Spontaneous bacterial peritonitis : pathogenesis, diagnosis, and management

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Abstract

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascitic fluid which arises in the absence of any other intraabdominal infection source. SBP may develop in all cirrhotic patients with ascites. Gram-negative aerobic bacteria and non-enterococcal Streptococcus spp. are the most common organisms isolated from ascites. Diagnosis necessarily relies on paracentesis and requires a high index of suspicion. The incidence of mortality of the first episode varies between 10% and 46%. Early antibiotic treatment is warranted. Renal impairment develops in approximately one-third of patients with spontaneous bacterial peritonitis and is postulated to arise as a result of a further reduction in effective arterial blood volume. Cefotaxime has been the most extensively studied antibiotic for this infection. It is considered to be one of the first choice antibiotics because of low toxicity and excellent efficacy. Although parenteral antibiotics are generally used, studies evaluated the efficacy of several oral antibiotics in patients with relatively good clinical conditions. The reported probability of spontaneous bacterial peritonitis recurrence one year after the first attack averaged 40 to 69%. Selective intestinal decontamination with 400 mg norfloxacin per day decreased the overall probability of recurrence from 68% to 20% in 1 year of follow-up. (Acta gastroenterol. belg., **2006**, 69, **293-299**).

Key words : cirrhosis; spontaneous bacterial peritonitis ; cefotaxime ; ascites ; infection.

Definition

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of cirrhotic ascitic fluid which arises in the absence of any other intra abdominal infection source. SBP is diagnosed when there is a positive ascitic fluid culture and an elevated ascitic fluid absolute PMN count (at least 250 cells/mm^3) without evidence of secondary bacterial peritonitis (1,2). SBP is a common and serious complication of cirrhosis (3). A neutrophilic count over 250/mm^3 and a negative ascitic fluid culture is defined as culture-negative neutrocytic ascites (CNNA) (4).

Prevalence and risk factors

The prevalence of SBP in cirrhotic patients admitted to the hospital because of ascites averages 10 to 30% (3). Nearly half of the SBP events are diagnosed at hospital admission and the others are acquired during hospitalization (3,5,6).

The risk of developing SBP is greater in those with a coexisting gastrointestinal bleeding, a previous episode of SBP or low ascitic protein levels (7-12). Long term prospective studies reported that the probability of first SBP attack in patients with ascitic protein < 1.0 g/dL (see serum-ascites albumin gradient) was 20-43% (11, 13) ; The cumulative probability of any infection during a single hospitalization for bleeding is approximately 40-45% (14,15). The infection of those with bleeding may be mediated by shock induced increase of bacterial translocation from the gut to extra-intestinal sites (16). Urinary tract infections are also an under-recognized risk factor for SBP (17). Repeated peritoneal paracentesis was proposed as a risk factor for ascitic fluid infection, but this has not been substantiated in prospective studies (18).

Poor nutritional status, increased serum bilirubin levels, increased serum AST levels, decreased prothrombin activity and reduced total protein concentration in ascitic fluid were commonly associated with first episode of SBP in cirrhosis with ascites (13). In a study involving 109 cirrhotic patients with low ascitic fluid protein high serum bilirubin level (> 3.2 mg/dL) and low platelet count (< 98.000/mm^3) independently correlated with the risk of developing the first spontaneous bacterial peritonitis (19).

Etiology and pathogenesis

All cirrhotic patients with ascites may develop SBP. [3] Gram-negative aerobic bacteria and non-enterococcal Streptococcus spp. are the most common organisms isolated from ascites, in most series (20-23). The most common isolates are the Escherichia coli, Pneumococci, Klebsiella pneumoniae and Enterobacteriae (4,6,24-27). But Gram-positive bacteria are isolated more frequently during the recent years, which are, in their vast majority, resistant to quinolones (28). Patients on norfloxacin prophylaxis and those submitted to invasive procedures presented with a higher rate of infections caused by gram-positive cocci (29).

It is proposed that enteric organisms cross the intestinal mucosal barrier to the mesenteric lymph nodes and enter the systemic blood circulation via the thoracic duct (30-32). Animal models have confirmed that bacterial translocation is involved in the pathogenesis of SBP (32-34). It has been demonstrated that translocation

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of enteric organisms to mesenteric lymph nodes is increased in patients with advanced cirrhosis ; selective intestinal decontamination decreases the incidence of bacterial translocation to levels seen in non-cirrhotic patients (35). The prevalence of mesenteric bacterial translocation was found to be increased by the severity of cirrhosis. These ratios were found to be 3.4% in Child A, 8.1% in Child B, 30% in Child C patients, and 4.5% in the cirrhotic patients undergoing selective intestinal decontamination, in a study involving 101 cirrhotic patients (35). It has been proposed that structural and functional changes due to portal hypertension increases the bacterial translocation (35,36).

Intracellular functions of PMN and monocytes like chemotaxis and phagocytosis decrease in proportion with the liver disease stage, and therefore explain the decreased clearance of bacterial content of mesenteric lymph nodes (20). Opsonic activity of ascitic fluid correlates with protein concentration of the fluid (9). Low-protein ascitic fluid (e.g., < 1 g/dL) is particularly susceptible to SBP (8). Specific etiology of cirrhosis affects neither SBP development nor the prognosis (37,38). The entry of neutrophils into ascitic fluid also indicates failure of peritoneal macrophages to control the infection (39). Spontaneous decrease of neutrophilic count in ascitic fluid was observed in sequential paracenteses (before the initiation of antibiotic treatment) in patients with CNNA and the culture was negative in the second specimen (40). Bacterial DNA (most commonly E. coli) was detected simultaneously in blood and culture negative ascitic fluid in 32.1% of patients by a polymerase chain reaction (PCR)-based method (41). It has also been shown that bacterial DNA can bind to toll-like receptor-9 of cells of innate immune system and activate them (42). Runyon BA proposed that the presence of either whole bacteria or DNA in serum or ascitic fluid would have consequences (stimulation of immune system, effector molecules and cytokines) which have impacts on haemodynamics, renal function and survival (43). Although culture negativity is commonly attributed to insensitive culture methods, it could be also speculated that culture negativity may be due to the bacterial DNA or fragment which triggers the inflammatory response.

