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REVIEW ARTICLE

SPONTANEOUS BACTERIAL PERITONITIS

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascitic fluid which arises in the absence of any other source of sepsis with in the peritoneum or adjacent tissues. It is a serious complication of cirrhotic ascites, arising most commonly in those with advanced liver disease. It often develops insidiously and may remain unrecognized. The mortality rate of a single episode is similar to that of a variceal bleed at 20 to 40% [1,2].Thus survival of patient with SBP depends on an aggressive approach to diagnosis and treatment and measures should be taken to prevent its occurrence.

Ascites is thought to arise as a result of marked circulatory and renal abnormalities that are associated with cirrhosis [3] and patients who develop this complication have a 2 year survival of approximately 50% [4]. Patients with cirrhosis and ascites exhibit a precarious hemodynamic imbalance. If they are exposed to additional insult such as gastrointestinal bleed, nephrotoxic drugs (e.g. NSAIDs, Diuretics, Aminoglycosides) or systemic infection, they are at risk of developing renal impairment and hepatorenal syndrome [5,6].

The prevalence of SBP in cirrhotic patients with ascites has been estimated at 10 to 30% [7-9]. The risk of developing SBP (table-1) is greater in those with a coexistent gastrointestinal bleed, high serum bilirubin, a previous episode of SBP, or low ascitic fluid protein concentration(less than 1gm/dl) [10-13]. Although SBP is usually considered to occur in patients with cirrhotic ascites, in India SBP has been noted in 18% of patients with ascites secondary to fulminant hepatic failure [14].

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ETIOLOGY

Gram negative aerobic bacteria from the family of Enterobacteriaceae and non-enterococcal Streptococcus spp are the most common organisms isolated from ascites [15-17]. The three most common isolates are Escherichia coli, Klebsiella pneumoniae, and the Streptococcus pneumoniae. E.coli and Klebsiella are seen in 60% of the isolates, 35% are Gram positive cocci mostly streptococcal species. These include Streptococcus pneumoniae, group B Streptococci, Streptococcus bovis, Sterptococcus constellatus, nontypeable Streptococci and Staphylococcus aureus. The other organisms which may be implicated in the aetiology are Haemophilus influenzae, Enterococci, Vibrio cholera, Proteus mirabilis, Acinobacter, Citrobacter, Enterobacter, Brucella melitensis and Salmonella species. Anaerobes (Bacteroides and Clostridial organisms) are rarely seen [18-20].

In patients with AIDS and immunocompromised hosts, the causative organisms for SBP are usually the same. In a study by Shaw E et al. Streptococcus pneumoniae was isolated more frequently in the HIV patients than in non HIV patients [21]. Mycobacteria and fungi (e.g. Cryptococcus neoformans) may be implicated in the aetiology of SBP in immunodeficient and AIDS patients.

NOSOCOMIAL VERSUS COMMUNITY ACQUIRED SBP

Community acquired SBP is more common than nosocomial SBP. Gram negative bacilli such as Escherichia coli are dominant

in both types of SBP. Staphylococcus aureus is increasingly recognized as an important pathogen in nosocomial SBP. There is no significant difference in age, sex, and other clinical features between the two types. Diabetes mellitus has been reported as a more common comorbidity in patients with nosocomial SBP than in those with community acquired SBP [22]. Serum creatinine, BUN, and ascitic fluid total protein are higher in nosocomial SBP compared to community acquired SBP. There is significantly higher resistance to Cefotaxime and ciprofloxacin in nosocomial isolates compared to community acquired isolates. Infection acquisition sites are not related to short or long term prognosis [22].

PATHOGENESIS

In liver cirrhosis three mechanisms are proposed for the pathogenesis of SBP: intestinal bacterial overgrowth, the alterations (structural and functional) of intestinal mucosal barrier and deficiencies of local immune response [23].

It is proposed that these enteric organisms cross the intestinal mucosal barrier to the mesenteric lymph nodes (a process called translocation) and enter the systemic blood stream via the thoracic duct [24,25]. This is followed by secondary seeding of the ascitic fluid deficient in antibacterial activity. Animal models have confirmed that bacterial translocation is involved in the pathogenesis of SBP [26]. Infection of the ascites is facilitated by both the impaired local and systemic immune responses [11,27].Once bacteria enter the fluid in the abdomen, by whatever route, a battle ensues between the virulence factors of the organism and the immune defenses of the host. Low protein ascitic fluid (e.g., less than 1gm/dl) is particularly susceptible to SBP. The endogenous antimicrobial activity (opsonic activity) of human ascitic fluid correlates directly with the protein concentration of the fluid. Patients with deficient ascitic fluid opsonic activity are predisposed to SBP.

