Spontaneous bacterial peritonitis: How to deal with this life-threatening cirrhosis complication?

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Abstract: Spontaneous bacterial peritonitis (SBP) is one of the most common and life-threatening complications of cirrhosis. It occurs in 10% to 30% of patients admitted to hospital and recent studies tend to demonstrate that SBP incidence seems to be decreasing in its frequency. A bacterial overgrowth with translocation through the increased permeable small intestinal wall and impaired defense mechanisms is considered to be the main mechanism associated with its occurrence. The Gram-negative aerobic bacteria are the major responsible for SBP episodes and Gram-positive bacteria, mainly *Staphylococcus aureus*, are being considered an emergent agent causing SBP. The prompt diagnosis of SBP is the key factor for reduction observed in mortality rates in recent years. The clinical diagnosis of SBP is neither sensitive nor specific and the search for new practical and available tools for a rapid diagnosis of SBP is an important endpoint of current studies. Reagent strips were considered a promising and faster way of SBP diagnosis. The prompt use of empirical antibiotics, mostly cefotaxime, improves significantly the short-term prognosis of cirrhotic patients with SBP. The recurrence rate of SBP is high and antibiotic prophylaxis has been recommended in high-risk settings. Unfortunately, the long-term prognosis remains poor.

Keywords: cirrhosis, ascites, diagnosis, peritonitis, treatment

Introduction

The relevance of infections in cirrhotic patients has been demonstrated since that 30% to 50% of patients have one type of infectious complication when admitted to hospital and 15% to 35% develop infections after being in hospital (Navasa et al 1999). Urinary, respiratory, ascitic fluid infections and bacteremia are the most common infectious complications found mostly in Child-Pugh B and C cirrhotic patients (Krencker 1907; Brule et al 1939; Cachin 1955; Navasa et al 1999). Spontaneous bacterial peritonitis (SBP), reported by Caroli and Platteborse (1958) has had its importance increased since Kerr and colleagues (1963) and Conn (1964) published two papers about this cirrhosis complication almost simultaneously. Kerr and colleagues (1963) described 11 episodes of ascitic fluid infection in 9 cirrhotic patients while Conn (1964) introduced the term "spontaneous bacterial peritonitis" for the first time in English literature.

SBP is defined as the infection of ascitic fluid without a contiguous source of intra-abdominal infection (eg, intra-abdominal abscesses, intestinal perforation) and in the absence of intra-abdominal focus of inflammation; cholecystitis or acute pancreatitis (Rimola et al 2000). SBP is one of the most frequent and life-threatening complications of patients with cirrhosis. Mortality rates have stayed constant in spite of the development of new antibiotic treatments and early diagnosis of SBP infection (Fernandez et al 2002). In their study, Singh and colleagues (2003) described the mortality rate of SBP in two different cohorts over a ten-year period and did not find any difference between the cohorts. The in-hospital mortality rate can reach 30% in spite of infection control measures; mortality being generally due to complications such as acute variceal bleeding, development of the

hepato-renal syndrome, or progressive liver failure (Sette et al 1986; Hurwich et al 1993; Mattos 1994; Jeffries et al 1999; Thuluvath et al 2001; Fernandez et al 2002).

The incidence of SBP has been estimated in 10% to 30% of unselected patients admitted to hospital (Hurwich et al 1993; Rimola et al 1995; Jeffries et al 1999; Thuluvath et al 2001; Fernandez et al 2002; Singh et al 2003). Nevertheless, recent studies tend to demonstrate that SBP incidence seems to be decreasing (Sette et al 1986). A recent multicenter study carried out in 70 different centers observed an incidence of SPB of 5.5% (Nousbaum et al 2007). We studied prospectively 200 samples of ascitic fluid of 106 cirrhotic patients and detected SBP in 11% of the studied population in both inpatient and outpatient settings. In asymptomatic outpatients that were submitted to therapeutic paracenteses the incidence of SBP seems to be lower and is estimated at 0.57% to 3.5% (Evans et al 2003; Castellote et al 2008).The outcome of SBP in this group of patient has been demonstrated to be better than in hospitalized cirrhotic patients (Evans et al 2003). The probability of development of the first episode of SBP over a one-year period in patients with end-stage-liver disease and ascites is around 10%.

