Bacterial Infections in Patients with Cirrhosis

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Bacterial infection is a frequent and severe complication of cirrhosis that may present on admission or develop during hospitalization in 30–60% of hospitalized cirrhotic patients. The most frequent infective complications include spontaneous bacterial peritonitis, urinary tract infections, respiratory infections, and bacteremia, mostly due to the concomitant presence of various facilitating mechanisms such as changes in the reticuloendothelial system, decreased opsonic activity of the ascitic fluid, neutrophil leukocyte dysfunction, and iatrogenic factors. In fact, up to 25% of cases of death in cirrhotic patients are believed to be related to bacterial infections. This paper aims to provide a brief overview of the epidemiology, pathogenesis, treatment and prophylaxis of bacterial infection in cirrhosis. [*J Chin Med Assoc* 2005;68(10):447–451]

Key Words: bacterial infection, cirrhosis, gastrointestinal hemorrhage, spontaneous bacterial peritonitis

Introduction

Bacterial infection in cirrhotic patients is frequently associated with impairment in circulatory, hepatocellular, and renal function. Circulatory dysfunction is characterized by arterial hypotension and marked activation of the renin–angiotensin and sympathetic nervous system.[1] Hepatorenal syndrome (HRS) is the most severe presentation of renal function deterioration, caused by a decrease in effective arterial blood volume, of which bacterial infection is the most important precipitating factor.[2] In most patients, HRS follows a rapidly progressive course associated with a very high hospital mortality rate, which is 4-fold higher than that observed in patients with bacterial infection not developing renal failure.[3] Other patients may develop a steady type of renal failure.

Cirrhosis complicated by gastroesophageal variceal hemorrhage is characterized by high mortality and rebleeding rates.[4] Rebleeding episodes occur in 1-third of patients within 6 weeks of the index bleeding, and more than 80% of rebleeding occurs within 2 weeks.[4,5] Gastrointestinal bleeding is associated with bacterial infection in up to 66% of patients with cirrhosis,[6] who are vulnerable to infection because of the disruption of the intestinal mucosal barrier and the frequent invasive manipulations during hemorrhage.[7] The close association between gastrointestinal bleeding and infection in cirrhosis is possibly related to a trigger of the cytokine cascade with release of vasoactive substances, leading to increased variceal pressure and impairment of primary hemostasis, which in turn causes variceal bleeding.[8] Bacterial infections were recently identified as independently associated with failure to control gastrointestinal bleeding within 5 days and associated with early rebleeding.[9] A recent randomized controlled study showed that antibiotic prophylaxis prevented infection and rebleeding as well as decreased the amount of blood transfused in patients with acute variceal bleeding.[10]

As we have little control over the underlying liver disease, only early detection and appropriate management of infectious processes can be expected to improve outcome.

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Spontaneous Bacterial Peritonitis

Definition and outcome

Spontaneous bacterial peritonitis (SBP) represents spontaneous infection of ascitic fluid without any apparent intra-abdominal source of infection. The prevalence of SBP in unselected cirrhotic patients with ascites admitted to a hospital ranges between 10% and 30%.[3,11] Approximately half of the episodes of SBP are present at the time of hospital admission.[3,11] The 1-year probability for development of the first episode of SBP in cirrhotic patients with ascites is approximately 10%.[11] The outcome in cirrhotic patients with SBP has improved dramatically during the last 20 years. In studies published before 1980, the rate of SBP resolution ranged between 25% and 50% and the survival of patients ranged between 0% and 20%. The corresponding values in recent studies are 70–90% and 50–70%, respectively.[11]

Pathogenesis

Several abnormalities in immune response have been documented in the setting of cirrhosis.[12,13] The pathogen of SBP in ascitic fluid may translocate from the intestine or blood with contamination of ascitic fluid. A direct correlation has been found between impairment of the local defensive mechanisms of ascites (assessed by either the opsonic activity or the local protein concentration in ascitic fluid) and the risk of SBP in cirrhotic patients hospitalized with ascites.[13,14]

Clinical features and diagnosis

Most patients with SBP have symptoms and/or signs clearly suggestive of peritoneal infection, especially abdominal pain, fever, and altered gastrointestinal motility. Other patients have no or minor symptoms with deteriorating liver or renal function.[15] SBP diagnosis is shown in Table 1. In comparison with conventional culture techniques, culture of ascitic fluid directly into blood culture bottles increases the yield of bacteria up to 90%.[16] Due to the relatively low concentration of bacteria in ascitic fluid compared with infections in other organic fluid (e.g. urine), the minimum amount of ascitic fluid inoculated into each bottle should be 10 mL.[16] A new leukocyte esterase reagent strip is reported to be a rapid, easy-to-use and inexpensive tool for bedside diagnosis of SBP.[17,18]

Special conditions other than SBP

Culture-negative neutrocytic ascites (CNNA) is diagnosed when the ascitic fluid culture does not grow pathogenic bacteria, the ascitic fluid neutrophil count is at least 250/mm^3, and there is no evident intra-abdominal surgically treatable source of infection. CNNA is considered a variant of SBP since they share the same short- and long-term course.[19]

Table 1. Recommendations on diagnosis of spontaneous bacterial peritonitis (SBP) and special conditions

Diagnosis of SBP

1. Ascitic fluid polymorphonuclear neutrophil (PMN) count > 250/mm^3; in patients with bloody ascites, subtract 1 PMN per 250 red blood cells
2. Cultures
   - Ascitic fluid cultures: bedside inoculation into blood culture bottles (≥ 10 mL)
   - Blood cultures: simultaneous to ascitic fluid cultures

Special conditions

1. Bacterascites: positive ascitic fluid culture, ascites PMN < 250/mm^3, and no evidence of local or systemic infection
   - Repeat paracentesis once bacterascites is diagnosed and initiate antibiotic if:
     - Ascites PMN > 250/mm^3
     - Ascites PMN < 250/mm^3, but culture continues to be positive

2. Secondary peritonitis: suspected when any of the following:
   - Lack of response to antibiotic treatment
   - Two or more organisms isolated (particularly anaerobes or fungi)
   - At least 2 of the following findings in ascitic fluid:
     - glucose < 50 mg/dL; protein > 10 g/L; lactate dehydrogenase > normal serum levels

   Once secondary peritonitis is suspected:
   - Initiate appropriate radiologic investigation
   - Add antibiotics against anaerobes and enterococci

Bacterascites is diagnosed as in Table 1. It is a prerequisite to the development of SBP or a transient and spontaneously reversible colonization of ascites.[20]

Secondary peritonitis is caused by perforation or acute inflammation of intra-abdominal organs, abdominal wall infections, or previous abdominal surgical procedures.[15,21,22] Differentiation between primary and secondary peritonitis is important because secondary peritonitis usually does not resolve unless patients are treated surgically. Conversely, surgical therapy may be accompanied by significant deterioration in the clinical status of cirrhotic patients with SBP.[23]

Treatment

Empiric antibiotic therapy must be initiated immediately after the diagnosis is made. Initial antibiotic therapy should cover *Enterobacteriaceae* and non-enterococcal *Streptococcus* spp.[16] Recently, infections caused by Gram-positive cocci have markedly increased in cirrhosis, probably because of the current high degree of instrumentation of cirrhotic patients and long-term norfloxacin prophylaxis.[24]

Cefotaxime is the most extensively investigated parenteral antibiotic in patients with SBP. Two comparative studies reported that cefotaxime was more effective than ampicillin plus tobramycin or aztreonam in the treatment of SBP, with higher resolution rates and less nephrotoxicity and fewer superinfections.[25,26] Another 2 controlled trials showed that the optimal cefotaxime regimen in cirrhotic patients was 5-day therapy with cefotaxime 2 g, 3 times daily.[25,27] Other cephalosporins, including cefonicid, ceftriaxone and ceftazidime, are as effective as cefotaxime in improving SBP resolution and patient survival.[28,29]

In patients with non-severely complicated SBP (no septic shock, ileus, or serum creatinine > 3 mg/dL), oral ofloxacin (400 mg/12 hours) can be as effective as cefotaxime (2 g/6 hours) with similar rates of infection resolution, patient survival and superinfection.[30] Another comparative trial also showed that amoxicillin–clavulanic acid was as effective as cefotaxime in the treatment of SBP, without relevant adverse effects.[31]

Sort et al demonstrated that, in patients with SBP, treatment with intravenous albumin plus antibiotics reduced the incidence of renal impairment and improved hospital survival.[32] Albumin was given at a dose of 1.5 g/kg of body weight at the time of diagnosis, followed by 1 g/kg of body weight on day 3. Renal impairment (10% vs 33%) and hospital mortality (10% vs 29%) were significantly lower with cefotaxime plus albumin than with cefotaxime alone. The beneficial effects of albumin administration on systemic hemodynamics and renal function in SBP are related to both an improvement in cardiac function and a decrease in the degree of arterial vasodilatation.[33]

Prophylaxis

Cirrhotic patients recovering from an episode of SBP or during a gastrointestinal bleeding episode should receive prophylaxis against bacterial infection.[6] The probability of SBP recurrence is approximately 70% 1 year after resolution of the first SBP episode.[17] Previous studies have found no differences between orally administered (*per os* or through a nasogastric tube) versus intravenously administered antibiotics.[34,35] A concern with the use of prolonged antibiotic prophylaxis is that it will lead to selection of antibiotic-resistant bacteria.[36] One recent study showed that about 2-thirds of infections in untreated cirrhotic patients were due to Gram-negative organisms, while infections in patients receiving quinolone prophylaxis were mostly due to Gram-positive organisms.[36,37] Thus, antibiotic is only necessary in patients at greatest risk of SBP (Table 2).[38] Finally, it should be kept in mind that cirrhotic patients with recurrent SBP have a poor prognosis. The 1- and 2-year probability of survival after an episode of SBP are 30–50% and 25–30%, respectively.[3] Since survival expectancy after liver transplantation is high, patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation.

Table 2. Recommendations on prophylaxis of spontaneous bacterial peritonitis (SBP)

In cirrhotics with upper gastrointestinal hemorrhage

1. Oral administration of norfloxacin 400 mg/12 hours for ≥ 7 days
2. Alternative regimens: combinations of systemic antibiotics (ciprofloxacin, ofloxacin, amoxicillin–clavulanic acid)

In non-bleeding cirrhotic patients with ascites

1. Recovering from first SBP episode: continuous oral administration of norfloxacin 400 mg/day
2. Without history of SBP but low ascitic fluid protein (< 10 g/L): no consensus on the necessity of prophylaxis

Other Infections

Urinary tract infections

Urinary tract infections (UTIs) in cirrhosis are usually asymptomatic, and bacteriuria alone is found in a high proportion of UTI episodes in cirrhotics. Its potential role in causing bacteremia may be underestimated. The incidence is markedly higher in cirrhotics with indwelling catheters and female cirrhotics.[39] Thus, empiric administration of a modern quinolone (norfloxacin, ofloxacin or ciprofloxacin) or amoxicillin–clavulanic acid or oral cephalosporin should be considered in high-risk patients.[3,39]

Pneumonia

Community-acquired pneumonia is a frequent complication in subjects with active alcoholism.[40] *Streptococcus pneumoniae* is the causative organism in most lower respiratory tract infections in alcoholics. However, other pathogens normally present in the oropharyngeal area, especially anaerobic bacteria or *Haemophilus influenzae*, *Klebsiella pneumoniae*, mycoplasma pneumonia, or *Legionella* spp., have also been reported.[40] In these subjects, empiric antibiotics could include erythromycin combined with 1 of the following: cefotaxime, ceftriaxone, amoxicillin–clavulanic acid, or imipenem. Hospital-acquired pneumonia is mainly caused by Gram-negative bacilli and *Staphylococci*.[41] Some procedures or clinical conditions, such as tracheal intubation, esophageal tamponade, and hepatic encephalopathy, are clearly predisposing factors for pneumonia in cirrhotic patients. The empiric antibiotic for these subjects is the third-generation cephalosporins (i.e. cefotaxime). If aspiration is suspected, clindamycin should be added.[41]

Cirrhotic patients with hydrothorax can develop spontaneous bacterial empyema, which is thought to have the same pathogenesis as SBP, since their isolated bacteria are the same.[42] Therefore, patients with spontaneous bacterial empyema may be treated with the same antibiotic regimens.

Endocarditis

Endocarditis complicating the course of cirrhosis usually arises from a previously normal endocardium. *Streptococcus* spp. (*Streptococcus viridans*, *Streptococcus enterococcus*, *Streptococcus bovis*) and *Staphylococcus aureus* are the most common causative organisms, but the possibility of endocarditis caused by enterobacteria should not be underestimated.[43]

Soft-tissue infections

Lymphangitis of the lower extremities and abdominal wall are frequent in cirrhotic patients with ankle edema and ascites. Although *S. aureus* and *Streptococcus pyogenes* are the most frequent causative organisms, *Enterobacteriaceae* and anaerobes may also complicate these infections.[44] Amoxicillin–clavulanic acid may be an adequate empiric antibiotic treatment. More recently, quinolones such as ofloxacin have been proposed for the treatment of soft-tissue infections.

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