Although the number of bacteria present in an episode of SBP is very low (3,43-46), they elicit an intense inflammatory response. There is a dramatic increase in the concentrations of polymorphonuclear leucocytes (PMN) and inflammatory cytokines within the ascitic fluid. Although these defense mechanisms aim at defeat the infection, they may be associated with adverse haemodynamic effects (43-46).

Clinical setting

Patients with SBP have Child-Pugh class B or C cirrhosis (47). Classification according to the Child–Pugh score system in 185 cirrhotics with SBP showed that 22% of the patients were Child B and 74% Child C (5).

Patients may present with fever (38.8 to 66%) and abdominal pain (42 to 73%), but abnormal liver functions or renal impairment may be the only findings (4,5, 23,27,38). However, SBP may be asymptomatic in one third of the patients (4,48). Deterioration in ascitic fluid control has been reported in 22.2% of the cases (38). In a study evaluating 281 SBP episodes, icterus was present in 54.5%, hepatic encephalopathy in 50.7%, and fatigue in 46.7% of the episodes (23).

Diagnosis

Diagnosis must rely on paracentesis. Occurrence of SBP should be suspected in every ascitic cirrhotic patient whose condition is worsening and paracentesis should therefore be performed systematically. Although the prevalence of SBP is almost very low in asymptomatic patients presenting with chronic, even tense ascites, International Ascites Club (IAC) recommends performing a diagnostic paracentesis on hospital admission in all cirrhotic patients with ascites, even in patients admitted for reasons other than ascites (3). Although peritoneal carcinomatosis, pancreatitis, hemorrhage into ascites, and tuberculosis can lead to an elevated ascitic fluid PMN count, most cases of neutrocytic ascites are caused by infection (39). In patients with hemorrhagic ascitic fluid (i.e. ascites red blood cell count > l0 000/mm^3), PMN count must be decreased at the rate of 1 PMN per 250 red blood cells. Ascitic fluid total WBC count alone has low diagnostic value because it may increase in sterile ascites (49,50) and also may be influenced by diuretic therapy (50,51).

Because the mortality, clinical signs and symptoms of patients with CNNA were not different from those of culture-positive SBP, it has been presumed that CNNA is similar to SBP (4). It has also been called as culture-negative SBP (4). It has been suggested that CNNA could be less severe than SBP (52,53), but this was not confirmed in other studies (5,54,55). Culture positivity was not considered necessary for diagnosis of SBP in many studies (4-6,21,27,38,52,56-58). Thus, diagnosis of SBP is based on ascitic fluid PMN count, not the culture in the absence of primary inflammatory abdominal disease.

The automated blood cell counter for the PMN determination in ascitic fluid had been compared with the manual method, which is presently considered as the "gold standard". In the study (59), it has been showed that the automated blood cell counter had a sensitivity of 94% and a specificity of 100% ; positive and negative predictive values were 100% and 99.1%, respectively. The possible advantages of automated cell counters are the availability in case of emergency, the possibility of providing the results in short times, and a low cost (59).

Despite the use of sensitive methods, ascites culture is negative in approximately 40% of patients with clinical manifestations suggestive of SBP and increased ascites PMN count (4,58,60-62). Culture negativity

reported to be 70-75% of the cases in some studies (23, 38,55). Antibiotic – even single dose – before culture, conventional culture method and low bacterial load in ascites of SBP are factors implicated in the quite low sensitivity of culture in SBP diagnosis (61,63). Gram stain of the ascitic fluid is most helpful in detecting secondary peritonitis, but is of little value in guiding the choice of empirical antibiotic treatment for spontaneous ascitic infections (39).

Differential diagnosis

Secondary peritonitis should be considered in any patient with neutrocytic ascites. Clinical symptoms and signs do not distinguish patients with secondary peritonitis from those with SBP (63). Gut perforation can be suspected and pursued if a specimen of ascites is neutrocytic and meets two of the following three criteria : Total protein greater than 1 g/dL, glucose less than 50 mg/dL, and LDH greater than the upper limit of normal for serum (63). Secondary bacterial peritonitis should be suspected if ascitic culture yields more than one organism (especially anaerobes or fungi), or if there is no response to recommended empirical antibiotics (63). Ascitic fluid with high bilirubin and amylase concentrations are also indicative of secondary peritonitis (64). Ascitic fluid carcinoembryonic antigen (CEA) and alkaline phosphatase (AP) are also valuable in differentiating secondary peritonitis from SBP (65). In the study, 92% of secondary peritonitis patients fulfilled at least one of both predetermined criteria (either CEA > 5 ng/ml or AP > 240 units/l) versus only 12% of SBP patients. Their use showed a sensitivity of 92% and a specificity of 88% in differentiating secondary peritonitis from SBP.

Treatment

Because the mortality of an SBP attack is high, early antibiotic treatment is warranted. Empirical antibiotic treatment is recommended after diagnosis of the infection and must not depend on delayed culture results (3,37). The antibiotic of choice must cover common causative microorganisms, have appropriate pharmacokinetic characteristics, and be safe.

Cefotaxime, a third generation cephalosporin, has been the most extensively studied antibiotic in treatment patients with SBP. It is considered to be the first choice antibiotic because of low toxicity and excellent efficacy. Schemes involving lower doses and shorter durations of cefotaxime in treatment of SBP have been investigated. The elimination of cefotaxime and its active metabolites decreases in cirrhotic patients due to the functional renal failure and failure of liver to excrete and metabolize xenobiotics. Spontaneous bacterial peritonitis usually occurs in advanced cirrhotics, and there is low bacterial load in the infection when compared with other infections. It is reported that in vitro resistance to cefotaxime does not predict SBP resolution (5). In the study cefotaxime cured 82% of the cefotaxime resistant SBP cases.

Ampicillin plus tobramycin combinations were commonly used until 1985 when Felisart *et al.* (24) showed superiority of cefotaxime for the treatment of SBP. Cefotaxime was more effective in achieving infection resolution than the combination. Also cefotaxime did not cause superinfection or nephrotoxicity which occurred in 19% of the patients receiving combination therapy (24). Following this study, cefotaxime is considered as one of the first choice antibiotic in treatment of SBP (2). Because of possessing an unpredictable volume of distribution in patients with ascites and high superinfection or nephrotoxicity rates, aminoglycosides should be avoided in treatment of SBP (3,39).

In 1991, Runyon *et al.* (66) compared 5 and 10 day durations of cefotaxime treatment at the same doses. They found no differences between the groups in means of infection resolution, in-hospital mortality, and in hospital recurrence. This study demonstrated that a five-day course of cefotaxime treatment for SBP is as effective as the long one.

In 1995, Rimola *et al.* (58) compared efficacy of cefotaxime in 143 patients receiving either 2 gram per 12 hours or 2 gram per 6 hours. The rate of SBP resolution and patient survival were similar in both groups. This study also showed that undetectable cefotaxime trough levels of serum and/or ascitic fluid samples were not associated with poorer outcomes in patients receiving the low dose. In the light of these facts, IAC recommended cefotaxime for SBP treatment in a minimum dose of 2 gram per 12 hours and duration of 5 days (3). The much lower doses were also used in two new prospective studies. The first one reported similar results with low dose of either cefotaxime or ofloxacin for treatment of patients with uncomplicated SBP (67). The other one compared 2 g/12 h and 1 g/12 h dosages of cefotaxime in non selected patients with SBP and found similar results regarding mortality and other complications (Ozmen *et al.* *2004 unpublished data). Minor points of both studies were the low patient number. So they need to be supported by studies with larger patient number. Cefotaxime is also effective in patients developing SBP while receiving quinolone prophylaxis (3,6,68).

A study of 580 episode of SBP reported a significant increase in strains that were resistant to cefotaxime in Gram-negative bacilli from 7% in 1995 to 28% in 1999, and those to ciprofloxacin from 10% to 32% (69). The frequency of multiple-antibiotic resistance in bacteria increased from 8.3% to 38.5% in the earlier (1991-95) as compared to the later (1996-2001) cohort. The mortality rate was significantly higher in patients with multiply-antibiotic-resistant bacteria (70). Restricting antibiotic prophylaxis to patients at high risk of SBP, knowledge of local bacterial antibiotic resistance, narrowing spectrum coverage after results of susceptibility, precising role of non-antibiotic prophylaxis (lactobacillus, bile acids) may help us to cope with the emerging resistance problem.

Several studies have been performed to asses the efficacy of other antibiotics for treatment of SBP (67,71-74). Because of a narrow bacteria spectrum and a high risk of superinfection, aztreonam was not considered to be adequate for empirical treatment of SBP (3,72). Ceftriaxone (73), amoxicillin-clavulanic acid (25,74), and cefonicid (73) are all used successfully in treatment of SBP. The results are similar to those obtained by cefotaxime.

Although parenteral antibiotics are generally used to treat SBP, studies evaluating the efficacy of several oral antibiotics in patients with relatively good clinical conditions were performed (6,67,75). Navasa *et al.* (6) compared oral ofloxacin (400 mg/12 h) and intravenous cefotaxime (2 g/6 h) in 123 patients with uncomplicated SBP (no shock, ileus, gastrointestinal haemorrhage, grade II-IV hepatic encephalopathy nor serum creatinine > 3 mg/dl). Infection resolution rate, patient survival, and duration of antibiotic therapy were similar in both groups. But cost of therapy was lower in oral ofloxacin group. Taskıran *et al.* (67) assigned 30 cirrhotic patients with uncomplicated spontaneous bacterial peritonitis to receive either intravenous cefotaxime (1 g/12 h) for 7 days or intravenous ofloxacin (200 mg/12 h) for 2 days followed by oral ofloxacin (200 mg/12 h) for 5 days. Resolution rates and hospital survival rates of the cefotaxime and ofloxacin groups were similar. Another study (75) has demonstrated the efficacy of intravenous ciprofloxacin 200 mg every 12 hours for 2 days followed by oral ciprofloxacin 500 mg every 12 hours for 5 days.

To determine effects of plasma volume expansion on renal impairment and mortality Sort *et al.* (57) randomly assigned 126 patients with cirrhosis and spontaneous bacterial peritonitis to receive treatment with either cefotaxime alone or cefotaxime plus an intravenous infusion of albumin given at a dose of 1.5 g per kilogram of body weight during the first six hours after randomization, with the infusion repeated at a dose of 1 g per kilogram three days later. Renal impairment developed in 33% of patients in the cefotaxime group and 10% in the cefotaxime-plus-albumin group. In-hospital mortality rate was 29% and 10%, respectively. The results of another study (76) combining ceftriaxone with albumin infusion for SBP therapy indicates that the beneficial affects of albumin infusion on systemic haemodynamics and renal function are related with both improvement in cardiac function and a decrease in the degree of arterial vasodilatation.

