INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a common, serious complication in patients with cirrhosis and ascites. It is a bacterial infection of ascitic fluid in the absence of an adjacent, surgically amenable infection source. Since its description in 1964 (1) numerous studies, guidelines, and both national and international consensus conferences have brought significant advancement to the diagnosis and treatment of this condition, and significantly changed its prognosis (2-12).

Initially considered a fatal complication of cirrhosis, with mortality above 90%, the condition may be currently treated with an in-hospital mortality rate around 20-30% (13). However, it still is a highly relevant condition in clinical practice given its high prevalence (it affects 10-30% of inpatients with cirrhosis and ascites), high recurrence rate (up to 70% in the first year), and poor long-term prognosis with mortality reaching 50-70% at one year, which leads to consider patients recovering from SBP potential candidates for liver transplantation (4-10).

PATHOPHYSIOLOGY

The key pathogenic mechanism that starts SBP is bacterial translocation (BT), a process by which both viable and non-viable enteric bacteria, as well as their products (endotoxins, DNA), cross the intestinal mucosal barrier to infect mesenteric lymph nodes, whence they enter the bloodstream and then ascitic fluid (AF) (14). Patients with a reduced defensive capacity in their AF have been shown to be more susceptible to peritonitis development (13).

All three major defense mechanisms preventing BT in normal subjects are impaired during cirrhosis -intestinal flora stability, intestinal epithelium integrity, and the host’s immune defense (15). In advanced cirrhosis, intestinal motility is highly reduced because of sympathetic nervous system hyperactivation, which leads to intestinal bacterial overgrowth (16). Bacterial overgrowth has been shown to favor BT (17). On the other hand, in patients with advanced cirrhosis intestinal mucosal permeability is increased, a direct consequence of portal hypertension and local proinflammatory events mainly triggered by endotoxin release (18). Lastly, defective local and systemic defense mechanisms have been seen in cirrhotic patients: neutrophile and macrophage phagocytosis is reduced, as is the effector function of immunocompetent cells circulating in the blood, which limits the bacteriostatic ability of serum and AF (19). AF opsonization capacity is correlated with total protein levels in AF. It is a well-established fact that patients with reduced total proteins in AF have a greater risk for SBP (20).

The on-and-off passage of bacterial products (endotoxins, bacterial DNA) into the systemic circulation leads to a chronic inflammatory status characterized by persistent innate immunity and cytokine synthesis activation (21). The activation of the systemic immune-inflammatory system in turn contributes to the worsened circulatory dysfunction seen in cirrhosis. Circulating proinflammatory cytokines such as TNF-α activate nitric oxide production thus favoring peripheral vasodilation. The impact of BT also extends to AF (22). Bacterial product (LPS, DNA) and proinflam-
Inflammatory cytokine (IL-6, TNF-α) hyperproduction activates peritoneal macrophages and the synthesis of proangiogenic and vasodilator molecules (VEGF, nitric oxide). Finally, as a consequence of arterial vasodilation endogenous vasoactive systems become activated, and renal function is ultimately impaired, which usually complicates the natural course of SBP (23,24) (Fig. 1).

**CLINICAL MANIFESTATIONS**

The symptoms and signs of SBP are usually subtle, hence a high index of suspicion is needed to prevent diagnostic delay, which entails a considerable worsening of prognosis, especially in patients with a greater impairment of liver function. Up to 13% of cases may be
asymptomatic (8,10). Clinical manifestations usually consist of a worsening of symptoms commonly associated with cirrhosis, including increased ascites, diuretic therapy failure, encephalopathy development or worsening, vomiting, etc. (13). Hence, when a cirrhotic patient with ascites is admitted to hospital SBP should be searched for even in the absence of obvious clinical manifestations. Outside the hospital setting, SBP in cirrhotic patients with ascites is less common, occurs in patients with better liver function, and usually has a more favorable prognosis (25). Whenever a cirrhotic patient presents with temperature above 37.8 °C infection should be ruled out (up to 68% of patients with SBP have fever). Other common symptoms include abdominal pain and tenderness (present in 49 and 39% of patients with SBP, respectively), rebound sign (present in 10% of patients with SBP), and altered, often mildly, mental state (in 54% of patients) (26). The development of paralytic ileus, hypotension or hypothermia occurs in advanced stages and entails a poorer prognosis. Laboratory changes such as leukocytosis, metabolic acidosis or impaired renal function should always prompt the exclusion of SBP, even in the absence of other clinical manifestations (8).

