49%), diarrhea (32%), ileus (30%), shock (21%), hypothermia (17%), chills (16%), and rebound tenderness (10%). GI bleeding, nausea, and vomiting can also be present **(14).**

Typical symptoms

Fever (most common symptom) Diffuse abdominal pain or tenderness Nausea and vomiting Diarrhea or ileus Worsening ascites New or worsening hepatic encephalopathy Renal dysfunction or hypotension Importantly, up to 30% of patients with SBP may present without any abdominal symptoms or fever. In such cases, mental status changes (hepatic encephalopathy), leukocytosis, or renal impairment may be the only clues **(15).**

This emphasizes the importance of performing diagnostic paracentesis in all cirrhotic patients with ascites at admission, regardless of symptoms. Furthermore, patients with advanced liver dysfunction (e.g., high MELD score or Child-Pugh class C) are more likely to have atypical presentations and are at higher risk for complications such as sepsis, hepatorenal syndrome, and death. Delays in diagnosis and treatment significantly worsen prognosis, which underscores the necessity for prompt recognition and empirical antibiotic therapy **(16).**

If SBP is suspected, a paracentesis should be performed with analysis of the ascitic fluid. It is important that the paracentesis be performed prior to the administration of any antibiotics. Appropriate handling of the ascitic fluid is crucial to ensure the proper tests are obtained, to minimize the risk of skin flora contaminating the cultures, and to avoid obtaining a falsely negative culture. Tests obtained on the fluid include aerobic and anaerobic cultures, cell count and differential, and fluid chemistries (albumin, protein, glucose, lactate dehydrogenase, amylase, and in some cases bilirubin) **(17).**

Diagnosis :

The diagnosis of Spontaneous Bacterial Peritonitis (SBP) is fundamentally based on the analysis of ascitic fluid, obtained through diagnostic paracentesis, which should be performed in all cirrhotic patients with ascites who are admitted to the hospital or present with clinical deterioration, regardless of whether classical symptoms are present **(18).**

Key Diagnostic Criteria: Polymorphonuclear leukocyte (PMN) count ≥250 cells/mm³ in ascitic fluid is diagnostic of SBP, even in the absence of positive culture results. Positive ascitic fluid culture, particularly for E. coli, Klebsiella, or Gram-positive organisms, supports the diagnosis but is not required. In fact, up to 60% of cases are culture-negative SBP (CN-SBP) **(19).**

Bedside inoculation of ascitic fluid directly into aerobic and anaerobic blood culture bottles significantly increases culture positivity rates and is strongly recommended by guidelines. Additional Diagnostic Tools: Serum-Ascites Albumin Gradient (SAAG): Helps confirm portal hypertension but is not specific for SBP. Ascitic fluid total protein: Low levels (<1.0 g/dL) increase SBP risk. Ascitic fluid glucose, LDH, and pH: May help differentiate SBP from secondary bacterial peritonitis, especially when multiple intra-abdominal sources are suspected. Procalcitonin and CRP: Useful biomarkers for infection but limited specificity in cirrhosis. PCR-based methods (e.g., 16S rRNA gene amplification) are being explored to detect bacterial DNA in ascitic fluid with higher sensitivity, especially in culture-negative cases **(20).**

The ascitic fluid should be tested for the following: Aerobic and anaerobic culture, Cell count and differential, Gram stain, Albumin Protein, Glucose, Lactate, dehydrogenase, Amylase, and Bilirubin (if the fluid is dark orange or brown)Typically, two 20 mL syringes of ascitic fluid will be needed for these tests **(21).**

If tuberculous peritonitis is suspected, additional fluid should be obtained and sent for an acid-fast bacteria smear and mycobacterial culture. However, these tests will frequently fail to detect tuberculous peritonitis, so if there is high suspicion, peritoneoscopy with mycobacterial culture and histology of a biopsied tubercle are the most rapid route to the diagnosis **(22).**

In cases where SBP is suspected but atypical findings are present (e.g., high PMN count with high protein or LDH), clinicians must consider secondary peritonitis, which typically requires surgical management

and carries a worse prognosis. Prompt diagnosis is critical, as delayed antibiotic initiation is directly linked to increased mortality **(23).**

Laboratory Investigational tests of SBP :

Ascetic fluid tests and interpretations of results:

1. **Cultures and gram stain:** Cultures should be sent in blood culture bottles. At least two bottles (one for aerobic and one for anaerobic culture) should be inoculated immediately at the bedside using a new, sterile needle. A needle that has passed through the skin should not be used to inoculate the bottles because it may lead to contamination of the sample with skin flora. Ideally, at least 10 mL of fluid should be introduced into each bottle. It is important to use blood culture bottles because SBP is a low-colony-count monomicrobial infection similar to bacteremia. If a syringe or tube of fluid is sent to the laboratory for culture, the sensitivity for detecting SBP is dramatically decreased**.** In the setting of an elevated PMN count (≥250 cells/mm3), positive culture results from ascitic fluid not only confirm a diagnosis of SBP, but also allow for tailored antibiotic therapy. However, antibiotic therapy should not be delayed while awaiting culture results in patients with a PMN count ≥250 cells/mm3. Instead, patients should be started on broad-spectrum antibiotics, with narrowing of the antibiotic coverage once a pathogen has been identified. Pathogens commonly associated with SBP included Escherichia coli, streptococcal species, and Klebsiella pneumoniae **(24).** A few milliliters of ascitic fluid should be sent for Gram stain in a sterile urine container or red-top tube. Centrifugation of the fluid prior to performing a Gram stain is not necessary since it does not increase the yield and may actually decrease the likelihood of obtaining a positive result. Gram stain is notoriously insensitive for detecting SBP and is associated with a high false-positive rate. Gram stain can help differentiate SBP from secondary bacterial peritonitis due to gut perforation. In the latter, the Gram stain may show multiple different bacterial forms **(25).**
2. **Cell count:** Approximately 1 mL of fluid should be injected into apurple-top EDTA blood-drawing tube for cell count. The cell count and differential should be ordered "stat," The absolute PMN count in the ascitic fluid is calculated by multiplying the total white blood cell count (or total "nucleated cell" count) by the percentage of PMNs in the differential. The diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute PMN count (≥250 cells/mm3). If the laboratory provides an "expanded differential" including bands or even earlier forms of PMNs, these should be added to the count of PMNs. The cell count and differential are performed manually, so the accuracy of the differential is dependent upon the skill of the medical technologist. Some investigators have found that automated cell counts can be accurate **(26).**

Nevertheless, the automated approach has the potential to improve the speed with which results are obtained if it can be validated. One potential source of error in the PMN count is that hemorrhage into the ascitic fluid, as in a traumatic paracentesis, leads to red cell and white cell entry into the fluid. A corrected PMN count should be calculated if there is bloody fluid One PMN is subtracted from the absolute PMN count for every 250 red cells/mm3 **(27).**

3. Ascitic fluid chemistries:

Examination of the fluid chemistries may help confirm the diagnosis or suggest an alternative diagnosis (chemistry tests of ascetic fluid have been mentioned in detail in chapter Ascites) **(21).**

2. Urinary reagent strips

Urine reagent strip that tests for leukocyte esterase in the ascitic fluid has demonstrated a positive predictive value of 97% in detecting a PMNC count higher than 250 cells/mm3, and may be a more rapid and cost-effective alternative for detecting the presence of SBP, although further research is needed on this method before it becomes an accepted means of diagnosis. A urine analysis and urine culture should be obtained, given that bacteriuria is a risk factor for SBP and the possibility that an underlying urinary tract infection led to its development. Similarly, blood cultures should be obtained given the potential of occult bacteremia leading to, or resulting from, SBP **(28).**

2) Procalcitonin

Interesting evidence is emerging from the measurement of procalcitonin (PCT) in serum of patients with SBP. Su et al. performed a literature search to identify original studies that reported the diagnostic performance of PCT alone or in combination with other biomarkers for the diagnosis of SBP **(29).**

3) Fecal calprotectin (FC)

FC has emerged in diagnosing the onset and severity of hepatic encephalopathy and SBP and demonstrated that FC concentrations may serve as a screening tool for SBP **(30).**

Differential Diagnosis:

Distinguishing spontaneous from secondary bacterial peritonitis It is important to distinguish SBP from secondary bacterial peritonitis because of the critical need to determine whether surgical intervention is needed **(17).**

Specifically, mortality approaches 100% in patients with secondary bacterial peritonitis who receive treatment with antibiotics alone (without surgery); mortality is approximately 80% in patients with cirrhosis and SBP who undergo an unnecessary exploratory laparotomy **(31).**

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/mm3 (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 **(32).**

