Chapter 8

SPONTANEOUS BACTERIAL PERITONITIS

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Spontaneous Bacterial Peritonitis (SBP) is a common complication in cirrhotic patients with ascites, characterized by an infection of the pre-existing peritoneal fluid without other intra-abdominal causes. Early diagnosis and treatment are crucial, as the lack thereof can result in fatal complications

(Milevoj Kopcinovic *et al.*, 2020). The mortality associated with SBP is approximately 20%, and recurrence rates remain high, even with therapeutic advances (Biggins *et al.*, 2021). Recent guidelines suggest that the global peritonitis episode rate should not exceed 0.40 per year and that more than 80% of patients should be free of peritonitis annually, emphasizing the importance of seeking evidence for strategies to reduce and prevent SBP (Li *et al.*, 2022).

The diagnosis of SBP requires a detailed investigation of ascites, including medical history, physical examination, and complementary tests (Li *et al.*, 2022). Imaging studies are valuable, especially in cases of small volumes of ascitic fluid, and diagnostic paracentesis is essential to identify the etiology (Milevoj Kopcinovic *et al.*, 2020). The polymorphonuclear (PMN) cell count in peritoneal fluid is the most reliable test to confirm SBP, with a count of 250 cells/mm³ or more being indicative of the disease (Sandhu; John, 2023). Empirical treatment should include third-generation cephalosporins, even in the absence of bacterial confirmation, and antibiotic prophylaxis is recommended for patients with cirrhosis, ascites, and hepatic or renal dysfunction (Sandhu; John, 2023). It is also important to consider evaluation for liver transplantation and the initiation of Renal Replacement Therapy (RRT) (Li *et al.*, 2022). In cases of persistent infection, such as Tertiary Peritonitis (TP), an integrated approach according to the Surviving Sepsis Campaign should be applied, including resuscitation, rapid source control, and empirical antibiotic therapy (Bass *et al.*, 2022).

Molecular techniques, such as PCR, have proven effective in rapidly detecting bacterial DNA in peritoneal fluid, and biomarkers can predict the development of SBP, improving diagnostic accuracy and enabling early interventions (Chaudhry *et al.*, 2019). Initial treatment with third-generation cephalosporins, such as cefotaxime, is recommended, with alternative options like ceftriaxone in case of resistance or allergy. Continuous prophylaxis with norfloxacin or ciprofloxacin is indicated for patients with low protein content in ascitic fluid or a history of SBP to reduce recurrence (Biggins *et al.*, 2021). The recent emphasis on multidisciplinary management and combined therapies aims to optimize clinical outcomes. Preventive strategies, such as the administration of prophylactic antibiotics before invasive procedures and strict hygiene practices in peritoneal dialysis, are essential to minimize infection risk (Chaudhry *et al.*, 2019).

EPIDEMIOLOGY

Demographic data indicate that peritonitis predominantly affects patients undergoing peritoneal dialysis (PD), with advanced age being a significant risk factor. There is no clear difference in incidence between genders; however, hygiene factors and underlying conditions may influence prevalence. Geographic incidence can vary depending on healthcare standards and peritoneal dialysis practices (Kotani *et al.*, 2021).

Historically, the incidence and prevalence of PD-related peritonitis have shown a downward trend, attributed to improvements in dialysis techniques, hygiene, and prophylactic antibiotic use. However, emerging antimicrobial resistance poses a significant challenge, impacting treatment efficacy and potentially increasing the associated mortality rate (Fiore *et al.*, 2019).

Statistics indicate that the mortality rate from peritonitis can be high, particularly in patients with severe underlying conditions. Studies show that survival rates can vary significantly depending on the speed and adequacy of the administered treatment. In some cases, mortality rates range from 20% to 40% in severe cases, especially when multidrug-resistant pathogens are involved (Kotani *et al.*, 2021).