DIAGNOSIS

Diagnostic paracentesis and cell count

The diagnosis of SBP is primarily based on the polymorphonuclear (PMN) count in AF as obtained using diagnostic paracentesis. SBP is established when PMN numbers are equal to or greater than 250/µl in the absence of a surgically amenable intra-abdominal infectious site. This value enjoys high sensitivity, specificity, and diagnostic accuracy (4). Traditionally, neutrophil count in AF was manually performed given the poor precision of automated counts regarding low neutrophil values in this setting. However, a study demonstrated an excellent correlation between both methods, hence automated counts may well replace manual ones in the near future (27). In the presence of hemorrhagic ascites (> 10,000 RBCs/µl), one PMN must be subtracted per 250 red blood cells. Total leukocytes in AF is useless in the diagnosis of SBP (5,6). On the other hand, reactive strips used to assess urine leukocytes have shown a lower sensitivity than PMN counting for the diagnosis of SBP, and their use is therefore discouraged (28,29).

Other infection markers such as serum procalcitonin and ascitic lactoferrin have proven useful for diagnostic uncertainty, but further studies are needed before its use may be recommended (30-32). Markers such as ascitic pH or lactate were successfully used in some studies, but have been discontinued as of today (33,34).

As mentioned above, diagnostic paracentesis is indicated for all cirrhotic patients with ascites who are admitted to hospital. Furthermore, it should always be performed when a patient has: a) signs or symptoms suggesting peritonitis, including abdominal pain, painful abdominal decompression, and altered intestinal motility (vomiting, diarrhea, ileus); b) evidence of systemic infection including temperature above 37.8 °C, peripheral leukocytosis, or septic shock; c) impaired liver (hepatic encephalopathy) or renal function; and d) digestive bleeding before antibiotic prophylaxis onset (4-6,8).

Asitic fluid cultures

In addition to cell counts, AF samples should be always obtained for culture. A positive culture is not necessary for diagnosis given its low sensitivity because of low bacterial levels in AF. At the time of paracentesis at least 10 mL should be inoculated into hemoculture bottles for both aerobes and anaerobes, and promptly delivered to a microbiology lab. In this way culture performance in this setting has been increased to 50-70% of cases, and 90% is reached in some studies (35-37).

In a high number of patients, hemocultures have been seen to be positive and, since in such cases germs isolated from peripheral blood are presumably those responsible for SBP, samples for hemoculture should be always obtained when SBP is suspected (38).

SBP variants

Neutrocytic ascites with negative culture

In this situation PMN count is ≥ 250/µl in AF but culture is negative. However, these patients have similar signs, symptoms, and prognosis when compared to subjects with SBP and positive AF culture. Therefore, “SBP with negative culture” seems a more appropriate designation, as is also the case with other infections where no causal germ is isolated and denominations or therapies remain unchanged (38,39). Nevertheless, other causes of increased neutrophils in AF should be excluded, including peritoneal carcinomatosis, peritoneal tuberculosis, hemorrhagic ascites, and pancreatitis (3).

Bacteriascites

It is characterized by bacterial AF colonization in the absence of inflammatory response; PMN < 250/µl in AF with a positive bacterial culture. Patients with bacteriascites make up a heterogeneous population. Some patients suffer from spontaneous colonization while in others colonization is secondary to extraperitoneal infection. The natural history of untreated bacteriascites is also variable, from spontaneous remission in over 60% of patients (particularly in asymptomatic subjects)
to the development of full-fledged SBP. Patients who develop SBP usually have infection signs or symptoms at the time of paracentesis (fever, abdominal pain, encephalopathy), and should receive empiric antibiotics pending AF culture results regardless of PMN count (40).

A diagnosis of bacteriascites is reached at 2-3 days after paracentesis (time needed for culture growth). Asymptomatic patients do not require immediate therapy, and a repeat paracentesis with cell count and culture is recommended on day 3, following which measures are to be taken according to results obtained. When PMN count in the second sample is ≥ 250/µl, antibiotics must be initiated because of potential progression to SBP. If counts remain < 250/µl and cultures remain positive, antibiotic therapy initiation is perhaps most recommended. If PMN count remains < 250/µl and culture has become negative, bacteriascites may be said to have spontaneously subsided and no therapy is needed (5,6).

**Secondary bacterial peritonitis**

AF infection from visceral perforation or an abdominal organ abscess is designated secondary bacterial peritonitis (SecBP). Clinical manifestations will not help in differentiating patients with SBP—who only need antibiotics—from those with SecBP, who will need a surgical procedure.