RISK FACTORS

Patients with cirrhosis are unusually predisposed to bacterial infection because of multiple defects in immune defence. The risk of developing SBP (table-1) is greater in those with a coexistent gastrointestinal bleed, high serum bilirubin, a previous episode of SBP, severe liver disease(Child-Pugh Class C) and low ascitic fluid protein concentration(less than 1gm/dl) [10-13]. Low ascetic fluid total protein concentration as well as the phagocytic(both motile and stationary) dysfunction associated with cirrhosis are risk factors for bacterial infection. Gastrointestinal haemorrhage is an unrecognized risk factor for the development of spontaneous bacteremia and SBP. The cumulative probability of infection during a single hospitalization for bleeding is approximately 40%. The risk appears to peak 48 hours after the onset of haemorrhage. The high risk of infection is probably mediated by a shock induced increase in the translocation of bacteria from the gut to extra intestinal sites. Urinary tract infection is also an unrecognized risk factor for SBP. Iatrogenic sources of bacteremia such as urinary bladder and intravascular catheterization may be potential risk factors for SBP.

CLINICAL FEATURES

Symptoms and signs of SBP are outlined in table-2. About 10% of patients are asymptomatic. The clinical presentation can be variable, ranging from the acute onset of severe abdominal pain, fever, chills, and hemodynamic instability to the slow, insidious onset of abdominal discomfort, low-grade fever, renal impairment or hepatic encephalopathy [17]. Although by definition ascites must be present for SBP to occur, free peritoneal fluid may not always be clinically apparent. An elevated temperature may not be detected in 20% to 50% of cases.

Physical examination may vary from only mild tenderness to abdominal rigidity and guarding with rebound tenderness. Signs

of severe peritonitis such as rigid abdomen may be absent [2]. Patients with ascites and unexplained deterioration clinically or in term of laboratory parameter should have a diagnostic paracentesis. Although the number of bacteria involved in an episode of SBP is very low, they excite an intense inflammatory response. There is a dramatic increase in the concentration of Polymorphs and inflammatory cytokines within ascitic fluid [28]. Approximately 30% of patients with SBP will develop renal impairment and this is the most sensitive predictor of in-hospital mortality [29]. HIV seropositive cirrhotic patients present with similar clinical findings as other patients with ascites. However median survival after the initial diagnosis of SBP is shorter in HIV patients than non HIV group. This data is particularly relevant for determining the optimal time for liver transplantation in this population [21].

DIAGNOSIS

As SBP may pass unrecognized, the international ascites club has recommended diagnostic paracentesis in the following situations.

- All cirrhotic with ascites on admission to hospital
- In-patient with ascites ,who develop signs of sepsis, hepatic encephalopathy, renal impairment and altered gastrointestinal motility
- All ascitic patients with a GI bleed.

Ascitic fluid should always be sent for determination of white cell count and protein level and culture. About 10 ml of ascitic fluid should be injected directly into blood culture bottles at the bed side because there is evidence that yield increases from less than 50% to approximately 90%. The reagent strips are very sensitive and specific for the rapid diagnosis of SBP in cirrhotic patients allowing immediate commencement of empirical antibiotic therapy [30,31]. In addition to standard tests ascetic fluid should be sent for mycobacterial and mycological histological stains and culture in HIV patients [32].

DIAGNOSTIC CRITERIA

1. Spontaneous Bacterial Peritonitis

a. Ascitic Fluid Polymorpho-nuclear Leukocyte Count

Despite using sensitive methods, culture of ascites is negative in 40 % of cases with clinical features of SBP and an elevated ascitic polymorphonuclear leukocyte count (culture negative neutrocytic ascites) [33]. Furthermore initiation of therapy cannot be delayed while awaiting culture results. Therefore ascitic fluid polymorphonuclear leukocyte count is used as an indirect indicator of the presence of SBP. Patient with an ascitic fluid polymorph count of greater than 250/mm^3 should be considered to have SBP and is an indication to prescribe antibiotics [9,23].

b. Ascitic fluid culture

Ascitic fluid should be obtained for culture at the same time as for routine examination. Ascitic fluid inoculation directly into blood culture bottles leads to a significantly increased percentage of culture positivity up to 90% [34,35] and reduces the time needed for detection of SBP from 48 hours to 24 hours. 10 ml of ascitic fluid should be inoculated directly into blood culture bottles (aerobic and anaerobic) at the bed side. Bacterascites describes a positive ascitic fluid culture with ascitic polymorph count of less than 250/mm^3.

