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REVIEW

Diagnosis and management of bacterial infections in decompensated cirrhosis

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Abstract

Bacterial infections are one of the most frequent complications in cirrhosis and result in high mortality rates. Patients with cirrhosis have altered and impaired immunity, which favours bacterial translocation. Episodes of infections are more frequent in patients with decompensated cirrhosis than those with compensated liver disease. The most common and life-threatening infection in cirrhosis is spontaneous bacterial peritonitis followed by urinary tract infections, pneumonia, endocarditis and skin and soft-tissue infections. Patients with decompensated cirrhosis have increased risk of developing sepsis, multiple organ failure and death. Risk factors associated with the development of infections are severe liver failure, variceal bleeding, low ascitic protein level and prior episodes of spontaneous bacterial peritonitis (SBP). The prognosis of these patients is closely related to a prompt and accurate diagnosis. An appropriate treatment decreases the mortality rates. Preventive strategies are the mainstay of the management of these patients. Empirical antibiotics should be started immediately following the diagnosis of SBP and the first-line antibiotic treatment is third-generation cephalosporins. However, the efficacy of currently recommended empirical antibiotic therapy is very low in nosocomial infections including SBP, compared to community-acquired episodes. This may be associated with the emergence of infections caused by *Enterococcus faecium* and extended-spectrum β-lactamase-producing Enterobacteriaceae, which are resistant to the first line antimicrobial agents used for treatment. The emergence of resistant bacteria, underlines the need to restrict the use of prophylactic antibiotics to patients with the greatest risk of infections. Nosocomial infections should be treated with wide spectrum antibiotics. Further studies of early diagnosis, prevention and treatment are needed to improve the outcomes in patients with decompensated cirrhosis.

Key words: Cirrhosis; Infections; Spontaneous bacterial peritonitis; Ascites; Antibiotics

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INTRODUCTION

Bacterial infections are one of the most frequent complications in cirrhosis, particularly in decompensated

patients, and account for significant mortality. The current prevalence of this complication ranges between 25% and 30%[1,2] and is responsible for 30%-50% of deaths in these patients[3]. The cumulative mortality after any infection in patients with cirrhosis is 43.5%. It has been suggested that the occurrence of bacterial infection could be considered a further prognosis stage, defining the critically ill cirrhotic[4]. Risk factors associated with the development of infections are high Child-Pugh score, variceal bleeding, low ascitic protein level and prior episodes of spontaneous bacterial peritonitis (SBP).

The most common infections in cirrhosis are SBP[5], followed by urinary tract infections, pneumonia and cellulitis[6]. Sixty percent of bacterial infections are community-acquired and 40% are nosocomial. In hospitalized cirrhotic patients, the most frequent infections are healthcare-associated or hospital-acquired and these infections are frequently resistant to antibiotics. The most frequent causative organisms in community-acquired infections are gram-negative bacilli, mainly *Escherichia coli* (*E. coli*) (60%). The emergence of extended-spectrum beta-lactamase (ESBL)-producing enterobacteria in nosocomial infections has meant that gram-positive cocci are no longer the main bacteria isolated in hospital-acquired infections. Moreover, nosocomial SBP are mainly caused by gram-negative bacteria. However, cultures are positive only in 40%-70% of infections. The treatment of choice for the most common infections occurring in cirrhosis is third-generation cephalosporins since they are active against Enterobacteriaceae and non-enterococcal streptococci as well as being well tolerated[7-9]. However, recent studies have shown that the prevalence of infections caused by multiresistant bacteria is increasing in cirrhosis[10].

Immune defects, mainly acquired but also genetic, and bacterial translocation are the principal mechanism involved in the pathogenesis of infection in cirrhosis[11]. Liver dysfunction is associated with an impaired defense against bacteria, which worsens over time and with disease progression. Both humoral and cell-mediated immunity are depressed. In cirrhosis, decreased bacterial clearance as well as structural and functional alterations in the intestinal mucosa lead to an increase in permeability to bacteria and derived products. This favours bacterial translocation, which increases the susceptibility to infection, particularly SBP. Deficiencies in C3 and C4, impairment of macrophage Fcγ-receptor mediated clearance of antibody-coated bacteria and down-regulation of monocyte human leukocyte antigen-DR expression, may also contribute to this altered defense[12]. In some cases a deregulated immune response produces an important production of inflammatory mediators, which leads to an excessive pro-inflammatory response. This process may contribute to renal impairment, multiple organ failure and high mortality rate[13].

Bacterial infections, regardless of the aetiology, are a severe complication of decompensated cirrhosis, and result in increased mortality and longer hospital stay. The most important predictive factor for mortality after infection is renal failure. The release of inflammatory mediators during infection leads to systemic, renal, and hepatic hemodynamic impairment, which dramatically affects the prognosis even after resolution of infection. The mortality rate after infection in patients with cirrhosis remains high and has not significantly changed over recent decades[4]. The widespread use of quinolones and other antibiotics in cirrhosis has favoured changes in bacterial flora and the development of antibiotic resistance. To improve outcomes, new studies of early diagnosis, prevention and treatment are needed.

DIAGNOSIS OF BACTERIAL INFECTIONS

Early diagnosis and treatment of infections are of paramount importance for the management of patients with decompensated cirrhosis, since bacterial infections are important causes of mortality and morbidity in these patients. Patients with decompensated cirrhosis have increased risk of developing sepsis, multiple organ failure and death[14]. Mortality associated to infections is twenty times higher in patients with cirrhosis than in the general population.

Bacterial infections in patients with cirrhosis can be asymptomatic or pauci-symptomatic, and have to be suspected in any cirrhotic patient with a sudden impairment of liver function[15]. The prognosis of these patients is mainly dependent on a prompt and accurate diagnosis[2]. Identification of the source of infection is the primary concern when deciding on the appropriate antibiotic therapy. The first evaluation must include a detailed physical examination including vital signs (temperature, respiratory and heart rates, mean arterial pressure), abdominal and chest examination, and evaluation of the presence of skin lesions. A complete work-up must include a range of diagnostic tests such as blood cell count and culture, urinary sediment and culture, chest X-ray, sputum culture, ascitic/pleural fluid cultures and abdominal ultrasonography[11].

Diagnosis of spontaneous bacterial peritonitis

SBP is defined as an infection of the ascitic fluid in the absence of a contagious cause of infection (e.g., intestinal perforation or abscess)[7]. SBP is a frequent and severe complication of cirrhosis, with an incidence in hospitalized patients with cirrhosis of 7%-25%. Prospective studies have shown that one-year mortality rates following an episode of SBP, range from 65% to 93%[16]. Risk factors for SBP include impaired liver function, gastrointestinal bleeding, high bilirubin levels, low ascitic fluid protein (< 10-15 g/L), and a prior episode of SBP.

Abdominal pain and fever are the most common symptoms, followed by vomiting, hepatic encephalopathy, gastrointestinal bleeding and renal dysfunction. However, symptoms and signs are sometimes absent[17]. In 40%-60% of cases, the organism responsible for SBP is isolated in ascitic fluid or blood cultures[1-4,6]. Diagnostic paracentesis

should be carried out in all patients with ascites who are admitted to hospital, regardless of symptoms[18].

Diagnosis of SBP is based on the demonstration of an absolute number of polymorphonuclear cells in ascitic fluid equal to or greater than 250/mm^3. Diagnosis of SBP constitutes an indication to initiate an empirical antibiotic therapy and must not be delayed until the ascites bacteriological culture results are available[7,8]. The best specificity for diagnosis has been reported[19-22] with a cut-off of 500 PMN/mm^3. It is unclear whether a positive culture in the absence of elevated ascitic fluid PMN count (bacteriascites), requires antibiotic therapy. In these cases, some guidelines recommend antibiotic treatment only if the patient shows signs of infection[8]. Leukocyte reagent strips have been suggested as a rapid screening test for the diagnosis of SBP at the bedside[23-26]. However, sensitivity varying between 45% and 100%, makes this method suboptimal for the diagnosis of SBP. In patients with hemorrhagic ascites (red blood cell count > 10 000/mm^3), subtraction of one PMN per 250 red blood cells should be made. When there is a predominant lymphocytosis in the ascitic fluid, the differential diagnosis must include tuberculous peritonitis, neoplasms, congestive heart failure, pancreatitis and myxedema, but usually not SBP[18]. Other markers that have been suggested for the diagnosis of SBP are lactoferrin, an iron-binding protein contained in PMN, which has a sensitivity of 96% and a specificity of 97% with cut-off value of ