CHAPTER 84

Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome

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OBJECTIVES

This chapter will:

1. Discuss the pathophysiology, diagnosis, and treatment of spontaneous bacterial peritonitis.
2. Discuss prevention of acute kidney injury and hepatorenal syndrome in patients with spontaneous bacterial peritonitis.
3. Discuss the management of hepatorenal syndrome in the setting of spontaneous bacterial peritonitis.

Patients with cirrhosis and ascites have a high risk of developing bacterial infections and sepsis compared with the general population, and the development of a bacterial infection has been associated with a fourfold increase in mortality risk in patients with cirrhosis.[1] Among infections, spontaneous bacterial peritonitis (SBP) is one of the most frequent and life threatening in these patients.[2] SBP is defined as a bacterial infection of ascitic fluid developed in patients without any intraabdominal, surgically treatable source of infection.[3] SBP is the second most common infection in hospitalized patients with cirrhosis and ascites, with an incidence of approximately 20%.[2] Approximately 25% of the episodes of SBP are present at the time of hospital admission, and the remainder are acquired during hospitalization.

PATHOGENESIS OF SPONTANEOUS BACTERIAL PERITONITIS

A pathologic bacterial translocation (BT) from intestinal lumen to mesenteric lymph node is the main character in the pathogenesis of SBP.[4] This "pathologic BT" in cirrhosis is related to several factors, including quantity and quality of intestinal bacteria, increased intestinal permeability, and systemic and local defects in host immunity. The intestinal bacterial overgrowth plays a key role in BT in cirrhosis. It is the result, at least partly, of decreased small-bowel motility and the delayed intestinal transit.[5] Autonomic dysfunction, increased nitric oxide (NO) synthesis, and the oxidative stress of the mucosa are the main causes for decreased intestinal motility. In patients with cirrhosis there is not only an increase in quantity of bacteria in the bowel but also a change in quality. In fact, a depletion of the beneficial phyla Lachnospiraceae and enrichment in the phyla Proteobacteria (mainly Enterobacteriaceae) and Enterococcaceae have been demonstrated in the microbiota of patients with cirrhosis.[6] Interestingly, Enterobacteriaceae (e.g., *Escherichia coli, Klebsiella pneumoniae*) and Enterococcaceae have been found to be the most adept at translocating from intestinal lumen to mesenteric lymph node, and they are the pathogens most frequently found in patients with SBP.[7,8]

Patients with cirrhosis also demonstrate an alteration in the integrity of intestinal mucosal barrier. In fact, portal hypertension leads to ultrastructural changes of intestinal

BOX 84.1

Signs and Symptoms of Spontaneous Bacterial Peritonitis

Signs and/or symptoms of systemic inflammation:
- Hyper/hypothermia
- Chills
- Altered WBC count
- Tachycardia
- Tachypnea

Septic shock

Symptoms and/or signs of peritonitis:
- Abdominal pain
- Abdominal tenderness
- Vomiting
- Diarrhea
- Ileus

Worsening of liver function (e.g., development of hepatic encephalopathy)

Renal failure:
- Hepatorenal syndrome
- Acute tubular necrosis
- Prerenal failure

Gastrointestinal bleeding

WBC, White blood cell.

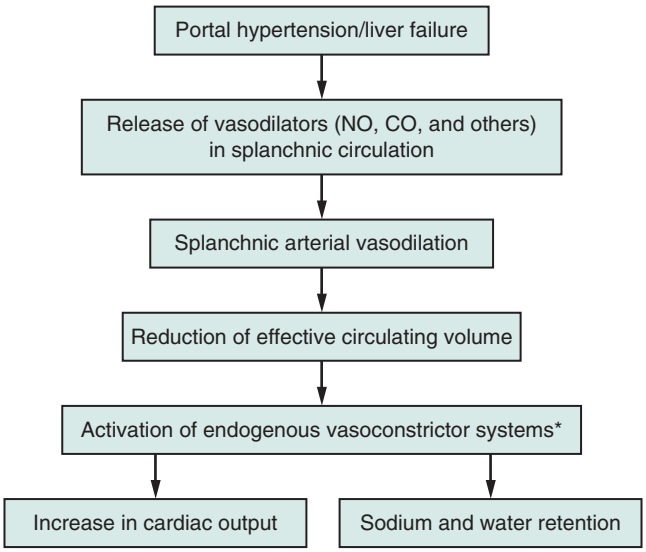

FIGURE 84.1 Pathogenesis of circulatory dysfunction and sodium and water retention in cirrhosis. *CO,* carbon monoxide; *NO,* nitric oxide. *Renin-angiotensin-aldosterone system, adrenergic system, nonosmotic secretion of vasopressin.

mucosa, such as widening of intracellular spaces, vascular congestion, wall thickening, and tight junctions disruption.[9] These alterations lead to an increased intestinal permeability that facilitates pathologic bacterial translocation.

Finally, alteration of innate and acquired immunity has been observed in patients with cirrhosis. The detailed description of the alterations of immune response in cirrhosis is beyond the purpose of this chapter, but it plays a significant role in the development of SBP because of a lack of control of bacterial translocation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF SPONTANEOUS BACTERIAL PERITONITIS

Patients with SBP may have classic symptoms of infections, such as fever, abdominal pain, and ileus, and lab data may show leukocytosis and an increase in acute phase protein (Box 84.1). However, sometimes the clinical scenario may be more complex without clear signs of infection, and the appearance of hepatic encephalopathy, difficult to control ascites, and/or acute kidney injury (AKI) may be the only clinical signs of SBP. Thus a diagnostic paracentesis should be performed in all patients with ascites admitted for an acute decompensation of cirrhosis. SBP is diagnosed when polymorphonuclear (PMN) cells in ascitic fluid are higher than 250 cells/μL.[3] In all patients, ascitic and blood samples should be collected for microbiologic cultures. Ascitic fluid should be inoculated at the bedside, using blood culture bottles, including aerobic and anaerobic media. Despite the use of sensitive methods, ascites cultures are negative in 60% of cases.[3]

PATHOGENESIS OF HEPATORENAL SYNDROME IN PATIENTS WITH SPONTANEOUS BACTERIAL PERITONITIS

Hepatorenal syndrome (HRS) is a functional renal failure occurring in patients with cirrhosis and ascites.[10] HRS occurs as a consequence of a severe reduction of effective hypovolemia not responsive to diuretic withdrawal and plasma volume expansion, a severe activation of systemic vasoconstrictor systems causing renal hypoperfusion. Two different types of HRS have been described.[10,11] Type 1 HRS is a rapid, progressive type of AKI defined by a doubling of the initial serum creatinine (SCr) concentrations.[12] Type 2 HRS is characterized by a moderate and steady or slowly progressive renal failure (SCr > 1.5 mg/dL). The dominant clinical features are different, progressing from type 1 HRS to type 2 HRS, being AKI for the former and refractory ascites for the latter. Precipitating events such as infections, bleeding, and large-volume paracentesis without albumin administration can trigger type 1 HRS; SBP is one of the most important triggers.

The onset of SBP is associated to the worsening of circulatory dysfunction in patients with cirrhosis.[13] Indeed, in patients with decompensated cirrhosis, portal hypertension leads to the production of vasodilators (mainly nitric oxide and carbon monoxide) in the splanchnic circulation leading to splanchnic arterial vasodilation.[14] The consequent reduction in effective circulating volume is recognized by baroreceptors that stimulate the activation of endogenous vasoconstrictor systems (adrenergic system, renin-angiotensin-aldosterone system, and nonosmotic secretion of vasopressin) resulting in an increased cardiac output and in sodium and water retention (Fig. 84.1). This is a pivotal mechanism aimed to guarantee an adequate perfusion of noble organs.

However, the onset of SBP dramatically changes this precarious balance. Indeed, bacteria and bacterial product (pathogen-associated molecular patterns, PAMPs) are recognized by monocytes through the bond with pattern recognition receptors, such as Toll-like receptors 4 (TLR4) and TLR2. This bond activates monocytes to release proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β). TNF-α and IL-6 concentrations are strong predictors of AKI

development in patients with SBP.[13] The inflammatory response causes a further increase in nitric oxide and carbon monoxide production leading to a maximal splanchnic vasodilation and a consequent maximal activation of endogenous vasoconstrictor system. These events cause a severe renal vasoconstriction with a reduction in renal perfusion and glomerular filtration rate (GFR) that represent the main features of HRS.

In addition, systemic inflammation leads to a further impairment of cardiac output in patients with cirrhosis. More in detail, TNF-α stimulates nitric oxide synthesis via nuclear factor-κB, resulting in a reduced cardiac contractility.[15,16] As a consequence, there is further reduction in effective circulating volume and mean arterial pressure. The impaired cardiac function is crucial for the development of SBP. In fact, it has been shown that patients who develop HRS after an episode of SBP have a significantly lower cardiac output than patients who did not.[13]

Nevertheless, the effects of inflammation on cardiovascular function may not explain fully the pathogenesis of AKI and HRS in patients with compensated cirrhosis. The latter have a low degree of cardiovascular dysfunction, and in these patients inflammation may lead to renal and/or other organ failures, regardless of its effect on cardiovascular function.[17] Indeed, it has been shown in clinical[18] and experimental studies[19] that an upregulation of renal tubular TLR4 may occur in the setting of cirrhosis. It is associated with the development of renal dysfunction, tubular damage, and apoptosis, suggesting a potential role of TLR4 as mediator of renal injury.

Stretching this concept, a new hypothesis on the pathogenesis of AKI in patients with sepsis has been proposed recently, in which AKI is the result of an adaptive response of the tubular cells to an injurious, inflammatory danger signal[20,21] (Fig. 84.2). The interplay of inflammation and microvascular dysfunction amplify this signal, leading tubular cells to a metabolic downregulation and reprioritization, which favors individual cell survival processes (such as the maintenance of membrane potential and cell cycle arrest) at the expense of "kidney function." All these features develop in the context of normal or even increased renal blood flow and provide the framework of the dramatic decrease in glomerular filtration rate and the development of uremia observed in these patients.[21]

These new concepts challenge the pure functional form of HRS, but they are in agreement with two recent findings concerning renal biopsy and urinary biomarkers of renal tubular damage in patients with cirrhosis and AKI. Trawalè et al. found glomerular lesions, chronic tubulointerstitial lesions, and acute tubulointerstitial lesions in most of patients with cirrhosis and renal impairment and without proteinuria/hematuria.[22] Furthermore, patients with HRS showed higher concentrations of urinary neutrophil gelatinase-associated lipocalin than patients with prerenal AKI.[23]

TREATMENT OF SPONTANEOUS BACTERIAL PERITONITIS

Antibiotic Treatment

Antibiotic treatment should be administered as soon as possible in patients with SBP, because a delayed effective treatment has been associated with poor survival in these patients.[24] Third-generation cephalosporins are the antibiotic of choice in patients with community-acquired

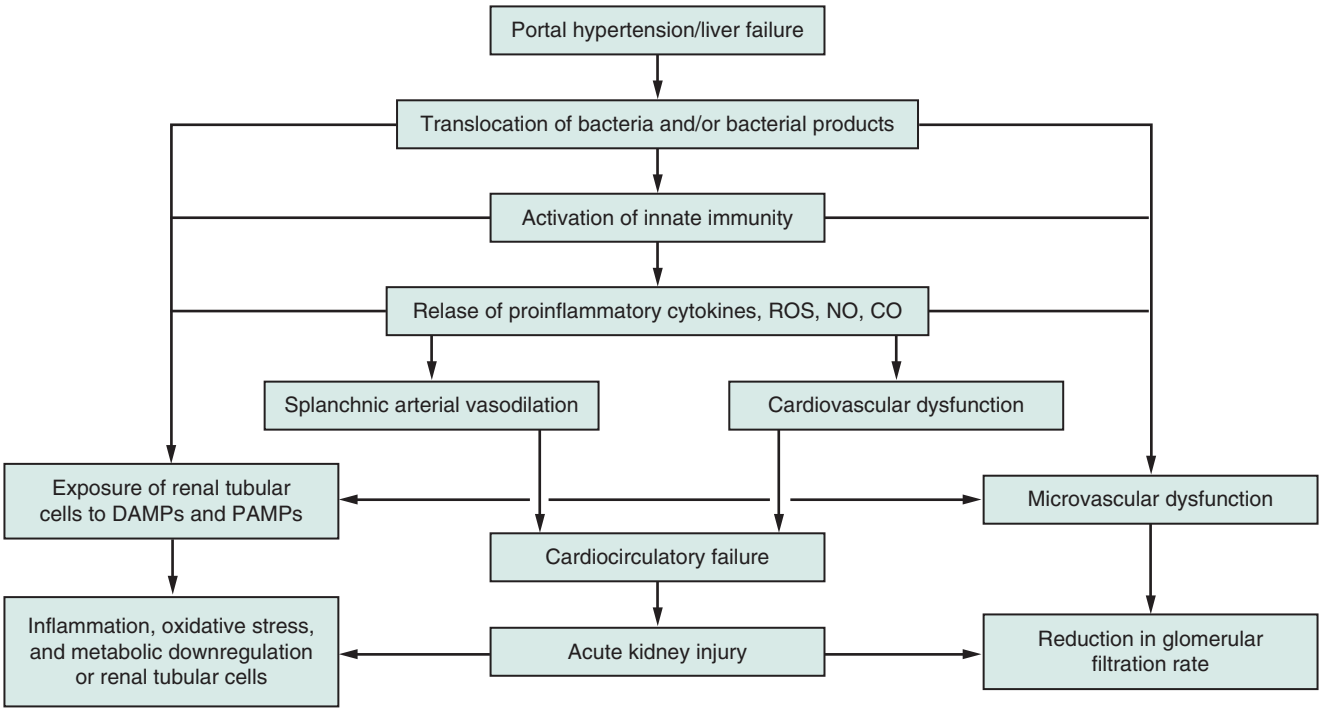

FIGURE 84.2 Role of bacterial translocation in the pathogenesis of acute kidney injury in cirrhosis. *CO,* carbon monoxide; *DAMPs,* danger-associated molecular patterns; *NO,* nitric oxide; *PAMPs,* pathogen-associated molecular patterns; *ROS,* reactive oxygen species.

SBP, because they have been shown to be effective in more than 80% of patients.[7,25] The combination of β-lactams plus β-lactamases inhibitors is a valid alternative.[26] Quinolones may be used in patients not in chronic prophylaxis and/or in countries with a low prevalence of strains resistant to quinolones. In patients with nosocomial SBP the efficacy of above-mentioned antibiotic is poor,[7,27] because these episodes frequently are sustained by multi-drug–resistant bacteria. In nosocomial SBP an empiric antibiotic treatment with broad-spectrum antibiotic treatment should be used according to local epidemiology.[28] In centers with a high prevalence of extended-spectrum β-lactamases Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus,* and enterococci, the combination of meropenem plus daptomycin showed to be more effective than ceftazidime in a randomized controlled trial.[27] In addition, an effective empiric treatment was found to be an independent predictor of survival.[27] The antibiotic treatment should be deescalated when cultures results are available to minimize the risk of developing further antibiotic resistance.

Prevention of Acute Kidney Injury

As mentioned previously, patients with SBP are prompt to develop AKI, and the development of AKI is a strong predictor of mortality in these patients.[27,29] The treatment with albumin at the dose of 1.5 g per kg of body weight on day 1 of treatment and 1 g per kg of body weight on day 3 has been shown to reduce the incidence of AKI and improve survival in patients with SBP in a randomized controlled clinical trial.[29] When compared with other plasma expanders, albumin, but not hydroxyethyl starch, was able to significantly increase cardiac stroke volume and systemic vascular resistance in patients with SBP.[30] It has been claimed these effects may be due to the nononcotic properties of albumin. Indeed, in an experimental model of cirrhosis, albumin exerted a positive cardiac inotropic effect, mainly counteracting oxidative stress-induced and TNF-α–induced activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inducible nitric oxide synthase (iNOS) pathway.[31]

Management of Acute Kidney Injury and Hepatorenal Syndrome in Patients With Spontaneous Bacterial Peritonitis

In patients with SBP and AKI the management should follow the International Club of Ascites recommendation (Fig. 84.3).[12] Patients with AKI stage ≥ 2 should receive plasma expansion with albumin (1 g per kg of body weight for 2 days). Patients without response to albumin expansion should be investigated for HRS criteria (Box 84.2). Although liver transplantation represents the optimal treatment of HRS, only a small group of patients are eligible for liver transplantation, and the time needed to get a graft is not predictable. Moreover, in the context of SBP, the infection has to be treated before liver transplantation. Other medical treatments have been developed in the last 15 years, the most effective being the combination of vasoconstrictors plus albumin. The rationale behind the use of vasoconstrictors is to counteract splanchnic arterial vasodilation. Albumin counteracts the reduction in effective circulating volume and seems to have beneficial effects on cardiac contractility in clinical and experimental studies.[30,31]