c. Reagent strips

Reagent strips detecting leukocyte esterase activity have been validated for the diagnosis of urinary tract infections, pleural infections, meningitis and ascitic

fluid infections [30,31]. Reagent strip is a quick bed side test, highly sensitive and specific for the diagnosis of SBP based on polymorphonuclear count in ascetic fluid. A positive result should be an indication for empirical antibiotic therapy and a negative result may be useful as a screening test to exclude SBP [36]. Combur 2 LN, Combur 10, Uriscan, Multistix SG 10 and Multistix SG 8 are the various commercial leukocyte esterase reagent strips available for clinical use.

2. Secondary Bacterial Peritonitis

This should be suspected if ascitic culture yields more than one organisms (especially anaerobes or fungi) or if there is no response to standard empirical antibiotics. It can arise following abdominal surgery or secondary to inflammation or perforation of an intra-abdominal organ. Secondary bacterial peritonitis is likely if 2 of the following are present in ascitic fluid [37].

- Glucose less than 50mg/dl.
- Protein more than 10gm/dl.
- Lactate dehydrogenase more than the normal serum levels [35].

In secondary bacterial peritonitis antibiotic regimen should cover anaerobes and enterococci and investigations should be directed at the cause.

TREATMENT

Antibiotics

Following the diagnosis of SBP based on ascitic fluid polymorph count of greater than 250/mm^3 empirical therapy should be commenced. The antibiotic chosen should cover the most likely organism, achieve antibiotic concentration with in the ascitic fluid greater than the minimal inhibitory concentration (MIC90 i.e. the lowest concentration of antibiotic required to inhibit 90% of colonies of a particular organism. The lower the MIC the more sensitive the organism to that agent and vice versa) of these organisms and should not impair renal function [23,38,39]. (table-3) gives various empirical antibiotic regimens for the treatment of SBP.

Cephalosporins

Cefotaxime is the most widely studied cephalosporin in patients with SBP. It is the empiric antibiotic of choice and has been shown to cure SBP episodes in 85% of patients [38,39]. A landmark, randomized comparative study by Felisart et al demonstrated that cefotaxime was superior in the treatment of severe infection in patients with cirrhosis [18]. In patient with SBP treated with cefotaxime none developed superinfection or nephrotoxocity compared to 19% of those with a combination of ampicillin and tobramycin. A regimen of 2 gm of cefotaxime 8 hourly for 5 days is optimum. Furthermore cefotaxime is effective in treating SBP which arises in subjects taking oral quinolones as prophylaxis. Its spectrum of activity covers the gram positive cocci and quinolone resistant gram negative bacilli which are frequently implicated in these cases [40].

Once daily injectable cephalosporins such as ceftriaxone appear to be as effective as cefotaxime [41].

Amoxicillin plus Clavulanic Acid

Amoxicillin 1 gm plus clavulanic acid 200mg intravenously 8 hourly for 7 days is effective in 85% of cases of SBP [42]. This combination was recently compared with cefotaxime [43]. It proved to be as effective as cefotaxime with no relevant side effects. Efficacy was not compromised on switching to oral therapy.

Quinolones

Although intravenous antibiotics have been preferred in the treatment of SBP, recent data suggests that oral quinolones may be

equally efficacious. Ofloxacin is a quinolone which is well absorbed from the gastrointestinal tract. Trials of oral ofloacin versus intravenous cefotaxime in patients without septic shock, encephalopathy, azotemia, gastrointestinal bleed or ileus showed SBP resolution rate of 84% in ofloxacin group versus 85% in the cefotaxime group [44,45]. Survival rate was 81% in both groups. Use of this drug is recommended by the international ascites club if SBP is uncomplicated and patient has not received prophylactic quinolones. Dose is 400mg twice daily for 7 days.

A randomized control trial has reported that 5 days of oral ciprofloxacin (500mg twice daily) after 2 days of intravenous therapy (200mg i.v. twice daily) is as effective as a one week intravenous course [46]. This provides further evidence for the benefit of oral quinolones. In addition quinolones are the drug of choice for patients with SBP who are sensitive to beta-lactam antibiotics.

Aminoglycosides

There is now consensus that aminoglycosides have no place in the empirical treatment of SBP due to the unacceptable risk of nephrotoxicity.