We may suspect SecBP based on AF characteristics when 2 or more of the following are identified: glucose level < 50 mg/dl, proteins > 1 g/dl, and LDH higher than in plasma (26). However, the specificity of these criteria is low, and the definition of other criteria has been therefore attempted to help in the differential diagnosis. Carcinoembrionary antigen > 5 ng/ml in AF or alkaline phosphatase > 240 U/l in AF have been successfully used in the diagnostic of peritonitis secondary to intestinal perforation with high sensitivity and specificity, although they have proven useless when peritonitis does not result from visceral perforation (41).

SecBP should also be suspected in cases of polymicrobial ascites after Gram staining or culture, particularly when fungi, enterococcus, or anaerobes are identified. In addition, when a patient diagnosed with SBP does not respond to initial antibiotic therapy should SecBP be ruled out.

In any patient with cirrhosis, ascites, and suspected SecBP antibiotic therapy must cover anaerobes and enterococci, and further studies with conventional X-rays, tomography and labeled-leukocyte scanning should be performed (26,41) (Fig. 2).

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**Fig. 2. Algorithm for the differential diagnosis between spontaneous and secondary bacterial peritonitis (modified from reference 26) (PMN: polymorphonuclear; AF: ascitic fluid; TP: total proteins).**
TREATMENT

Antibiotic therapy

Empiric antibiotic therapy should be initiated immediately following the diagnosis with SBP, and then subsequently modified according to the antibiogram. The antibiotic used must cover all germs commonly responsible for SBP (3-6). Gram-negative bacteria cause nearly 80% of events, primarily *Escherichia coli* and *Klebsiella pneumoniae*. The remaining 20% results from Gram-positive aerobes, mainly *Streptococcus* species and enterococci (42,43). Antibiotics should also reach adequate AF levels. Third-generation cephalosporins are currently considered the treatment of choice, cover 95% of isolated germs, and clear infection in 77-98% of patients (44-46). Cefotaxime at 2 g/12 hours has proven as effective as in doses of 2 g/6 hours (47). Similarly, cefotaxime in doses of 2 g/8 hours for 5 days is as effective as scheduled for 10 days (48). Other third-generation cephalosporins have also been successful, including ceftriaxone and cefazidine (49-51). Amoxicillin plus clavulanic acid, first given intravenously and then by mouth, has shown results similar to those of cefotaxime in a comparative study, albeit with an inadequate number of patients (45). In patients with allergy to –lactams quinolones may be used, including intravenous ciprofloxacin (52-54). Aminoglycoside and –lactam combinations have also been tried; however, these are not more effective for infection clearance and are associated with a high incidence of nephrotoxicity, hence they are not recommended for the empiric management of SBP (55). Despite the above, according to a recent systematic review discussing thirteen studies, there is no clear evidence yet on the optimal antibiotic, dose, and duration that should be selected for treatment (56).

As a result of the widespread use of quinolones for the prophylaxis of SBP in groups at risk, an increase in infections by gram-negative germs resistant to quinolones and gram-positive bacteria has been identified. However, third-generation cephalosporins remain effective in the management of SBP by said microorganisms, and data available are inadequate to change recommendations in this setting (43,57). In contrast, a recent study has shown an increased frequency of infections by multiresistant bacteria in cirrhotic inpatients, and fewer probabilities to solve infection with the standard empiric therapy, this being why the authors suggest that extended-spectrum antibiotics such as carbapenems and glycopeptides be included in the empiric management of nosocomial infection in cirrhotic patients (58). In another study where 220 SBP events were analyzed, 23.6% were caused by cefotaxime-resistant germs. Risk factors included antibiotic use in the previous three months, presence of diabetes, and inpatient SBP episodes (59).

In patients with non-complicated SBP, that is, stable patients with no GI bleeding, paralytic ileus, severe renal failure signs (creatinine < 3 mg/dL) or severe hepatic encephalopathy (grade < II) oral antibiotics may be indicated. In a multicenter, randomized, controlled study of such selected patients oral ofloxacin 400 mg/12 hours for 8 days was as effective as conventional therapy with intravenous cefotaxime (46). Patients with non-complicated SBP have also been successfully managed with oral courses of cefixime (60) and ciprofloxacin (61), or with IV therapy followed by oral amoxicillin-clavulanic acid (47) or ciprofloxacin (53,54).