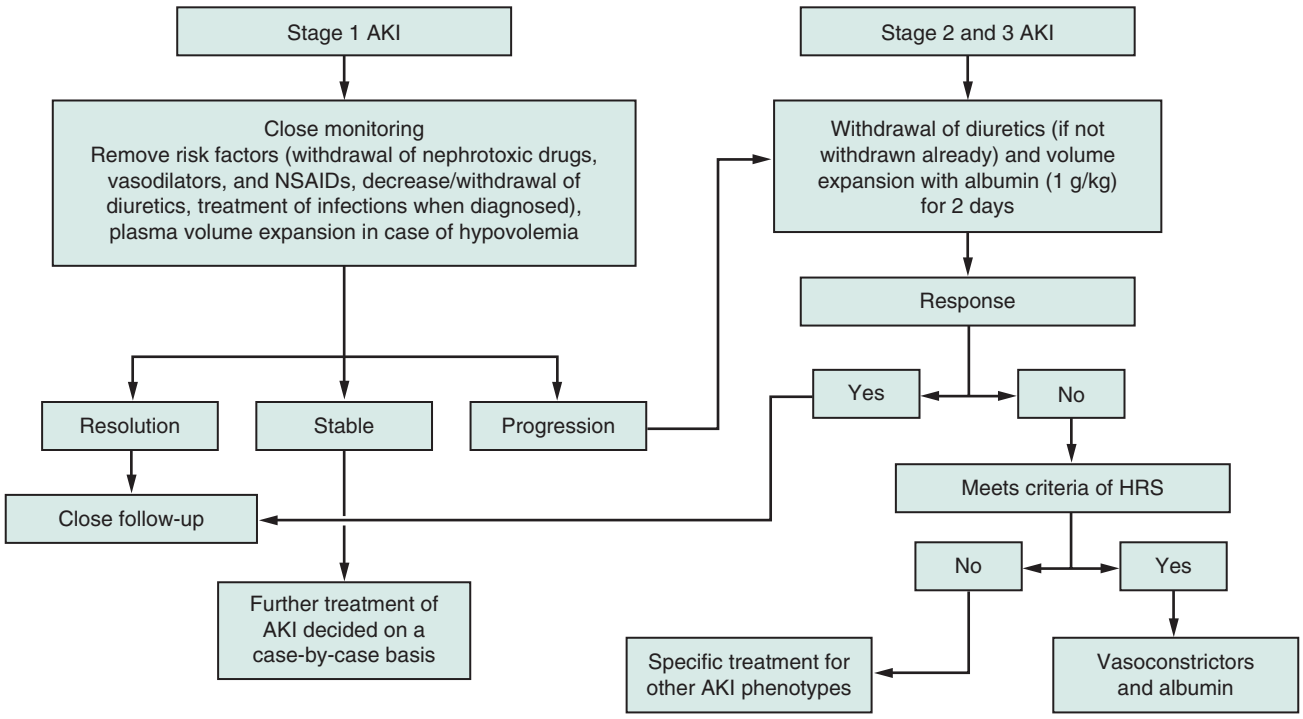

FIGURE 84.3 Management of acute kidney injury in cirrhosis. *AKI,* acute kidney injury; *HRS,* hepatorenal syndrome; *NSAIDs,* nonsteroidal antiinflammatory drugs. (Modified from Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62:968–974.)

BOX 84.2

Diagnostic Criteria of Hepatorenal Syndrome According to International Club of Ascites Criteria

HRS-AKI
Diagnosis of cirrhosis and ascites
Diagnosis of acute kidney injury according to ICA criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
Absence of shock
No current or recent use of nephrotoxic drugs (e.g., NSAIDs, aminoglycosides, iodinated contrast media)
No macroscopic signs of structural kidney injury, defined as:
- Absence of proteinuria (>500 mg/day)
- Absence of microhematuria (>50 RBCs per high-power field)
- Normal findings on renal ultrasonography

AKI, acute kidney injury; *HRS,* hepatorenal syndrome; *ICA,* International Club of Ascites; *NSAIDs,* nonsteroidal antiinflammatory drugs; *RBC,* red blood cells.
Modified from Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62:968–974.