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 **(32).**

Patients who meet criteria 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 **(33).**

B. Distinction from alcoholic hepatitis

The patient with alcoholic hepatitis regularly develops fever, peripheral leukocytosis, and abdominal pain, which can manifest as SBP. Furthermore, they also can develop SBP. An important distinguishing point is that peripheral leukocytosis does not lead to an elevated ascitic fluid PMN count. Thus, an levated ascitic fluid PMN count must be presumed to represent SBP. If the patient has already been started on empiric antibiotic treatment because of a fever and/or peripheral leukocytosis, the antibiotics can be discontinued after 48 hours if ascitic fluid, blood, and urine cultures demonstrate no bacterial growth and the ascitic fluid PMN count is <250/mm3 **(34).**

Complications And Prognosis:

Despite remarkable developments in earlier detection, medical and surgical therapy, the average mortality rate of SBP remains elevated, approaching 30%, and ranging from <5% in low-risk patients to approximately 90% in those at higher risk **(35).**

Advanced age, child score >2, the presence of bacteremia, lack of infection resolution, modification of antibiotic treatment and culture positivity, nosocomial origin, along with increased concentrations of serum

bilirubin and creatinine are the predictive factors associated with poor outcome in cirrhotic patients with SBP **(36).**

In these patients, approximately half of all deaths occur after resolution of infection and are consequent to development of complications such as upper gastrointestinal bleeding, renal dysfunction, hepatic encephalopathy and paralytic ileus. Among these complications, renal impairment is probably the strongest independent predictor of mortality and occurs as a result of a decreased arterial blood volume, mediated by vasoactive cytokines, with a resultant increased renin–angiotensin–aldosterone system activation **(37).**

The stronger predictors of poor outcome both in SBP and secondary BP patients include the concurrent development of sepsis and subsequent multiple organ failure (MOF). Several studies have described an increased risk of death along with transition from sepsis to severe sepsis and septic shock **(38).**

Treatment and Management

Early and appropriate treatment of Spontaneous Bacterial Peritonitis (SBP) is essential, as delays in initiating antibiotics are associated with significantly increased mortality. Empirical treatment should begin immediately after diagnostic paracentesis, even before culture results are available **(39).**

First-Line Empirical Antibiotic Therapy: Community-acquired SBP: The standard of care remains 3rd-generation cephalosporins, particularly: Cefotaxime 2 g IV every 8 hours for 5 days Ceftriaxone 1–2 g IV daily as an alternative These antibiotics are highly effective against the traditional pathogens (E. coli, Klebsiella pneumoniae) and have good peritoneal penetration **(40).**

Hospital-acquired or nosocomial SBP: Increased risk of MDR organisms necessitates broader-spectrum antibiotics: Piperacillin-tazobactam, meropenem, or cefepime + vancomycin (depending on local resistance patterns) Empirical coverage for MRSA and VRE may be warranted in critically ill patients or those with previous antibiotic exposure or nosocomial infections **(41).**

Duration of Therapy: Generally, 5 days is sufficient in uncomplicated SBP with clinical response. Treatment duration may be extended in complicated or culture-positive SBP, especially with resistant pathogens or poor clinical response. Adjunctive Therapy: Albumin Infusion Albumin administration has been shown to reduce the incidence of hepatorenal syndrome and improve short-term survival in SBP. Recommended regimen **(42).**

1.5 g/kg IV albumin on day 1 1 g/kg on day 3 Albumin is particularly important in patients with: Serum creatinine > 1 mg/dL Serum bilirubin > 4 mg/dL Monitoring and Response: Clinical improvement is usually seen within 48–72 hours. Repeat paracentesis is not routinely needed unless the patient fails to respond or worsens clinically. Treatment Failures: Consider MDR organisms or alternative diagnoses (e.g., secondary peritonitis) **(43).**

Change antibiotics according to culture and sensitivity results or escalate empirically in case of deterioration **(43).**

Prophylaxis of Spontaneous Bacterial Peritonitis (SBP)

Primary and secondary prophylaxis of SBP play a crucial role in reducing its incidence and improving survival in cirrhotic patients with ascites.