The risk factors associated with peritonitis include age over 50 years (Gueiros *et al.*, 2022). When age is 65 years or older, in elderly patients, there is a higher likelihood of developing generalized peritonitis. This is due to factors such as late presentation to health services, altered clinical manifestations, and diminished local peritoneal responses. Generalized peritonitis has a high mortality rate, and its risk factors are multifaceted. For example, in sub-Saharan Africa, specific etiologies such as perforation caused by typhoid fever, postoperative peritonitis, and peptic ulcer perforation have been identified as major contributors to high mortality rates (Tochie *et al.*, 2020). Additionally, organ dysfunction and the presence of malignancy are significantly associated with mortality, which increases proportionally with age (Gueiros *et al.*, 2022).

In patients undergoing peritoneal dialysis, C-reactive protein (CRP) is a laboratory marker that acts as a risk factor. Elevated CRP levels indicate an immune inflammatory response, while elevated alkaline phosphatase (ALP) reflects a higher risk of short-term adverse outcomes and is associated with technical failures. High levels of low-density lipoprotein (LDL) are also associated with an increased risk of technical failures, as is the presence of fungi, which represent an additional risk in peritoneal dialysis (Yu *et al.*, 2023).

Although Serratia, a gram-negative organism, is a rare cause of peritonitis, it is a notable risk factor, with studies indicating that it accounts for approximately 1% of total cases (Au *et al.*, 2021). Peritonitis caused by Streptococcus oralis, although rare, presents a risk of recurrence months after the first episode and can result in long-term refractory peritonitis, with up to 41% of cases attributed to viridans group streptococci (Kotani *et al.*., 2021).

Risk factors for peritonitis after gastroscopy in peritoneal dialysis patients mainly include the use of gastric acid suppressants, which are associated with higher rates of adverse events and an increased risk of enteritis. Other relevant factors include the post-procedural microbiological profile, the timing of peritonitis onset, and the potential impact of prophylactic antibiotics (Chan *et al.*, 2022).

In patients with end-stage liver disease, risk factors for spontaneous bacterial peritonitis include increased bacterial resistance, the growing use of quinolones for

prophylaxis, and the severity of cases. Inadequate antibiotic therapy contributes to morbidity and mortality in patients with SBP (Fiore *et al.*, 2019).

DIAGNOSIS

The prevalence of SBP varies from 3.5% to 30% depending on the clinical setting, and early diagnosis is crucial to reducing mortality, which has decreased from 90% to about 20% with more rapid interventions. Each hour of diagnostic delay is associated with a 3.3% increase in hospital mortality risk (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021). Late diagnosis can result in treatment delays, generating high hospital costs and compromising patients' quality of life due to additional complications (Buckup *et al.*, 2022).

The gold standard for diagnosing peritonitis is the polymorphonuclear cell count in ascitic fluid, with values above 250 cells/mm³, a process that can be time-consuming (Patel *et al.,* 2022). The diagnosis of refractory ascites is also important, as it increases the risk of peritonitis, with relevant criteria including early recurrence, diuretic resistance, or intolerance (Khan; Linganna, 2023). Patients with recent ascites, increased abdominal distension, and signs indicating SBP should undergo diagnostic paracentesis (Khan; Linganna, 2023).

CLINICAL MANIFESTATIONS

Patients with SBP may present a wide range of symptoms or even be asymptomatic, especially in the early stages of the disease, making early diagnosis challenging (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021). The symptoms most frequently associated with SBP include abdominal pain and tenderness on palpation, with a diagnostic sensitivity of 94%. Other clinical manifestations may include vomiting, diarrhea, hyper or hypothermia, chills, tachycardia, tachypnea, jaundice, and leukocyte changes. Complications associated with SBP may involve liver failure, mental state alterations due to hepatic encephalopathy, hepatorenal syndrome, coagulopathies, and gastrointestinal bleeding (Luo *et al.*, 2019; Popoiag; Fierbințeanu-Braticevici, 2021).