Antibiotics plus Albumin

In patitents with cirrhosis and SBP treatment with intravenous albumin in addition to an antibiotic reduces the incidence of renal impairment and death in comparison to treatment with an antibiotic alone. In a multicentre randomized study 126 patients with SBP were assigned to receive treatment with cefotaxime alone (2gm 8 hourly) or cefotaxime plus albumin [8,47-49]. The albumin was given at a dose of 1.5 gm/kg in the first 6 hours after diagnosis, followed by a further infusion of 1gm/kg on the third day. With standard treatment, renal impairment developed in 33% of patients, whereas with combination therapy it occurred only in 10%. The in-hospital mortality rates were 28% and 10% respectively. The greatest benefit of additional albumin infusion may be in those with more advanced liver disease or impaired renal function. Identification of such a high risk subgroup is important when considering the cost implications of prescribing large volumes of albumin. Before recommending this expensive therapy further studies are needed to confirm these results and in particular to determine whether small volumes of albumin or cheaper plasma expanders would suffice.

Assessing Treatment Response

The resolution of SBP is commonly associated with a rapid improvement in the patient general condition. If there is no such rapid improvement, a follow up paracentesis is recommended 48 hours after commencement of antibiotics [50]. A fall in the ascitic fluid polymorphonuclear leukocyte count of more than 25% suggests that choice of antibiotic is appropriate. If there is no fall in the polymorph count alternative antibiotics should be given, either empirically or according to available sensitivities and possibility of secondary bacterial peritonitis should be reconsidered.

Consider Referral for Liver Transplantation

If a patient survives an episode of SBP the prognosis remains poor. The 1-year and 2-year survival rates following a first episode of SBP are estimated to be 30-50% and 20-30% respectively and can be attributed to the severity of underlying liver disease [51,52]. Survival after liver transplantation is higher; therefore it is recommended that such patients should be considered for this procedure.

Prevention of SBP

In view of high mortality following an episode of SBP prevention is clearly important. Patients who have survived an episode of SBP have a 40-70% 1-year probability of a further episode [53,54]. Prevention of SBP involves treatment of the ascites and underlying liver disease, prophylaxis in high risk patients and

eliminating potential source of bacteremia. Patients should be counselled to avoid alcohol. Diuretics by decreasing amount of ascites have been shown to lead to improved ascitic fluid opsonic activity. One randomized placebo controlled trial has examined the efficacy of antibiotics purely for secondary prophylaxis of SBP [55]. Long term norfloxacin 400mg/day reduced the recurrence of SBP at 1 year from 68% to 20% with a particular reduction in SBP secondary to gram negative bacilli [55]. On the basis of these results, long term oral norfloxacin 400mg/day or ciprofloxacin 750mg weekly is advised for all patients recovering from an episode of SBP until resolution of ascites, liver transplantation or death [56].

Primary Prophylaxis

Specific subgroups of ascitic patients have been demonstrated to be at high risk of a first episode of SBP namely those with low ascitic fluid total protein (less than 1gm/dl) and those hospitalized with a gastrointestinal hemorrhage. Indication for SBP prophylaxis and various recommended antibiotic regimen are listed (table-4).

Low Ascitic Fluid Total Protein

Ascitic fluid total protein has been shown to be an independent predictor of SBP. In one study 15% of patients with ascitic protein less than 1gm/dl developed SBP compared to 2% of those with ascitic protein more than 1gm/dl [57].

Longer term prospective studies confirmed that patients with ascitic protein less than 10gm/l had a one year probability of developing SBP of 20-43% [11,58]. In those patients with ascitic fluid protein of more than 1gm/dl the incidence of SBP with up to 3 years of follow up was negligible. Therefore primary prophylaxis is inappropriate in this group. In a group of patients with low ascitic fluid protein concentration with or without previous episodes of SBP, ciprofloxacin 750mg weekly has been shown to decrease the incidence of SBP from 22% to 4 % at 6 months.

Table-1: Factors predisposing to SBP.

Following are the risk factors for the development of SBP:
• Severity of liver disease (70% of all SBP episodes are in patients with Child-Pugh class C cirrhosis)
• Ascitic fluid total protein level of < 1 g/dl and/or ascitic fluid complement factor C3 < 13 mg/dl
• Gastrointestinal bleeding
• Urinary tract infections
• Intestinal bacterial overgrowth
• Iatrogenic sources of bacteremia such as urinary bladder and intravascular catheters
• One or more previous SBP episodes
• Serum bilirubin of > 2.5 mg/dl

Table-2: Symptoms and signs of SBP.