Several vasoconstrictors have been investigated in the treatment of HRS, but terlipressin has been investigated most. The combination of terlipressin and albumin (20–40 g per day) has been shown to be more effective than albumin alone in the treatment of HRS in three randomized controlled trials.[32–34] Terlipressin may be administered as intravenous boluses (starting from 0.5 to 1 mg every 4 to 6 hours to a maximum dose of 2 mg every 4 hours) or as continuous intravenous infusion (starting from 2 mg per day to a maximum dose of 12 mg per day). The latter showed to be the most suitable way of administration in a randomized controlled trial, being associated with a lower incidence of adverse events.[35] The treatment with terlipressin and albumin showed to be effective in resolving HRS in 34% to 56% of cases.[32–36] Other strategies such as the combination of midodrine (starting from 7.5 mg every 8 h to 12.5 mg every 8 h) plus octreotide (starting from 100 μg every 8 h to 200 μg every 8 h) and albumin were found to be effective in the treatment of HRS.[37] However, in a recent multicenter randomized controlled trial, terlipressin and albumin were more effective than midodrine plus octreotide and albumin in the treatment of HRS.[36] Noradrenalin showed a similar efficacy than terlipressin in a randomized controlled trial,[38] but the sample size in this study was too small to detect a difference between the two groups, and further studies are warranted. Treatment with vasoconstrictors plus albumin should be continued until SCr reaches a value below 1.5 mg/dL. About 20% of patients may present a recurrence of HRS after treatment withdrawal, and retreatment is usually effective. Some patients may show a continuous recurrence of HRS at any attempt to discontinue terlipressin. These patients have been suggested as a high priority in liver transplant waiting list[39] and/or outpatient infusion.[40]

The management of patients who do not respond to treatment with vasoconstrictors plus albumin is a matter of debate. Transjugular intrahepatic portosystemic shunt (TIPS) has been shown to be effective in some pilot studies; however, TIPS is contraindicated in many patients with HRS.[41] In liver transplant candidate renal replacement therapy (RRT) often is used in clinical practice, but the optimal timing and modality of RRT as well as its clinical impact has never been evaluated so far.

Prophylaxis of Spontaneous Bacterial Peritonitis

After an episodes of SBP the probability of developing a recurrence of SBP is very high (about 70%) at 1 year.[42] In these patients, secondary prophylaxis with norfloxacin has been shown to significantly reduce the recurrence of SBP, although no significant benefit on survival was found.[42]

Furthermore, primary prophylaxis of SBP is recommended in other two conditions: after an episode of gastrointestinal bleeding and in patients with a protein concentration in ascitic fluid below 1.5 g/dL and advanced liver disease (Child Pugh ≥ 9 and bilirubin ≥ 3 mg/dL, serum sodium ≤ 130 mmol/L, or serum creatinine ≥ 1.2 mg/dL). Patients with cirrhosis have a high incidence of SBP after an episode of gastrointestinal bleeding, and norfloxacin prophylaxis has been shown to reduce the incidence of SBP.[43] In patients with gastrointestinal bleeding and severe cirrhosis (at least two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin>3 mg/dL), ceftriaxone showed to be more effective than norfloxacin in preventing bacterial infections.[44] Patients with cirrhosis and a protein concentration in ascetic fluid below 1.5 g/dL have a high risk of developing SBP. In a randomized placebo-controlled trial comparing norfloxacin versus placebo, norfloxacin significantly reduced the incidence of SBP and improved survival in patients with cirrhosis and advanced liver disease (see earlier).[45] Interestingly, norfloxacin also reduced the incidence of HRS. Finally, patients who survive an episode of SBP have a poor survival (25% to 30% at 2 years) and should be referred to a liver transplant center for considering liver transplant eligibility.

Key Points

1. Spontaneous bacterial peritonitis (SBP) is a life-threatening complication in patients with cirrhosis and ascites and is very common in hospitalized patients.
2. SBP can lead to the development of acute kidney injury (AKI) and hepatorenal syndrome (HRS) through an increase in splanchnic arterial vasodilation and systemic inflammation.
3. Prevention of AKI and HRS is crucial to improve prognosis in patients with SBP.
4. The optimal management of HRS in patients with SBP requires an adequate antibiotic treatment and the administration of terlipressin and albumin.

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