However, the diagnosis of SBP cannot be based solely on clinical signs. Although a history of fever in the past 24 hours has a specificity of 81%, it cannot differentiate SBP from other sources of infection. Clinical judgment, in turn, has shown limited sensitivity of 77% and specificity of 34% for detecting SBP, indicating that it is not sufficient for a definitive diagnosis. Therefore, it is necessary to perform a paracentesis to collect and analyze ascitic fluid (Popoiag; Fierbințeanu-Braticevici, 2021).

One of the complications of SBP is acute kidney injury, defined as an increase in creatinine greater than 0.3 mg/dL in 48 hours or a 50% increase in creatinine in 7 days. Hepatorenal syndrome is diagnosed after excluding hypovolemia/shock, exposure to nephrotoxic agents, and structural kidney damage in a patient with ascites (Khan; Linganna, 2023).

DIAGNOSTIC METHODS

Paracentesis is an essential procedure, not only to relieve ascites symptoms but also to diagnose potentially serious conditions. This method confirms the presence of infection and identifies the underlying cause of peritonitis, guiding appropriate treatment. Studies indicate that patients with SBP who undergo paracentesis within the first 12 hours of hospitalization have a mortality rate of 5.5%, compared to 7.5% for those who undergo the procedure later (Popoiag; Fierbințeanu-Braticevici, 2021).

Diagnostic paracentesis is recommended primarily in patients who present one of the following conditions: grade 2 or 3 ascites, hospitalization for worsening ascites, or complications arising from liver cirrhosis (Popoiag; Fierbințeanu-Braticevici, 2021). The gold standard for diagnosing peritonitis is the polymorphonuclear neutrophil (PMN) count in the collected fluid, with a value greater than 250 cells/mm³ confirming the disease in patients with SBP (Luo *et al.*, 2019). Flow cytometry is an innovative alternative, with a sensitivity and specificity of about 100% for detecting PMN at levels above 250 cells/mm³. Ascitic fluid culture is essential to guide antibiotic treatment, although it is not decisive for confirming the diagnosis (Popoiag; Fierbințeanu-Braticevici, 2021).

Blood culture analysis is important for diagnostic confirmation since the PMN count in ascitic fluid can be operator-dependent (Luo *et al.*, 2019). There are reports in the literature of cases where ascitic fluid analysis did not reveal the presence of bacteria despite the presence of polymorphonuclear leukocytes and a clinical picture suggestive of peritonitis. Thus, blood culture also plays a fundamental role in guiding treatment and defining the etiological diagnosis (Hadano, 2024).

RECENT ADVANCES IN DIAGNOSIS

Among biomarkers, procalcitonin (PCT) and high-sensitivity C-reactive protein (hs-CRP) have shown potential, although the association of PCT with SBP is still debated. Lactoferrin and calprotectin have demonstrated high sensitivity and specificity in diagnosing SBP but require further studies (Popoiag; Fierbințeanu-Braticevici, 2021). Additionally, prostaglandin E2 (PGE2) may be a promising biomarker for predicting hospital mortality in decompensated cirrhosis (Luo *et al.*, 2019).

Technologies like OpticLine, which use microscopy to detect infections early, and leukocyte esterase reagent strips (LERS) are being evaluated as useful diagnostic tools, despite variability in results (Patel *et al.*, 2022).

Recently, studies have suggested that low levels of potassium, albumin, and vitamin B12 may be associated with the risk of fungal peritonitis, with hypokalemia and oxidative stress potentially contributing to the condition's development. Hypoproteinemia and vitamin B12 deficiency are also linked to this pathology, highlighting the need for more reliable biomarkers for diagnosis (Liu *et al.*, 2021).