The resolution of the infection is associated with the disappearance of all systemic and local symptoms and signs of infection, reduction of the PMN count in ascitic fluid below 250/mm^3, normal WBC count and negative ascitic fluid culture (5,53,58,77). The resolution of SBP is commonly associated with a rapid improvement in the patient's general condition. If there is no such rapid improvement, a follow-up paracentesis is recommended (78). A decrease less than 25% in ascitic PMN count 48 hours after the beginning of the antibiotherapy strongly evoques his failure (3). Ascitic fluid shows a 80% reduction of PMN count and negativation of culture after 48 hours of adequate antibiotherapy (63). Ascitic fluid PMN count may be higher than the pre-treatment value if the control paracentesis is performed before 48 hours of the therapy (63).

Prophylaxis

The incidence of SBP recurrence was reported to be 40-69% at 1 year after the first attack (7,10,79). Selective intestinal decontamination with 400 mg norfloxacin per day, decreases the overall incidence of SBP recurrence at 1 year of follow-up from 68% to 20%. The probability of the infection recurrence caused by aerobic gram-negative bacilli decreased from 60% to 3% at 1 year of follow-up (79). In the light of these results long-term/continuous oral norfloxacin is advised for all patients recovering from an episode of SBP until resolution of ascites, transplantation or death (3,78). Emergence of faecal quinolone-resistant bacteria in cirrhotic patients is becoming one of the major problem. Thus, selective intestinal decontamination is a more appropriate approach for patients with high risk.

A meta-analysis involving 534 cirrhotic patients with gastrointestinal bleeding reported that short-term primary antibiotic prophylaxis for 4-10 days significantly increased the mean percentage of infection free patients and short-term (19.3 ± 8.0 days) survival rate (7). Another study involving total of 120 cirrhotic patients with acute upper gastrointestinal haemorrhage reported that the incidence of total proven bacterial infection and SBP in patients receiving primary prophylactic intestinal decontamination with oral ciprofloxacin 500 mg per 12 hours for 7 days decreased significantly from 45% to 10% and 8/60 patients (13.3%) to 2/60 patients (%3.3), respectively (15). Therefore, antibiotic prophylaxis should be administered to all cirrhotic patients with a gastrointestinal haemorrhage whether ascites is present or not. Oral norfloxacin, 400 mg per 12 hours for at least 7 days, was recommended by the IAC (3) and oral ciprofloxacin, 500 mg per 12 hours for 7 days, by the recent British Society of Gastroenterology guidelines (80).

For the primary prevention of ascitic infection in patients with low-protein ascites, prophylactic antibiotic is recommended to inpatients only (81). The AASLD guidelines suggest that patients with ascitic protein < 1 g/dl ought to receive prophylactic antibiotics during hospitalization (2). The incidence of first spontaneous bacterial peritonitis after 3 years of follow-up was negligible in patients with ascitic fluid protein content greater than or equal to 1 g/dl. Therefore, primary prophylaxis is not recommended in such patients (8,11,13). There is a lack of consensus of IAC on the necessity of antibiotic prophylaxis for cirrhotic patients who have never had SBP and in whom ascitic fluid protein concentration is low (3). Trimethoprim-sulfamethoxazole has also been shown to be effective for preventing SBP in an animal model and in patients (82,83).

Selective intestinal decontamination encompasses the risks of inducing antibiotic resistance in gram-negative flora and promoting overgrowth of gram-positive flora which have been reported in many studies (70,84-86). The frequency of multiple-antibiotic resistance in bacteria isolated from cirrhotic ascites increased from 8% (1991-1995) to 38% (1996-2001) (70). The study involving 102 E. coli-positive ascitic fluid cultures reported that norfloxacin prophylaxis and higher prevalence of associated immunosuppressive factors (immunosuppressive drugs, human immunodeficiency virus infection or cancer) were significantly more frequently seen in the quinolone-resistant group compared with patients with quinolone-sensitive E. coli SBP (86). Therefore, primary prophylaxis may be more suitable only in cirrhotics with high risk factors such as upper GI bleeding, low ascitic protein content. Primary prophylaxis could also be achieved in more natural ways. Oral administration of Lactobacillus (87) or conjugated bile acids (88) to prevent bacterial translocation and SBP are two of these options.

Complications and prognosis

Mortality of the first episode of SBP varies between 10% and 46% (5,10,27,38,47,55,57,89). Despite the improvement in short-term survival (0-20% vs. 50-70%) during the last two decades (20) the long-term prognosis of cirrhotic patients who survive an episode of SBP remains poor because of the severity of underlying liver disease and high rate of recurrence of infection. Therefore, cirrhotic patients who have recovered from an episode of SBP should be evaluated for liver transplantation (1,3). Survival after one episode of SBP has been reported to be very short. The l-year and 2-years probability of survival were 30-50% and 25-30%, respectively (20). Mortality of the recurrent SBP has been reported to be 50% (10).

Lipka *et al.* reported that an ascitic fluid PMN counts >1000/mm^3 was associated with a mortality rate of 88% (89). Renal impairment was the strongest independent predictor of mortality during hospitalization (77).

In-hospital mortality was independently correlated with BUN level (5,6,23,38,90-92), Child-Pugh score (5,23), ascitic fluid PMN cell count (27,38), bilirubin levels (38,91), serum aspartate aminotransferase level (5,55), age (5), presence of ileus (5), the existence of symptoms (27,38) like abdominal pain (55), community-acquired vs. hospital-acquired peritonitis (5), the presence of upper gastrointestinal bleeding at admission (27), encephalopathy (6,23), prothrombin rate (27), serum sodium (27), creatinine (23,27,38,55,91), cholesterol (27), hypotension (23), lower ascites protein level (< 1gr/ dl) (23), liver disease for longer time (23), developing superinfection (an infection other than SBP starting during SBP treatment) (23), and higher peripheral blood leukocyte count (> or = 12000/mm^3) (23). But no association was found between outcome and age, aetiology of liver disease, Child stage, ascitic fluid pH and culture positivity in another study (38). No microbiological data had predictive value for survival (5,55). The main causes of death were terminal liver failure and/or hepatorenal syndrome, gastrointestinal bleeding, and septic shock (6,38). The relapse was found to be associated with the Child stage (38), low ascitic fluid protein concentration (10), high bilirubin (10), and prothrombin activity (10). The infection resolution rate was 77-90% for all SBP episodes (5,25,26,38,58). Band neutrophils in WBC, community-acquired vs. hospital-acquired peritonitis, BUN, and serum aspartate aminotransferase level are identified as independent predictors of infection resolution (5). No microbiological data found to have predictive value for infection resolution (5). The mean of antibiotic therapy duration for SBP was reported to be between 5.3 and 10.6 days (5,6,27,58,67,93).