The mainstay of SBP physiopathology seems to be the association of bacterial translocation with the decrease in host immune system defenses. It has been demonstrated, firstly in animal models with ascites and later in cirrhotic patients, that passage of intestinal bacteria from the gut to extra intestinal sites could be increased (Garcia-Tsao et al 1995; Cirera et al 2001). Studies using oral nonabsorbable antibiotics reinforce the hypothesis that exist a causal relationship between bacterial translocation and the occurrence of SBP. The use of these antibiotics decreases the development of SBP and other spontaneous infections in cirrhotic patients (Rimola et al 1985; Ginès et al 1990; Soriano et al 1992).

The disturbance in small intestinal motility and the presence of hypochlorydria has been demonstrated to occur in cirrhotic patients and seems to be responsible for the bacterial overgrowth commonly observed in these patients (Bauer et al 2001). The actual role of intestinal overgrowth in the pathogenesis of SBP has not yet been settled. Chang and colleagues (1998) demonstrated that the prevalence of bacterial overgrowth was higher in patients with a history of SBP associated to disturbances in small intestinal motility. On the other hand, Bauer and colleagues (2001) were not able to confirm this hypothesis in their investigation.

These bacteria are translocated through the intestinal wall, which has its permeability altered by the portal hypertension; in consequence they reach the mesenteric lymph nodes. After that, they move to the systemic circulation until they contact the ascitic fluid. Other sites than gut have been demonstrated to originate bacteria seeding. These could be represented by pneumococcal sepsis, cellulites, urinary tract and dental infections (Chang et al 1998; Evans et al 2003).

Once the bacteria reach the ascitic fluid, the host immune defense is responsible for the occurrence or not of SBP. The macrophages are the first line of defense of the peritoneal cavity and the impairment in phagocytic activity of reticulendothelial system (RES) can cause a prolonged bacteremia. The liver is the largest organ of the RES and this dysfunction evidently imposes infectious risks. The next step of immune system defense is the activation of complement with further release of cytokines. The polymorphonuclear neutrophilic leukocytes (PMNs) try to destroy the bacteria by entering in the peritoneal cavity. The dysfunction of PMNs and the low levels of complement, both by decreasing in liver production associated to increased consumption as an acute phase response, are commonly observed in cirrhosis and seem to contribute to the conversion of ascitic fluid colonization into SBP (Runyon et al 1985; Guarner et al 1995; Homman et al 1997). For such reasons cirrhosis is considered one of the most common current forms of acquired immune deficiency. More recently, Christou and colleagues (2007) indicated bacteremia/sepsis, respiratory and urinary tract infection, meningitis, endocarditis, phlegmonous colitis and hepatic abscess as other common specific infectious complications beyond SBP, in hepatic cirrhosis.

Etiology

The Gram-negative bacteria are largely responsible for SBP episodes and were isolated in 80% of the cases of SBP that were culture-positive (Fernandez et al 2002). *Escherichia coli*, streptococci (mostly pneumococci), and *Klebsiella* cause most episodes of spontaneous bacterial peritonitis in patients who are not receiving selective intestinal decontamination (Garcia-Tsao 1992). On the other hand, in patients who have been treated with antibiotic prophylaxis (quinolones) the incidence of Gram-positive bacteria has increased and *Staphylococcus aureus* is being considered an emergent agent causative of SBP (Cholongitas et al 1995; Llovet et al 1997; Almeida et al 2007). The incidence of antibiotic resistance in Gram-negative bacteria is increasing mostly due to the widespread employment of quinolones for SBP prophylaxis. The frequency of multiple drug-resistant bacteria has increased from 8.3% to 38.5% while at same time fungal etiology has been noticed to range from 4% to 18.7% (Singh et al 2003).

Some authors have pointed the existence of several risk factors associated with SBP. The ascitic total protein has been recognized as predictive of SBP development and the risk is higher when values of less than 1 g/dL of total protein are found (Runyon 1986; Llach et al 1992) and some experts recommend primary prophylaxis (Frazee et al 2005). Others factors that have been pointed out are serum total bilirubin concentration above 2.5 mg/dL, variceal bleeding, and a prior episode of SBP (Andreu et al 1993; Guarner et al 1999).