TREATMENT

Bacterial peritonitis is an infection with a high mortality rate if not treated promptly, with its mortality associated with systemic inflammation and sepsis. Appropriate and timely antibiotic therapy is crucial for all forms of bacterial peritonitis, and the antibiotic strategy can vary considerably due to microbiological diversity. Patients with spontaneous bacterial peritonitis should receive intravenous broad-spectrum antibiotics along with albumin, while those on peritoneal dialysis should receive intraperitoneal treatment. Secondary peritonitis, on the other hand, usually requires surgical intervention or interventional procedures (Pörner *et al*., 2021).

Guidelines emphasize the importance of infection severity and local resistance profile in the initial treatment of SBP. Treatment should be initiated immediately after diagnosis to minimize complications and improve survival, with a diagnostic paracentesis performed 48 hours after treatment initiation to assess its effectiveness; a 25% reduction in leukocyte count indicates a good response (Popoiag; Fierbințeanu-Braticevici, 2021). Broad-spectrum treatments are recommended for critically ill patients, with variations in coverage for community-acquired and healthcare-related infections, with coverage for enterococci and multidrug-resistant bacteria indicated in specific situations such as septic shock (Montravers *et al.*, 2016).

The usual treatment for peritonitis in patients undergoing automated peritoneal dialysis (APD) involves the administration of antibiotics via the intraperitoneal (IP) route, preferably once a day, following recommendations based on continuous ambulatory peritoneal dialysis (CAPD) regimens. First-generation cephalosporins, such as cefazolin, are frequently used, with dosages adjusted according to pharmacokinetics. Studies suggest that continuous dosing may be more effective than intermittent dosing (Mancini; Piraino, 2019).

Empirical treatment for secondary peritonitis includes combining second- or third-generation cephalosporins with metronidazole or piperacillin/sulbactam. In more severe cases, carbapenems such as meropenem are used due to their broad antibacterial coverage. The combination of meropenem and vancomycin has demonstrated high efficacy, with a sensitivity rate of 98% for various bacteria. Treatment should be adjusted based on the patient's clinical response (Grotelüschen *et al*., 2020).

Surgical treatment options depend on the severity of peritonitis and findings during the procedure. Minimally invasive procedures are preferred when feasible, but severe cases may require open surgery. Perioperative care, including analgesia, sedation, hemodynamic and ventilatory monitoring, and nutritional support, is crucial for effective peritonitis management (Montravers *et al*., 2016).

Antibiotic treatment for SBP has evolved over time. Although serum levels have shown no significant difference between patients with and without dialysis-associated peritonitis

(DAP), ascitic fluid levels were significantly higher, with a cut-off value of 69.4 pg/mL showing a sensitivity of 80% and specificity of 72.7%, and an area under the curve (AUROC) of 0.77 for the diagnosis of DAP. The 2010 EASL guideline recommends cefotaxime (2 g every 12 or 8 hours for 5 days) as the first-line treatment. Alternatives include amoxicillin/clavulanic acid and quinolones such as ciprofloxacin and ofloxacin (Popoiag; Fierbințeanu-Braticevici, 2021).

Additionally, the administration of albumin has been shown to reduce mortality and the incidence of acute kidney injury (AKI) in patients with SBP. Albumin administration in DAP is recommended within 6 hours of diagnosis, especially in high-risk patients with the following laboratory results: serum creatinine > 1 mg/dL, blood urea nitrogen > 30 mg/dL, or total bilirubin > 4 mg/dL (Ebied *et al.*, 2022).

Peritonitis resulting from enteric conditions such as strangulated intestine, ischemic colitis, and appendicitis can be difficult to diagnose, leading to delays in appropriate treatment and consequently increased morbidity, with a mortality rate of around 50%. Additionally, peritonitis caused by coagulase-negative staphylococci presents an additional challenge due to the high proportion of methicillin-resistant strains and their ability to form biofilms. The methicillin resistance rate among these staphylococci, responsible for peritonitis, has increased to over 50% in most centers, potentially reaching up to 70%. This requires personalized approaches and strict monitoring to improve clinical outcomes and reduce the morbidity and mortality associated with the condition (Li *et al.*, 2022).

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