1. Primary Prophylaxis Primary prophylaxis is indicated in patients at high risk for developing SBP, particularly those with: Ascitic fluid protein <1.5 g/dL and at least one of the following: Serum bilirubin ≥2.5 mg/dL Serum creatinine ≥1.2 mg/dL BUN ≥25 mg/dL Serum sodium ≤130 mEq/L Child-Pugh score ≥9 with bilirubin ≥3 mg/dL In these patients, oral norfloxacin 400 mg/day is commonly used. Alternatively, ciprofloxacin 500 mg/day or trimethoprim-sulfamethoxazole (one double-strength tablet daily) may be used. These antibiotics reduce intestinal bacterial overgrowth and prevent bacterial translocation **(32).**

2. Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis.
3. Secondary Prophylaxis Patients who have recovered from an episode of SBP are at high risk for recurrence (up to 70% at 1 year), and thus require lifelong secondary prophylaxis. The standard regimen is norfloxacin 400 mg/day. In settings with high resistance rates or limited access to norfloxacin, trimethoprim-sulfamethoxazole (1 double-strength tablet daily or 5 times/week) is a viable alternative. Recent evidence suggests that prophylaxis must be used judiciously, as long-term antibiotic use may increase multidrug-resistant (MDR) bacterial colonization and infections. Therefore, prophylaxis should be individualized based on patient risk profile and local resistance patterns **(44).**

Prognosis and Outcomes

SBP Spontaneous Bacterial Peritonitis (SBP) remains a serious complication of cirrhosis with a high in-hospital mortality rate ranging from 20% to 30%, despite appropriate antibiotic treatment. Factors associated with poor prognosis include: Delayed diagnosis or delayed paracentesis Renal dysfunction at presentation (especially if serum creatinine >2 mg/dL) Hepatic encephalopathy High MELD or Child-Pugh scores Nosocomial origin of infection .Infection with multidrug-resistant organisms Even after successful treatment, recurrence rates of SBP can reach 70% within 1 year, highlighting the importance of secondary prophylaxis. Moreover, SBP is often a trigger for acute-on-chronic liver failure (ACLF), which significantly worsens the overall survival rate **(45).**

The development of hepatorenal syndrome (HRS) during or after SBP is one of the strongest predictors of mortality. Thus, early initiation of albumin and renal monitoring is essential. Liver transplantation remains the definitive treatment for eligible patients with recurrent or severe SBP and underlying end-stage liver disease **(46).**

Recent Advances and ResearchTrends in SBP Recent research in Spontaneous Bacterial Peritonitis (SBP) has focused on improving early detection, refining antibiotic strategies, and exploring novel biomarkers and non-antibiotic therapies **(9).**

1. Diagnostic Biomarkers Traditional diagnostic reliance on ascitic PMN count and culture has limitations due to frequent culture-negativity. Recent studies have investigated biomarkers such as calprotectin, procalcitonin, and ascitic lactoferrin as rapid, reliable tools for SBP detection. These markers can aid in point-of-care testing, especially in settings where immediate paracentesis is delayed or unavailable **(24).**
2. Ascitic calprotectin and lactoferrin as markers of spontaneous bacterial peritonitis. Antibiotic Resistance There is a growing concern over multidrug-resistant (MDR) organisms, especially in hospital-acquired SBP. Organisms such as extended-spectrum beta-lactamase (ESBL)-producing E. coli and Klebsiella, vancomycin-resistant Enterococcus (VRE), and methicillin-resistant Staphylococcus aureus (MRSA) have emerged. This has prompted guidelines to recommend risk-based empirical therapy and the use of local antibiograms to guide antibiotic choices. Newer antibiotics like ceftolozane-tazobactam and ceftazidime-avibactam are under evaluation for resistant Gram-negative infections in cirrhotic patients **(47).**
3. Management of bacterial and fungal infections in acute-on-chronic liver failure and cirrhosis.
4. Non-Antibiotic Therapies Immune dysfunction in cirrhosis is a key factor in SBP pathogenesis. As such, studies have explored the role of gut microbiota modulation using probiotics and fecal microbiota transplantation (FMT) to reduce bacterial translocation and SBP risk. Moreover, therapies targeting the gut-liver axis, such as rifaximin and prebiotics, have shown promise in reducing infection rates and inflammation **(1).**
5. Fecal microbiota transplant for cirrhosis reduces gut antibiotic-resistant bacteria and infections.

Artificial Intelligence and Risk Scoring Machine learning algorithms are being tested to identify high-risk patients for SBP, using combinations of lab data, vitals, and clinical history to predict infections before they become clinically evident. This can enhance early interventions and resource prioritization in liver units **(48).**

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