Diagnosis

The prompt diagnosis of SBP is the key aspect for the reduction in its mortality rates in recent years. The clinical diagnosis of SBP is neither sensitive nor specific. The signs and symptoms are likely to be insidious and the clinical picture of generalized peritonitis is uncommon. Almost 13% of patients have no signs of infection. The most frequent symptoms associated with SBP are abdominal pain and/or tenderness, fever or new development of encephalopathy. In our study, the disturbing in mental state was the most common feature related to SBP (52%), followed by abdominal pain (24%) and fever (21%). Change in bowel movements is also described and diarrhea can herald SBP. The occurrence of paralytic ileus, hypotension, and hypothermia are always signs suggesting advanced infection and carries on a poor prognosis. The blood samples could reveal leukocytosis, acidosis, and the worsening of renal function. In fact blood cultures are positive in a half of the episodes of SBP and should be done in order to maximize the possibilities of isolating an infecting pathogen (Runyon et al 1987; Rimola et al 2000).

Paracentesis should be done anytime a suspicion of SBP is considered and ascitic fluid analysis is the mainstay of SBP diagnosis. The performance of paracentesis is safe and although almost 70% of cirrhotic patients have an abnormal prothrombin time, less than 1 in every 1000 procedures may complicate with hemorrhagic events. The risk of such complication should not be a reason to avoid it, even in patients with obvious disseminated intravascular coagulopathy or clinically apparent fibrynolisis. Despite the risks the method is worth considering because of its benefits.

The PMN count – greater than 250 cel/mm^3 – and the yield of cultures of the ascitic fluid are considered the gold standard for the diagnosis of SBP (Rimola et al 2000). Ascitic fluid should be cultured at bedside in blood culture bottles, as soon as the paracentesis is done, as firstly demonstrated by Runyon and colleagues (1987) in order to achieve a positive result in almost 91% of the samples. Although many studies have confirmed Runyon's results, Brazilian studies could

not reach this accuracy in isolating SBP pathogens (Sette et al 1986; Mattos 1994; Figueiredo et al 1999; Coral et al 2002). In our studied group of patients, ascitic fluid culture was positive in only 28.5% of samples although it has been cultured at bedside and in accordance to previously described standard techniques. Therefore, the ascitic fluid culture has some shortcomings. First of all, the results of culture are not readily available, which postpones the diagnosis and treatment of the infection. Secondly, one of the most frequent variants of ascitic fluid infection is culture-negative neutrocytic ascites, which occurs in approximately 30% to 50% of patients (Sette et al 1986; Runyon et al 1987; Figueiredo et al 1999; Coral et al 2002).

Not only does the PMN count seems to be accurate enough to determine which patients need to start empiric antibiotic therapy but they have also been considered the easiest way to establish the early diagnosis of SBP (Rimola et al 2000; Moore et al 2003; Runyon 2004). Although the total cell count of polymorfonuclear neutrophilic leukocyte can be easily performed and have a good sensibility for SBP diagnosis, it is not always promptly performed and depends on the interest and skills of the medical technician. This technique could also be not available in every setting (eg, small hospitals). Hence, other ways of establishing SBP diagnoses are under assessment. In spite of the accuracy of automated cell counts in this scenario, it needs to be validated and requires technology not yet widely available (Angeloni et al 2003).

The use of reagent strips for the prompt diagnosis of urinary tract infections is well recognized. It is also applied in the diagnosis of other forms of biologic fluid infections such as pleural effusions, meningitides, and spontaneous bacterial empyema (Moosa et al 1995; Azoulay et al 2000; Castellote et al 2005). The background of those reagents strips is granulocytes esterase activity. This enzyme has been found in ascitic fluid and is responsible for the release of 3-hydroxy-5-phenyl-pyrrole, which causes a color change in an azo dye (purple). The accuracy of those strips for urinary tract infections had been revised in a meta-analysis with a sensibility range from 56% (in emergency setting) to 87% (in outpatient setting) (Devillé et al 2004). This wide discrepancy could be explained mostly by the clinical setting in which it had been used. Other studies have addressed this issue in an SBP scenario and the results showed strips as a promising method with both sensibility and specificity reaching almost 100% (Vanbiervliet et al 2002; Castellote et al 2003; Thèvenot et al 2004; Braga et al 2006; Torun et al 2007). Since those initial studies others have evaluated

different brands of strips achieving good diagnostic accuracy too (Castellote et al 2003; Sarwar et al 2005; Wisniewski et al 2005; Rerknimitr et al 2006).