Renal impairment develops approximately in one-third of patients with SBP and is postulated to arise as a result of a further reduction in effective arterial blood volume, mediated by vasoactive cytokines, with a resultant increased renin-angiotensin-aldosterone system activity (44,77,94). If the renal failure is rapid and progressive its mortality rate is about 100%, whereas mortality rate of patients with moderate form of renal failure is 40% (77). If this reduction in effective arterial blood volume could be limited, the incidence of renal impairment and in-hospital mortality could be reduced. Sort *et al.* (57) tested this hypothesis and found that combination of albumin and antibiotic therapy has reduced renal failure (33% vs. 10%) and mortality (29% vs. 10%). BUN level before SBP (26,46,77), serum creatinine (46,57), age (77), positive ascitic fluid culture (77), IL-6 levels in ascitic fluid (46), mean arterial pressure (46), serum bilirubin level during infection (57,77), plasma renin activity (26), norepinephrine (26), peripheral vascular resistance (26), hepatic venous pressure gradient (26), band neutrophils count in blood (77), lower cardiac output (26), and treatment with cefotaxime alone (57) are found to be independent predictors for the development of renal impairment in different studies.

Summary

All cirrhotic patients with ascites may develop SBP but the risk is greater in those with a coexisting gastrointestinal bleeding, a previous episode of SBP or low ascitic protein levels. Gram-negative aerobic bacteria and non-enterococcal Streptococcus spp. are the most common isolates. But Gram-positive bacteria are isolated more frequently during the recent years. Increased bacterial translocation and decreased clearance of bacteria is involved in the pathogenesis of SBP. Most of patients with SBP have an elevated serum bilirubin level and abnormal prothrombin time, and they usually have Child-Pugh class B or C cirrhosis. They may present with fever, abdominal pain, abnormal liver functions or

renal impairment. However, one third of them may be asymptomatic. Because the mortality of a SBP attack is high, early antibiotic treatment is warranted even before culture results. Its low toxicity and excellent efficacy makes cefotaxime a first choice for even low doses and short duration antibiotherapy. Several oral antibiotics are found to be effective in patients with relatively good clinical conditions. Considering the high rate of recurrence of SBP, selective intestinal contamination should be discussed considering the prevalence of local bacterial resistances for all patients recovering from an episode of SBP until resolution of ascites, transplantation or death. Also, cirrhotic patients who have recovered from an episode of SBP should be evaluated for liver transplantation.

