Bacterial Infections in Patients with Liver Cirrhosis

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Bacterial infections are common and severe complication of liver cirrhosis which is frequently encountered in the emergency department and hospitalized cirrhotic patients. The most frequent infections include spontaneous bacterial peritonitis, pneumonia, urinary tract infections, and bacteremia. Cirrhotic patients are particularly susceptible to bacterial infections because of increased bacterial translocation, possibly related to liver dysfunction and reduced reticuloendothelial function, and iatrogenic factors. In fact, the in-hospital mortality of cirrhotic patients with infections is approximately 15%, more than twice that of patients without infection. In this article, we provide a brief overview of the epidemiology, manifestations, management and prophylaxis of these complications in cirrhotic patients.

Key words: bacterial infection, liver cirrhosis, spontaneous bacterial peritonitis, gastrointestinal bleeding

Introduction

Bacterial infections are common complication of liver cirrhosis(1-2) which are frequently encountered in the emergency department or develop during hospitalization. The most frequent infectious complications include spontaneous bacterial peritonitis (SBP), pneumonia, urinary tract infections (UTI), and bacteremia(3). Once infection develops, renal failure, shock, and hepatic encephalopathy may follow, which adversely affect survival. In fact, the in-hospital mortality of cirrhotic patients with infections is approximately 15%, more than twice that of patients without infection(4). Hepatorenal syndrome (HRS) is the most severe presentation of renal function deterioration. It is caused by a decrease in effective arterial blood volume, of which bacterial infection is the most important predisposing factor(5). More importantly, infection is directly responsible for 30-50% of deaths in patients with cirrhosis(4). Spontaneous bacterial peritonitis is one of the main infectious complications of cirrhosis and occurs in 8-30% of hospitalized patients with ascites(6). Recent advances in management strategies of infections in patients with cirrhosis have helped improve the prognosis of these patients. These include the use of prophylactic antibiotics in patients with gastrointestinal bleeding to prevent infection and use of albumin in patients with spontaneous bacterial peritonitis to reduce the incidence of renal impairment(4).

Spontaneous Bacterial Peritonitis

SBP is characterized by infection of the ascitic fluid (AF) in the absence of any primary focus of intra-abdominal infection(7). In liver cirrhosis, three
mechanisms are proposed for the pathogenesis of SBP, intestinal bacterial overgrowth, alterations (structural and functional) in the intestinal mucosal barrier and deficiencies in the local immune response(9). The incidence of mortality with the first episode varies between 10% and 46%. The reported probability of spontaneous bacterial peritonitis recurrence one year after the first attack averages 40 to 69%(7). 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 were 70-90% and 50-70%, respectively(9).

Clinical Presentation and Diagnosis
SBP may manifest as a relatively insidious asymptomatic colonization (bacterascites) or it can quickly emerge as a sepsis syndrome with a high mortality rate(10). Most patients with SBP have symptoms and/or signs clearly suggestive of peritoneal infection, such as abdominal pain, fever, and altered gastrointestinal motility. Other patients have no or minor symptoms with deterioration of liver or renal function(11). The diagnosis of SBP is shown in the Table. In response to the futility of finding pathogens using conventional means, it was eventually discovered that inoculation of 10-20 mL AF into 100 mL blood culture bottles at the patient’s bedside yields bacteria in up to 90% of cases(12). A new leukocyte esterase reagent strip is reported to be a rapid, simple and easily available method for the diagnosis of SBP(13,14).

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**Diagnosis of SBP**
- Ascitic fluid polymorphonuclear neutrophil (PMN) count >250/mm³; In patients with bloody ascites, subtract 1 PMN per 250 red blood cells
- Cultures
  - Ascitic fluid culture: beside inoculation into blood culture bottles (>10 mL)
  - Blood cultures: simultaneous to ascitic fluid culture

**Special Conditions**
- Bacterascites: positive ascitic fluid culture, ascites PMN <250/mm³, and no evidence of local or systemic infection
  - Repeat paracentesis once bacterascites is diagnosed and initiate antibiotic if:
    - Ascites PMN >250/mm³
    - Ascites PMN <250/mm³, but culture continued to be positive
- Secondary peritonitis: suspected when 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

**Ascitic Fluid Infection**
Ascitic fluid infection (AFI) consists of culture-negative neutrocytic ascites (CNNA) and
SBP. Although in-hospital mortality is higher in patients with SBP than CNNA, the clinical course of the two groups is similar after the first episode of AFI\(^{15}\). CNNA is diagnosed when the ascites fluid culture does not grow pathogenic bacteria, the ascites fluid neutrophil count is at least 250/mL, and there is no evident intraabdominal surgically treatable source of infection\(^{16}\). Bacterascites is diagnosed as in the Table. It is a prerequisite to the development of SBP or transient and spontaneously reversible colonization of ascites\(^{17}\). Secondary peritonitis is caused by bowel perforation or intraabdominal infections, abdominal wall infections, or previous surgical procedures\(^{11,18}\).