**Albumin overload**

Up to 30% of patients with SBP develop impaired renal function, which is the most relevant risk factor for inpatient mortality (62). SBP results in functional renal insufficiency because of a decrease in effective vascular volume, which adds to the altered circulatory status of a patient with advanced liver cirrhosis (62). In a controlled, randomized trial in patients with SBP on cefotaxime, expansion using intravenous albumin (1.5 g/kg at diagnosis and 1 g/kg on day 3) reduced the incidence of renal failure from 33 to 10%, and mortality from 29 to 10% (63). An increase in effective intravascular volume seems the primary mechanism through which albumin improves renal function in these patients. However, whether volume expansion is required for all patients or just those in the subset with a higher risk for impaired renal function, whether such expansion should be attempted with albumin or other plasma expanders, and whether doses as high as those administered in this trial are necessary are points that remain to be properly established (4). A recent study concludes that albumin use should be restricted to patients with severe liver failure (serum bilirubin > 4 mg/dl) or renal function impairment signs (BUN > 30 mg/dl or serum creatinine > 1 mg/dl) (64). In a recent report albumin was superior to hydroxyethyl for plasma volume expansion (65). In this study albumin improved systemic hemodynamics by also targeting peripheral arterial circulation through an increase in peripheral vascular resistance. These authors suggest that albumin may have an inhibitory effect on endothelial function.

**Treatment response assessment**

SBP is considered resolved when all local and systemic signs are gone, PMN count in AF and PMN count in peripheral blood are back to normal, and AF culture is negative. In patients where infection persists mortality is very high despite appropriate antibiotic therapy modification (66,67). Early recognition of treatment failure and timely therapy changes are crucial in these patients. To this end infection must be followed up closely. Some guidelines suggest the use of diagnostic paracentesis at 48 hours after antibiotic therapy initiation in order to con-
firm a reduced PMN count (a decrease inferior to 25% is suggestive of poor response) (4-6). However, the latest AASLD guidelines consider this measure unnecessary in patients with no diagnostic uncertainties and positive infection evolution (3). In case of negative progression the initial antibiotic should be changed (under antibiogram guidance if possible), and secondary bacterial peritonitis should be excluded.

PROPHYLAXIS

The frequency of SBP in cirrhotic patients and the high morbidity and mortality associated with this condition warrant the use of prophylactic measures. Since the primary mechanism of infection is the BT of gram-negative, enteric germs, antibiotics should provide selective intestinal decontamination, that is, a clearance of the gram-negative flora while preserving anaerobes. However, the high cost and risk of bacterial resistance development restricts prophylaxis to high-risk groups (68). Three categories of cirrhotic patients with ascites and higher risk for SBP have been identified—patients with no prior SBP and low proteins in AF and/or increased serum bilirubin (primary prophylaxis), patients who survived a previous SBP episode (secondary prophylaxis), and inpatients with GI bleeding.

Primary prophylaxis

Patients with low protein levels in AF and/or high serum bilirubin have a higher risk for SBP. The probability of a first SBP episode in patients with serum bilirubin higher than 2.5 mg/dl was up to 43% in one study (69). In other study 15% of patients with AF proteins below 10 g/l developed SBP during their hospital stay (70). When protein levels are high in AF (> 15 g/l) the risk for SBP is negligible and antibiotic prophylaxis is considered unnecessary (70-72). While no clear scientific evidence allows recommendations for patients with AF protein levels lower than 15 g/l, some studies suggest that antibiotic prophylaxis might be an appropriate strategy (73-77). The antibiotic used in most studies is norfloxacin 400 mg/day continuously (73-75,77). In a controlled, randomized study (77) patients with low AF proteins (< 15 g/l), advanced liver failure (Child-Pugh ≥ 9, bilirubin ≥ 3 mg/dl) or impaired renal function (creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl, serum sodium ≤ 130 mEq/l) receiving norfloxacin were less likely to develop SBP (7 vs. 61%) and hepatorenal syndrome (28 vs. 41%) after one year, and showed higher survival at 3 months (94 vs. 62%) when compared to patients receiving no antibiotic prophylaxis. Other antibiotics used in the primary prophylaxis of SBP include ciprofloxacin 500 mg/day (76) and trimethoprim-sulfamethoxazole 160/800 mg 5 days/week (78,79). Most recent clinical guidelines recommend antibiologic prophylaxis for SBP in these high-risk patients, preferably in a continuous schedule and not only during hospital admissions (3,4). However, available data are insufficient to recommend antibiotic prophylaxis for all patients on liver transplant waiting lists (3).

Secondary prophylaxis

Patients recovering from a SBP episode have an annual relapse probability of up to 70% (2). The use of antibiotic prophylaxis is widely established in these patients (3-10). There is only one controlled study of norfloxacin in patients who recovered from an SBP event where the probability of SBP relapse decreased from 68 to 20% in patients receiving antibiotic prophylaxis with norfloxacin (400 mg/24 hours, PO) (80). Other studies evaluating norfloxacin (73), ciprofloxacin 750 mg/week (81) or trimethoprim-sulfamethoxazole 160-800 mg 5 days/week (78,79) included patients with and without prior SBP. Daily dosing schedules have proven superior to intermittent schedules as the latter select bacterial resistance with a higher frequency (82).

Assessing liver transplantation is important in patients recovering from SBP given its poor prognosis (83,84). When liver function improves and ascites disappears, whether prophylaxis should be maintained indefinitely or discontinued is not clear (4,5).

Prophylaxis in cirrhotic patients with GI bleeding

Bacterial infection is a common issue in cirrhotic patients with acute GI bleeding—up to 20% are infected at admission and around 50% become infected during their hospital stay (85-94). In addition, infection risk has been shown to be higher in patients with advanced cirrhosis and severe GI bleeding (91,92,95). On the other hand, the presence of infection aggravates prognosis in these patients by increasing the risk of hepatorenal syndrome, failed bleeding management, and rebleed chances, and ultimately by increasing inpatient mortality (92,95). A meta-analysis of 5 studies of antibiotic prophylaxis in these patients concludes that antibiotics are effective for the prevention of bacterial infection, which is associated with significantly improved survival (by 9.1% in the treated group) (92). According to a prospective, randomized study, norfloxacin 400 mg/12 hours PO or via a nasogastric tube for 7 days prevents bacterial infection, specifically SBP, in cirrhotic patients with gastrointestinal bleeding (87). Intravenous ofloxacin may be used during active bleeding (88). However, the changes seen in recent years in the epidemiology of bacterial infection in patients with cirrhosis, with an increase in quinolone-resistant gram-negative bacilli, and a high frequency of infection by gram-positive germs in association with invasive endoscopic procedures have led some authors to...
reconsider antibiotic therapy (43,95). In a recent study in patients with GI bleeding and advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin > 3 mg/dl), ceftriaxone 1 g/24 hours was more effective than norfloxacin (400 mg/12 hours) for the prevention of infection and SBP (11 versus 33%, and 2 versus 12%, respectively) (95).

CONCLUSION

SBP is a common, serious complication in patients with advanced liver cirrhosis and ascites. Early diagnosis and treatment have improved prognosis in the last few years. However, its poor long-term prognosis leads to consider liver transplantation for patients recovering after 1 year. However, its poor long-term prognosis leads to reconsider antibiotic therapy (43,95). In a recent study in patients with GI bleeding and advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin > 3 mg/dl), ceftriaxone 1 g/24 hours was more effective than norfloxacin (400 mg/12 hours) for the prevention of infection and SBP (11 versus 33%, and 2 versus 12%, respectively) (95).

CONCLUSION

SBP is a common, serious complication in patients with advanced liver cirrhosis and ascites. Early diagnosis and treatment have improved prognosis in the last few years. However, its poor long-term prognosis leads to consider liver transplantation for patients recovering from a SBP episode.

Diagnosis requires a high index of suspicion given that, on occasion, SBP develops insidiously, which renders diagnostic paracentesis mandatory for all cirrhotic patients with ascites and signs or symptoms of infection, GI bleeding, or worsening renal or liver function, and even for asymptomatic inpatients. Once a diagnosis is reached based on elevated AF PMN counts, empiric antibiotic therapy should be initiated early using intravenous third-generation cephalosporins for seriously ill patients. For patients with no renal or liver failure evidence and good digestive tolerance oral antibiotics may be used, including quinolones and amoxicillin-clavulanate. In addition, in selected cases with high risk of renal failure the addition of quinolones and amoxicillin-clavulanate. In addition, in selected cases with high risk of renal failure the addition of volume expansion using intravenous albumin may be recommended. Preventive treatment is indicated for patients with a higher risk of developing SBP—those who recovered from a previous episode, subjects with GI bleeding, and selected individuals with low AF protein levels and/or elevated serum bilirubin.

REFERENCES

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