References

1. GUARNER C., RUNYON B.A. Spontaneous bacterial peritonitis : pathogenesis, diagnosis, and management. *Gastroenterologist*, 1995, **3** : 311-28.
2. RUNYON BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology*, 1998, **27** : 264-72.
3. RIMOLA A., GARCIA-TSAO G., NAVASA M. *et al.* Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis : a consensus document. *International Ascites Club. J. Hepatol*., 2000, **32** : 142-53.
4. RUNYON B.A., HOEFS J.C. Culture-negative neutrocytic ascites : a variant of spontaneous bacterial peritonitis. *Hepatology*, 1984, **4** : 1209-11.
5. TOLEDO C., SALMERON J.M., RIMOLA A. *et al.* Spontaneous bacterial peritonitis in cirrhosis : predictive factors of infection resolution and survival in patients treated with cefotaxime. *Hepatology*, 1993, **17** : 251-7.
6. NAVASA M., FOLLO A., LLOVET J.M. *et al.* Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology*, 1996, **111** : 1011-7.
7. BERNARD B., GRANGE J.D., KHAC E.N., AMIOT X., OPOLON P., POYNARD T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding : a meta-analysis. *Hepatology*, 1999, **29** : 1655-61.
8. RUNYON B.A. Low-protein-concentration ascitic fluid is predisposed to spontaneous bacterial peritonitis. *Gastroenterology*, 1986, **91** : 1343-6.
9. RUNYON B.A. Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis. *Hepatology*, 1988, **8** : 632-5.
10. TITO L., RIMOLA A., GINES P., LLACH J., ARROYO V., RODES J. Recurrence of spontaneous bacterial peritonitis in cirrhosis : frequency and predictive factors. *Hepatology*, 1988, **8** : 27-31.
11. ANDREU M., SOLA R., SITGES-SERRA A. *et al.* Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. *Gastroenterology*, 1993, **104** : 1133-8.
12. RIMOLA A., SOTO R., BORY F., ARROYO V., PIERA C., RODES J. Reticuloendothelial system phagocytic activity in cirrhosis and its relation to bacterial infections and prognosis. *Hepatology*, 1984, **4** : 53-8.
13. LLACH J., RIMOLA A., NAVASA M. *et al.* Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites : relevance of ascitic fluid protein concentration. *Hepatology*, 1992, **16** : 724-7.
14. BERNARD B., CADRANEL J.F., VALLA D., ESCOLANO S., JARLIER V., OPOLON P. Prognostic significance of bacterial infection in bleeding cirrhotic patients : a prospective study. *Gastroenterology*, 1995, **108** : 1828-34.
15. HSIEH W.J., LIN H.C., HWANG S.J. *et al.* The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding. *Am. J. Gastroenterol.*, 1998, **93** : 962-6.
16. SORELL W.T., QUIGLEY E.M., JIN G., JOHNSON T.J., RIKKERS L.F. Bacterial translocation in the portal-hypertensive rat : studies in basal conditions and on exposure to hemorrhagic shock. *Gastroenterology*, 1993, **104** : 1722-6.
17. CADRANEL J.F., DENIS J., PAUWELS A. *et al.* Prevalence and risk factors of bacteriuria in cirrhotic patients : a prospective case-control multicenter study in 244 patients. *J. Hepatol.*, 1999, **31** : 464-8.
18. RUNYON B.A. Paracentesis of ascitic fluid. A safe procedure. *Arch. Intern. Med.*, 1986, **146** : 2259-61.
19. GUARNER C., SOLA R., SORIANO G. *et al.* Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. *Gastroenterology*, 1999, **117** : 414-9.
20. RIMOLA A. Infections in Liver Disease. *In* : BIRCHERM J., BENHAMOU J.P., MC INTYRE N., RIZETTO M., RODÉS J. (eds). Oxfort Textbook of Clinical *Hepatology*, 1999, 1861-74.
21. HOEFS J.C., RUNYON B.A. Spontaneous bacterial peritonitis. *Dis. Mon.*, 1985, **31** : 1-48.
22. GARCIA-TSAO G. Spontaneous bacterial peritonitis. *Gastroenterol. Clin. North Am.*, 1992, **21** : 257-75.
23. FILIK L., UNAL S. Clinical and laboratory features of spontaneous bacterial peritonitis. *East Afr. Med. J.*, 2004, **81** : 474-9.
24. FELISART J., RIMOLA A., ARROYO V. *et al*. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology*, 1985, **5** : 457-62.
25. RICART E., SORIANO G., NOVELLA M.T. *et al.* Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. *J. Hepatol.*, 2000, **32** : 596-602.
26. RUIZ-DEL-ARBOL L., URMAN J., FERNANDEZ J. *et al.* Systemic, renal, and hepatic hemodynamic derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology*, 2003, **38** : 1210-8.
27. LLOVET J.M., PLANAS R., MORILLAS R. *et al.* Short-term prognosis of cirrhotics with spontaneous bacterial peritonitis : multivariate study. *Am. J. Gastroenterol.*, 1993, **88** : 388-92.
28. CHOLONGITAS E., PAPATHEODORIDIS G.V., LAHANAS A., XANTHAKI A., KONTOU-KASTELLANOU C., ARCHIMANDRITIS A.J. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. *Liver Int.*, 2005, **25** : 57-61.
29. FERNANDEZ J., NAVASA M., GOMEZ J. *et al.* Bacterial infections in cirrhosis : epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*, 2002, **35** : 140-8.
30. GARCIA-TSAO G., ALBILLOS A., BARDEN G.E., WEST A.B. Bacterial translocation in acute and chronic portal hypertension. *Hepatology*, 1993, **17** : 1081-5.
31. GUARNER C., RUNYON B.A., YOUNG S., HECK M., SHEIKH M.Y. Intestinal bacterial overgrowth and bacterial translocation in cirrhotic rats with ascites. *J. Hepatol.*, 1997, **26** : 1372-8.
32. LLOVET JM., BARTOLI R., MARCH F. *et al.* Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats : molecular epidemiologic evidence. *J. Hepatol.*, 1998, **28** : 307-13.
33. LLOVET JM., BARTOLI R., PLANAS R. *et al.* Bacterial translocation in cirrhotic rats. Its role in the development of spontaneous bacterial peritonitis. *Gut*, 1994, **35** : 1648-52.
34. RUNYON B.A., SQUIER S., BORZIO M. Translocation of gut bacteria in rats with cirrhosis to mesenteric lymph nodes partially explains the pathogenesis of spontaneous bacterial peritonitis. *J. Hepatol.*, 1994, **21** : 792-6.
35. CIRERA I., BAUER T.M., NAVASA M. *et al.* Bacterial translocation of enteric organisms in patients with cirrhosis. *J. Hepatol.*, 2001, **34** : 32-7.
36. VIGGIANO T.R., GOSTOUT C.J. Portal hypertensive intestinal vasculopathy : a review of the clinical, endoscopic, and histopathologic features. *Am. J. Gastroenterol.*, 1992, **87** : 944-54.
37. MOWAT C., STANLEY A.J. Review article : spontaneous bacterial peritonitis – diagnosis, treatment and prevention. *Aliment Pharmacol. Ther.*, 2001, **15** : 1851-9.
38. THANOPOULOU A.C., KOSKINAS J.S., HADZIYANNIS S.J. Spontaneous bacterial peritonitis (SBP) : clinical, laboratory, and prognostic features. A single-center experience. *Eur. J. Intern. Med.*, 2002, **13** : 194-198.
39. RUNYON B.A. Ascites and Spontaneous Bacterial Peritonitis. *In* : FELDMAN M., FRIEDMAN L.S., SLEISENGER M.H. (eds). Gastrointestinal and Liver Disease. Vol. 2 : Saunders, 2002 : 1517.
40. RUNYON B.A., HOEFS J.C. Ascitic fluid chemical analysis before, during and after spontaneous bacterial peritonitis. *Hepatology*, 1985, **5** : 257-9.
41. SUCH J., FRANCES R., MUNOZ C. *et al.* Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. *Hepatology*, 2002, **36** : 135-41.
42. WAGNER H. Interactions between bacterial CpG-DNA and TLR9 bridge innate and adaptive immunity. *Curr. Opin. Microbiol.*, 2002, **5** : 62-9.
43. RUNYON B.A. Early events in spontaneous bacterial peritonitis. *Gut*, 2004, **53** : 782-4.
44. BILLIAU A., VANDEKERCKHOVE F. Cytokines and their interactions with other inflammatory mediators in the pathogenesis of sepsis and septic shock. *Eur. J. Clin. Invest.*, 1991, **21** : 559-73.
45. BONE R.C. The pathogenesis of sepsis. *Ann. Intern. Med.*, 1991, **115** : 457-69.
46. NAVASA M., FOLLO A., FILELLA X. *et al.* Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis : relationship with the development of renal impairment and mortality. *Hepatology*, 1998, **27** : 1227-32.
47. SUCH J., RUNYON B.A. Spontaneous bacterial peritonitis. *Clin. Infect. Dis.*, 1998, **27** : 669-74, quiz 675-6.