Unlike SBP, secondary peritonitis usually requires surgical treatment. Conversely, surgical therapy may be accompanied by significant deterioration in the clinical outcome of cirrhotic patients with SBP\(^{19}\).

**Management**

When first described, the mortality of SBP exceeded 90%; however, with early recognition of the disease and prompt appropriate antibiotic therapy, mortality has been reduced to around 15 to 20%\(^{20}\). Since renal insufficiency is the most important predictor of mortality in SBP, large volume paracentesis, diuretic therapy and nephrotoxins should be avoided during acute infection\(^{21}\). Gram-negative aerobic bacteria and non-enterococcal *Streptococcus* spp. are the most common organisms isolated from ascites. Cefotaxime has been the most extensively studied antibiotic for this infection\(^{7}\). Two comparative studies reported that cefotaxime was superior to a combination of ampicillin and tobramycin or aztreonam in the treatment of SBP, with higher resolution rates, less nephrotoxicity and fewer superinfections\(^{22,23}\). The current recommendations for SBP advocate the administration of cefotaxime 2g intravenously every 12 hours for a minimum of 5 days therapy\(^{24}\). Since the median time to resolution of SBP was 8 days in prospective trials,\(^{24}\) we think it is safer to recommend 10-14 days therapy. Other cephalosporins, including cefonicid, ceftriaxone and ceftazidime, are as effective as cefotaxime in improving SBP resolution and patient survival\(^{25,26}\). In patients with uncomplicated 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 consequent superinfection\(^{27}\). Recent studies also showed good results for amoxicillin/clavulanate in the treatment of SBP\(^{28}\). One trial revealed that amoxicillin/clavulanic acid was as effective as cefotaxime with similar rates of infection resolution without relevant adverse effects\(^{29}\).

Another focus of treatment is to augment the effective blood volume with plasma expanders such as albumin. This protein contributes 75% of the colloid oncotic pressure in the vasculature of healthy subjects and is thought to be a key factor in maintaining effective vascular volume\(^{30}\). Additionally the negatively charged albumin molecule is thought to bind many pro-inflammatory substances (such as nitric oxide) implicated in the vasculator changes in infection\(^{31}\). Albumin administration in patients with SBP has been related to both an improvement in cardiac function and a decrease in the degree of arterial vasodilatation\(^{32}\). In a randomized non-blinded study, selected patients with uncomplicated SBP who received cefotaxime plus albumin had significantly lower rates of renal failure (10% vs. 33%) and hospital mortality (10% versus 29%) than those who received cefotaxime alone\(^{33}\). It is not clear at present whether the use of albumin is better than other colloids or crystalloids in preventing renal impairment complicating SBP. Preliminary evidence
suggests that albumin may be useful in reducing the development of HRS in those with pre-existing high levels of blood urea nitrogen.\(^{(33)}\)

**Prophylaxis**

Patients who have survived an episode of SBP and patients with low total protein contents in the AF are at high risk of SBP.\(^{(21,28,34)}\) Predictably, patients who have survived an episode of SBP have high recurrence rates (70% in 1 year). The one-year survival rate is equally dismal at 30-50%.\(^{(28)}\) Patients who have survived an episode of SBP should receive long-term prophylaxis with daily norfloxacin (400 mg once a day).\(^{(35)}\) In these patients, liver transplantation should be considered as the lethality after SBP is higher than that after liver transplantation.\(^{(36,37)}\) If transplantation is indicated, antibiotics should be applied until the operation. If transplantation is not indicated, the literature recommends that antibiotics be given for the rest of the patient’s life. Preventive application of antibiotics in patients at high risk of infection—patients with low total protein contents in the AF < 15 g/L has not been generally recommended so far.\(^{(38)}\) Long-term use of norfloxacin (or trimethoprim/sulfamethoxazole) can be justified in these patients if at least one of the following is present together with a low level of protein in the ascites: (1) serum creatinine >1.2 mg/dL, or (2) serum sodium <130 mEq/L with bilirubin >3 mg/dL.\(^{(39)}\) In clinical practice, an individual approach to each patient has been recommended.\(^{(38)}\)