Fever	69%
Abdominal pain	59%
Hepatic encephalopathy	54%
Abdominal tenderness	49%
Diarrhea	32%
Ileus	30%
Shock	21%
Hypothermia	17%
Asymptomatic	10%

Table-3: Treatment regimens for SBP.

• Cefotaxime 2 g intravenously every 8 hours x minimum of 5 days
• Other cephalosporins (cefonicid, ceftriaxone, ceftizoxime, ceftazidime)
• Amoxicillin (1 g) and clavulanic acid (200 mg) intravenously 3 times daily x ~5 days, then orally 500 mg/125 mg 3 times daily x ~3 days
• Ciprofloxacin 200 mg intravenously every 12 hours x 7 days
• Ciprofloxacin 200 mg intravenously every 12 hours x 2 days then 500 mg orally every 12 hours x 5 days

Cirrhotic Patients with Gastrointestinal Hemorrhage

All cirrhotic patients who develop an upper gastrointestinal bleed are at risk of a variety of bacterial infections including SBP with in the first few days following the bleed [59]. Bacteria of enteric origin are most commonly implicated [60] and the development of infection is associated with a poor prognosis [60,61]. A recent Meta analysis of antibiotic prophylaxis in cirrhotic patients with a gastrointestinal bleed reported a

reduction in SBP for patients given prophylactic treatment [62-65]. The antibiotic used included norfloxacin, ofloxacin, and ciprofloxacin with or with out amoxicillin-clavulanic acid. The benefit was greatest in those with more advanced liver disease.

Importantly the meta-analysis reported a significant improvement in short term survival for any cirrhotic patient with a gastrointestinal bleed given prophylactic antibiotics. Therefore antibiotic prophylaxis should be administered to all cirrhotic patients with a gastrointestinal bleed whether ascites is present or not. Oral norfloxacin 400mg twice daily for at least seven days was recommended by the international ascites club and oral ciprofloxacin 500mg twice daily for 7 days by the recent British society of gastroenterology (BSG) guidelines [66].

Drug Resistance and Cost

There are obvious concerns regarding the long term use of antibiotics in such patients. These include the emergence of antibiotic resistant bacteria and the cost of therapy [67]. There have been several reports of quinolone resistant bacteria in cirrhotic patients receiving prolonged norfloxacin prophylaxis [68,69]. This suggests that quinolone prophylaxis should be used with caution particularly in areas with high prevalence of quinolone resistant bacteria, and prophylaxis should be limited to those at greatest risk of SBP.

Prognosis

Despite effective antibiotic therapy for episodes of SBP, long term prognosis is still extremely poor, with probability of survival at 1 and 2 year of 30% and 20% respectively. An episode of SBP is an indication for liver transplantation.

CONCLUSION

SBP remains a serious complication of cirrhotic ascites and has a high mortality. Presentation is often insidious and therefore clinician must have a high index of suspicion and a low threshold for a diagnostic paracentesis. If SBP is confirmed antibiotic treatment should be immediately instituted and concomitant albumin infusion may improve the outcome. The prognosis is poor in those who survive and liver transplantation should be considered in suitable patients. Long term secondary prophylaxis with norfloxacin is required for all patients with proven SBP. Primary prophylaxis is recommended for patients presenting with gastrointestinal bleed and may be helpful in those with advanced liver disease and low ascitic protein levels.

Table-4: Recommendations for SBP prophylaxis.

In nonbleeding cirrhotic patients with ascites:
• Recovering from an SBP episode
▪ continuous oral administration of norfloxacin 400 mg daily or ciprofloxacin 750 mg weekly
• Without past history of SBP and with
▪ high ascitic fluid protein (> 1g/dL): no prophylaxis necessary
▪ low ascitic fluid protein (< 1g/dL): SBP prophylaxis with norfloxacin 400mg daily or ciprofloxacin 750 mg weekly
In cirrhotics with upper gastrointestinal hemorrhage:
• Exclusion of SBP and other infections before prophylaxis
• Oral administration of norfloxacin 400 mg every 12 hours x minimum of 7 days
• Alternative regimens:
▪ ofloxacin 400 mg/day x 10 days (first intravenously, then orally) and with each endoscopy 1 g of amoxicillin/200 mg clavulanic acid
▪ ciprofloxacin 500 mg twice daily x 7 days orally or via nasogastric tube after endoscopy
▪ amoxicillin/clavulanic acid 1 g/200 mg 3 times daily and ciprofloxacin 200 mg twice daily intravenously then orally until 3 days after cessation of bleeding.

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