48. ALMDAL T.P., SKINHOJ P. Spontaneous bacterial peritonitis in cirrhosis. Incidence, diagnosis, and prognosis. *Scand. J. Gastroenterol.*, 1987, **22** : 295-300.
49. KLINE M.M., MC CALLUM R.W., GUTH P.H. The clinical value of ascitic fluid culture and leukocyte count studies in alcoholic cirrhosis. *Gastroenterology*, 1976, **70** : 408-12.
50. WILSON J.A., SUGUITAN E.A., CASSIDY W.A., PARKER R.H., CHAN C.H. Characteristics of ascitic fluid in the alcoholic cirrhotic. *Dig. Dis. Sci.*, 1979, **24** : 645-8.
51. HOEFS J.C. Increase in ascites white blood cell and protein concentrations during diuresis in patients with chronic liver disease. *Hepatology*, 1981, **1** : 249-54.
52. PELLETIER G., SALMON D., INK O. *et al.* Culture-negative neutrocytic ascites : a less severe variant of spontaneous bacterial peritonitis. *J. Hepatol.*, 1990, **10** : 327-31.
53. FONG T.L., AKRIVIADIS E.A., RUNYON B.A., REYNOLDS T.B. Polymorphonuclear cell count response and duration of antibiotic therapy in spontaneous bacterial peritonitis. *Hepatology*, 1989, **9** : 423-6.
54. AL AMRI S.M., ALLAM A.R., AL MOFLEH I.A. Spontaneous bacterial peritonitis and culture negative neutrocytic ascites in patients with non-alcoholic liver cirrhosis. *J. Gastroenterol. Hepatol.*, 1994, **9** : 433-6.
55. SOYLU A.R., DOKMECI G., TEZEL A. *et al.* Predictors of short-term outcome of spontaneous bacterial peritonitis in Turkish cirrhotic patients. *J. Gastroenterol. Hepatol.*, 2005, **20** : 657-60.
56. GILBERT J.A., KAMATH P.S. Spontaneous bacterial peritonitis : an update. *Mayo Clin. Proc.*, 1995, **70** : 365-70.
57. SORT P., NAVASA M., ARROYO V. *et al.* Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N. Engl. J. Med.*, 1999, **341** : 403-9.
58. RIMOLA A., SALMERON J.M., CLEMENTE G. *et al.* Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis : results of a prospective, randomized, multicenter study. *Hepatology*, 1995, **21** : 674-9.
59. ANGELONI S., NICOLINI G., MERLI M. *et al.* Validation of automated blood cell counter for the determination of polymorphonuclear cell count in the ascitic fluid of cirrhotic patients with or without spontaneous bacterial peritonitis. *Am. J. Gastroenterol.*, 2003, **98** : 1844-8.
60. TERG R., LEVI D., LOPEZ P. *et al.* Analysis of clinical course and prognosis of culture-positive spontaneous bacterial peritonitis and neutrocytic ascites. Evidence of the same disease. *Dig. Dis. Sci.*, 1992, **37** : 1499-504.
61. RUNYON B.A., CANAWATI H.N., AKRIVIADIS E.A. Optimization of ascitic fluid culture technique. *Gastroenterology*, 1988, **95** : 1351-5.
62. BOBADILLA M., SIFUENTES J., GARCIA-TSAO G. Improved method for bacteriological diagnosis of spontaneous bacterial peritonitis. *J. Clin. Microbiol.*, 1989, **27** : 2145-7.
63. AKRIVIADIS E.A., RUNYON B.A. Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. *Gastroenterology*, 1990, **98** : 127-33.
64. RUNYON B.A. Ascitic fluid bilirubin concentration as a key to choleperitoneum. *J. Clin. Gastroenterol.*, 1987, **9** : 543-5.
65. WU S.S., LIN O.S., CHEN Y.Y., HWANG K.L., SOON M.S., KEEFFE E.B. Ascitic fluid carcinoembryonic antigen and alkaline phosphatase levels for the differentiation of primary from secondary bacterial peritonitis with intestinal perforation. *J. Hepatol.*, 2001, **34** : 215-21.
66. RUNYON B.A., MCHUTCHISON J.G., ANTILLON M.R., AKRIVIADIS E.A., MONTANO A.A. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology*, 1991, **100** : 1737-42.
67. TASKIRAN B., COLAKOĞLU O., SOZMEN B., UNSAL B., ASLAN S., BUYRAÇ Z. Comparison of cefotaxime and ofloxacin in treatment of spontaneous bacterial peritonitis. *Turk. J. Gastroenterol.*, 2004, **15** : 34-38.
68. LLOVET J.M., RODRIGUEZ-IGLESIAS P., MOITINHO E. *et al.* Spontaneous bacterial peritonitis in patients with cirrhosis undergoing selective intestinal decontamination. A retrospective study of 229 spontaneous bacterial peritonitis episodes. *J. Hepatol.*, 1997, **26** : 88-95.
69. PARK Y.H., LEE H.C., SONG H.G. *et al.* Recent increase in antibiotic-resistant microorganisms in patients with spontaneous bacterial peritonitis adversely affects the clinical outcome in Korea. *J. Gastroenterol. Hepatol.*, 2003, **18** : 927-933.
70. SINGH N., WAGENER M.M., GAYOWSKI T. Changing epidemiology and predictors of mortality in patients with spontaneous bacterial peritonitis at a liver transplant unit. *Clin. Microbiol. Infect.*, 2003, **9** : 531-7.
71. ARIZA J., XIOL X., ESTEVE M. *et al.* Aztreonam vs. cefotaxime in the treatment of gram-negative spontaneous peritonitis in cirrhotic patients. *Hepatology*, 1991, **14** : 91-8.