**Pneumonia**

High alcohol intake is frequently associated with liver cirrhosis, and is also the main risk factor for developing community-acquired pneumonia in middle-aged people. This situation also confers a worse prognosis in these patients, who should be treated with broad-spectrum antibiotics for a longer period.\(^{(40,41)}\) Gram-negative bacteria and *Pneumococci* are predominant organisms in lower respiratory tract infections.\(^{(42)}\) In another study, *Streptococcus pneumoniae* was the causative organism in most lower respiratory infections in alcoholics. However, other microorganisms normally present in the oropharyngeal area, such as anaerobic bacteria and *Hemophilus influenzae, Klebsiella pneumoniae, Mycoplasma pneumoniae*, and *Legionella* spp., have also been reported.\(^{(40)}\) In these subjects, empirical antibiotics could include erythromycin combined with cefotaxime, ceftriaxone, amoxicillin-clavulanic acid, or imipenem. Hospital-acquired pneumonia is mainly caused by Gram-negative bacilli and *Staphylococci*.\(^{(43)}\) Some procedures and clinical conditions, such as endotracheal intubation, esophageal tamponade, and hepatic encephalopathy, are clearly predisposing factors for pneumonia in cirrhotic patients. The empirical antibiotics for these patients are third generation cephalosporins (i.e cefotaxime). If aspiration pneumonia is suspected, clindamycin should be added.\(^{(43)}\) Spontaneous bacterial empyema, defined as the spontaneous infection of the pleural fluid, represents a distinct complication of hepatic hydrothorax. This term may be confusing because in most cases there is no evidence of pus or abscess in the thoracic cavity and indeed, the pathogenesis, clinical course and treatment strategy of spontaneous bacterial empyema are different from those of empyema secondary to pneumonia.\(^{(44)}\) The causative microorganisms in most cases of spontaneous bacterial empyema are *Escherichia coli, Streptococcus* species, *Enterococcus* and *Klebsiella*.\(^{(45)}\) Because repeated thoracenteses in cirrhotic patients can be harmful, chest tube drainage should not be used in the treatment of spontaneous bacterial empyema.\(^{(46)}\)
Urinary Tract Infection

In cirrhotic patients, UTI may be asymptomatic or oligosymptomatic; asymptomatic bacteriuria is found frequently\(^{(47)}\). The high frequency of UTI in cirrhotic patients, especially in those with ascites, could be related to the residual urinary volume and possibly, to frequently found vesical dysfunction\(^{(48)}\). In a study of non-hospitalized cirrhotic patients with no symptoms of UTI, the frequency of UTI was approximately 5%. Urine cultures were positive in 4.9% of these patients. Frequently found bacteria included *E. coli* and *K. pneumoniae*\(^{(49)}\). The incidence is markedly higher in cirrhotics with indwelling catheters and women\(^{(42)}\). Thus, empirical administration of a modern quinolone (norfloxacin, ofloxacin or ciprofloxacin), amoxicillin-clavulanic acid or an oral cephalosporin should be considered in these high-risk patients\(^{(42,50)}\).

Antibiotic Prophylaxis in Gastrointestinal Bleeding with Liver Cirrhosis

Gastrointestinal bleeding is associated with bacterial infection up to 66% of patients with cirrhosis\(^{(51)}\). These patients are vulnerable to infection because of disruption of the intestinal mucosal barrier and frequent invasive manipulation during hemorrhage\(^{(52)}\). Most cirrhotic patients develop esophageal varices (EV), with a lifetime incidence as high as 90%\(^{(6)}\). Approximately one third of cirrhotic patients with EV develop an episode of esophageal hemorrhage, with subsequent high morbidity and mortality\(^{(6)}\). 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\(^{(53)}\). Bacterial infection may adversely affect hemostasis in patients with gastroesophageal variceal bleeding. Antibiotic prophylaxis can prevent infection and rebleeding as well as decrease the amount of blood transfused in patients with acute gastroesophageal variceal bleeding following endoscopic treatment\(^{(5)}\). In one study, prophylactic treatment with systemic antibiotics was very effective in preventing bacterial infections in gastrointestinal bleeding with cirrhosis\(^{(51)}\). In another study, antibiotic prophylaxis using third generation cephalosporins prevented bacterial infection and early rebleeding in patients with a first acute episode of gastroesophageal variceal bleeding\(^{(54)}\). Therefore, intravenous ceftrixone for 7 days or norflaxacin 400 mg twice a day for 7 days should be given to prevent bacterial infections in patients with cirrhosis and gastrointestinal bleeding\(^{(35)}\).