Unfortunately, a recent prospective multicenter trial that enrolled 70 centers has evaluated the use of Multistix 8SG (Bayer HealthCare, São Paulo, Brazil), both in outpatient and inpatient settings and could not confirm the previous results (Nousbaum et al 2007). In this study sensibility was 45.3%, specificity 99.2%, positive predictive value 77.9% and negative predictive value 96.9%. The test performance was similar to the observed in our recently published study using Multistix 10SG (Ribeiro et al 2007). Hence, the results of these studies confirm the excellent specificity of these strips, but also make obvious its poor sensibility, placing this test as a supportive tool in SBP diagnosis that could not replace the cytological exam.

Moreover the diagnostic accuracy of those strips seems to differ according to the brand that had been used. Kim and colleagues (2005) studied the use of two brands of reagent strips, Uriscan (BioSys Laboratories, La Canada, CA, USA) and Multistix 10SG for SBP diagnosis and found different results in sensibility and specificity. The results obtained with Uriscan were better than those observed with Multistix 10SG. Sapey and colleagues (2005a, 2005b) also used different brands, Nephur Test (Roche Diagnostics GMBH, São Paulo, Brazil) and Multistix SG, and found that Nephur Test outperfomed Multistix SG.

The largest published study to date used Multistix 8SG (Nousbaum et al 2007), so it seems reasonable to carry out new research comparing different brands in a large number of patients to clarify this issue.

Treatment

The development of new antibiotics and the possibility of an earlier diagnosis of SBP have dramatically changed the natural history of its resolution from 25% before 1980 to 70%–90% in the last few years (Navasa et al 1999).

Felizart and colleagues (1985) demonstrated the first evidence of cefotaxime efficiency for SBP. The comparison of cefotaxime with the association of ampicillin and tobramicin showed a higher rate of infection resolution with neither nephrotoxicity nor super infection in those treated with cefotaxime. Since that, cefotaxime is being considered the treatment of choice for SBP and the dosage recommended is 2 g every 8h (Rimola et al 1995, 2000; Moore et al 2003). However, one study compared two different doses of cefotaxime in 143 patients with SBP, using 2 g every 6 h and 2 g every 12 h (Rimola et al 1995). The rate of infection

resolution was the same in both groups (77% versus 79%). The interval between doses could be less frequent, mainly in patients with renal function impairment. A similar third-generation cephalosporin, as ceftriaxone 2 g intravenous daily, is considered a reasonable choice for suspected SBP, in empiric therapy, while the result of ascitic fluid culture is not known (Javid et al 1998).

Other antibiotics have been studied and are an alternative for SBP treatment, but caution should be taken in avoidance of those that have nephrotoxicity and increased risk of multiresistant bacteria development. The use of amoxicillin/clavulanate seems to be secure and efficient alternative (Grange et al 1990).

Ofloxacin, an oral quinolone, has been demonstrated to be as effective as intravenous cefotaxime in treatment of uncomplicated patients with SBP, but the only drawback of this treatment is the recent observation of quinolone-resistant organism emergence (Navasa et al 1996; Moore et al 2003). Intravenous ciprofloxacin starting therapy followed by another oral antibiotic has also been demonstrated to produce good results in infection control (Terg et al 2000).

The increase in Gram-positive cocci as the causative pathogen of SBP has been attributed to the use of norfloxacin prophylaxis and invasive procedures that patients are submitted (Llovet et al 1997; Cholongitas et al 2005). Nevertheless, few data exist regarding the susceptibility of these agents (Navasa et al 2002; Almeida et al 2007). The occurrence of methicillin-resitant *S. aureus* to quinolone and trimethoprim-sulfamethoxazole is being shown (Almeida et al 2007).

One of the most important predictor of death in SBP is renal function impairment that occurs in almost 30%–40% of patients. The use of plasma volume expansion, such as albumin, decreases the risk of death from 10% to 30% (Bass 1999; Runyon 1999; Sort et al 1999). The incidence of 10% in-hospital mortality is the lowest reported in literature. The use of albumin is based on the theory that plasma volume expansion could attenuate the hemodynamic changes observed in those patients (Ginès et al 1997). Albumin infusion has been recommended in a 10 dosage of 1.5 g/kg of body weight at diagnosis, followed by 1 g/kg of body weight on day three (Salerno et al 2007). Although it is a currently practice, based on a single study that demonstrated lower mortality rates and lower occurrence of renal impairment, further controlled studies should be done to confirm these findings.

SBP Prophylaxis

The SBP recurrence rate is high; demonstrated in 40%–70% of patients after one year of development of the first episode

(Tito et al 1988). Consequently, the secondary prophylaxis treatment should be done in this setting. The mortality rates could be significantly reduced to 20% in patients submitted to the use of oral norfloxacin (400 mg/day) and the approach advised by the International Club of Ascites seems to be cost-effective (Moore et al 2003). The use of weekly quinolones could not achieve this efficacy and the emergence of resistant pathogens seems to be an actual problem.

The recommendation of primary prophylaxis is not well defined and there is no consensus about the matter. The risk of increased Gram-positive resistance in those who use prolonged antibiotic prophylaxis has been considered a problem to recommend it and some authors disagree of this strategy, limiting the antibiotic employment to in-hospital period (Novella et al 1997). Factors that have been associated with increased SBP incidence are: low protein ascitic fluid, low platelet counts ($<$98.000 mm^3) and high serum bilirubin levels ($>$3.3 mg/dL) (Guarner et al 1999). Further studies are necessary to figure out the actual factors, which predispose SBP occurrence and how to deal with them. Fernández and colleagues (2007) have recently demonstrated the efficacy of norfloxacin in preventing SBP as its importance in the delay of hepatorenal syndrome.

On the other hand, the role of SBP prophylaxis in patients with acute intestinal bleeding is renowned. A meta-analysis evaluated the use of antibiotic prophylaxis for patients with gastrointestinal hemorrhage and reports a significant reduction in the incidence of SBP and an improvement in short-term survival was also demonstrated (Bernard et al 1999). The decrease in the rate of variceal rebleeding could be observed in another recent study (Hou et al 2004). The International Ascites Club recommends the use of norfloxacin 400 mg every 12 h in every patient admitted to hospital with gastrointestinal bleeding whenever ascites is present or not (Moore et al 2003). Ciprofloxacin 500 mg every 12 h is also recommended by the British Society of Gastroenterology guidelines (Jalan and Hayes 2000).

The increased emergence of multiresistant pathogens, mostly quinolone-resistant bacteria, has demanded the search for alternative ways of SBP prophylaxis. Other antibiotics such as amoxicillin-clavulanate and trimethoprim-sulfamethoxazole are proved to be efficient (Lontos et al 2007). Other forms of SBP have being studied as the use of cisapride and propranolol that were evaluated in order to increase the intestinal motility and consequently decrease the bacterial translocation (Pardo et al 2000; Perez-Pararmo et al 2000). The studies in animal models reveal the efficacy

of such drugs, but the usage of them in humans needs to be demonstrated. The economic issue of long-term antibiotic prophylaxis was evaluated by two different studies that proved this approach as being cost-saving in high-risk patients. A recent study (Fernández et al 2006) calls attention to the higher effectiveness of ceftriaxone in comparison to oral norfloxacin in the prophylaxis of bacterial infections in patients with advanced cirrhosis and hemorrhage. Another relevant fact is the role of tumor necrosis factor-α (TNF-α) in SBP and its therapy since that in the experimental model of CCl4-induced rat with cirrhosis and ascitic fluid, anti-TNF-α mAb administration decreases the incidence of bacterial translocation, in a TNF-α/sTNF-α receptor-independent manner, without increasing the risk of systemic infections (Francés et al 2007).

Actually, the importance of this life-threatening condition is being widening studied and the early diagnosis associated with better treatments with drugs that have less nephrotoxicity have dramatically changed the current scenario of SBP. The widespread use of broad-spectrum antibiotics needs to be stopped and further studies on alternatives forms of SBP prophylaxis are waited for the perfect management of such hazardous cirrhosis complication.

Disclosure

The authors report no conflicts of interest in this work.

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