72. ARIZA J., GUDIOL F., DOLZ C. *et al.* Evaluation of aztreonam in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis. *Hepatology*, 1986, **6** : 906-10.
73. GOMEZ-JIMENEZ J., RIBERA E., GASSER I. *et al.* Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. *Antimicrob. Agents Chemother.*, 1993, **37** : 1587-92.
74. GRANGE J.D., AMIOT X., GRANGE V. *et al.* Amoxicillin-clavulanic acid therapy of spontaneous bacterial peritonitis : a prospective study of twenty-seven cases in cirrhotic patients. *Hepatology*, 1990, **11** : 360-4.
75. TERG R., COBAS S., FASSIO E. *et al.* Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis : results of a multicenter, randomized study. *J. Hepatol.*, 2000, **33** : 564-9.
76. FERNANDEZ J., NAVASA M., GARCIA-PAGAN J.C. *et al.* Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J. Hepatol.*, 2004, **41** : 384-90.
77. FOLLO A., LLOVET J.M., NAVASA M. *et al.* Renal impairment after spontaneous bacterial peritonitis in cirrhosis : incidence, clinical course, predictive factors and prognosis. *Hepatology*, 1994, **20** : 1495-501.
78. GARCIA-TSAO G. Current management of the complications of cirrhosis and portal hypertension : variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. *Gastroenterology*, 2001, **120** : 726-48.
79. GINES P., RIMOLA A., PLANAS R. *et al.* Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis : results of a double-blind, placebo-controlled trial. *Hepatology*, 1990, **12** : 716-24.
80. JALAN R., HAYES P.C. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. British Society of Gastroenterology. *Gut*, 2000, **46** Suppl. 3-4 : III1-III15.
81. NOVELLA M., SOLA R., SORIANO G. *et al.* Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. *Hepatology*, 1997, **25** : 532-6.
82. GUARNER C., RUNYON B.A., HECK M., YOUNG S., SHEIKH M.Y. Effect of long-term trimethoprim-sulfamethoxazole prophylaxis on ascites formation, bacterial translocation, spontaneous bacterial peritonitis, and survival in cirrhotic rats. *Dig. Dis. Sci.*, 1999, **44** : 1957-62.
83. SINGH N., GAYOWSKI T., YU V.L., WAGENER M.M. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis : a randomized trial. *Ann. Intern. Med.*, 1995, **122** : 595-8.
84. BORZIO M., SALERNO F., SAUDELLI M., GALVAGNO D., PIANTONI L., FRAGIACOMO L. Efficacy of oral ciprofloxacin as selective intestinal decontaminant in cirrhosis. *Ital. J. Gastroenterol. Hepatol.*, 1997, **29** : 262-6.
85. TERG R., LLANO K., COBAS S.M. *et al.* Effects of oral ciprofloxacin on aerobic gram-negative fecal flora in patients with cirrhosis : results of short- and long-term administration, with daily and weekly dosages. *J. Hepatol.*, 1998, **29** : 437-42.
86. CERETO F., MOLINA I., GONZALEZ A. *et al.* Role of immunosuppression in the development of quinolone-resistant Escherichia coli spontaneous bacterial peritonitis and in the mortality of E. coli spontaneous bacterial peritonitis. *Aliment Pharmacol. Ther.*, 2003, **17** : 695-701.
87. WIEST R., CHEN F., CADELINA G., GROSZMANN R.J., GARCIA-TSAO G. Effect of Lactobacillus-fermented diets on bacterial translocation and intestinal flora in experimental prehepatic portal hypertension. *Dig. Dis. Sci.*, 2003, **48** : 1136-41.
88. LORENZO-ZUNIGA V., BARTOLI R., PLANAS R. *et al.* Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. *Hepatology*, 2003, **37** : 551-7.
89. LIPKA J.M., ZIBARI G.B., DIES D.F., MC MILLAN R.W., AULTMAN D.F., MC DONALD J.C. Spontaneous bacterial peritonitis in liver failure. *Am. Surg.*, 1998, **64** : 1155-7.
90. WEINSTEIN M.P., IANNINI P.B., STRATTON C.W., EICKHOFF T.C. Spontaneous bacterial peritonitis. A review of 28 cases with emphasis on improved survival and factors influencing prognosis. *Am. J. Med.*, 1978, **64** : 592-8.
91. HOEFS J.C., CANAWATI H.N., SAPICO F.L., HOPKINS R.R., WEINER J., MONTGOMERIE J.Z. Spontaneous bacterial peritonitis. *Hepatology*, 1982, **2** : 399-407.
92. CAREY W.D., BOAYKE A., LEATHERMAN J. Spontaneous bacterial peritonitis : clinical and laboratory features with reference to hospital-acquired cases. *Am. J. Gastroenterol.*, 1986, **81** : 1156-61.
93. DALMAU D., LAYRARGUES G.P., FENYVES D., WILLEMS B., TURGEON F., TURGEON P. Cefotaxime, desacetyl-cefotaxime, and bactericidal activity in spontaneous bacterial peritonitis. *J. Infect. Dis.*, 1999, **180** : 1597-602.
94. GIRON-GONZALEZ J.A., RODRIGUEZ-RAMOS C., ELVIRA J. *et al.* Serial analysis of serum and ascitic fluid levels of soluble adhesion molecules and chemokines in patients with spontaneous bacterial peritonitis. *Clin. Exp. Immunol.*, 2001, **123** : 56-61.