Other Infections

Endocarditis

The site and type of infection is unrelated to the etiology of the liver disease. Bacteraemia, pneumonia, UTI, and SBP are most common but infective endocarditis, especially with *Pneumococci*, is easily overlooked. Clinical suspicion of infection must be high as the only indication may be a general deterioration in the patients’ clinical state, increasing encephalopathy or renal impairment\(^{(55)}\). In previous study, bacterial pathogens were identified in 25 patients, with *Staphylococcus aureus*, *viridans streptococci*, *Streptococcus sanguis*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis* the most common isolates. In one report, the hospital mortality rate for cirrhotic patients with infective endocarditis was 27\(^{(56)}\).
Meningitis

Bacterial meningitis in cirrhotic patients is associated with a high mortality rate and a large number of complications. A high index of suspicion is necessary because of the frequent absence of meningeal signs. In addition to the classic meningeal pathogens, other pathogens, including *E. coli* and *Listeria monocytogenes*, should be considered when prescribing empirical therapy\(^{(57)}\). In one study from Taiwan, *K. pneumoniae* was the most frequent causative pathogen in patients with liver cirrhosis. The overall case fatality rates for patients with and without liver cirrhosis were 38.5% (74/192) and 64% (16/25), respectively. Patients with liver cirrhosis have a more fulminant course with higher prevalences of disturbed consciousness, bacteremia, seizures and shock. When patients with liver cirrhosis develop disturbed consciousness, seizures and septicemia, immediate neuroimaging and cerebrospinal fluid studies should be undertaken to determine if bacterial meningitis is the cause. Early diagnosis and treatment are essential for survival\(^{(58)}\).

Skin and Soft-Tissue Infections

Although *S. aureus* and *Streptococcus pyogenes* are most frequent causative organisms, *Enterobacteriaceae* and anaerobes may also complicate skin and soft tissue infections\(^{(59)}\). Soft tissue infections account for 11% of infections overall in cirrhotic patients and the severe form of necrotizing infection carries a high mortality rate. It is essential that clinicians make an early diagnosis and start appropriate treatment to improve outcomes of cirrhotic patients with these infections. In previous study, Gram-negative bacterial infection was predominant in the nonsurvivor group and was statistically significant\(^{(60)}\). Hemorrhagic bullae in cirrhotic patients usually imply a fatal infection such as necrotizing infection and Gram-negative bacteria are the most common pathogens. Appropriate antimicrobial therapy and early surgical intervention are necessary to achieve survival in these patients\(^{(61)}\). *Aeromonas hydrophilia* is an infrequent cause of human infection. *Aeromonas* infection appears to be more common in Taiwan than in Western countries\(^{(62)}\). In recent study from Taiwan, *A. hydrophilia* bacteremia occurred most often in cirrhotic patients. It may frequently be overlooked as the cause of skin and soft tissue infection. The rapid onset of cellulitis in the setting of soft tissue trauma should alert the clinician to the possibility of *A. hydrophilia* infection, which is intrinsically resistant to common antibiotics used for cellulitis\(^{(63)}\).

References


肝硬化病患之細菌性感染

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肝硬化患者之細菌感染是常見的嚴重併發症，這些患者經常到急診室就醫或住院治療。最常見的併發症包括自發性細菌性腹膜炎、肺炎、泌尿道感染、菌血症和其他感染。肝硬化患者特別容易受到細菌感染，因為細菌移位增加可能與肝功能障礙、降低網狀內皮功能、醫源性因素有關係。事實上，肝硬化患者細菌感染後，住院治療中死亡率大約是15%，是無感染肝硬化患者的兩倍以上。在這篇文章中，我們將提供一個簡要概述有關流行病學、臨床表徵、治療和預防這些肝硬化患者之併發症。

關鍵詞：細菌感染，肝硬化，自發性細菌性腹膜炎，消化道出血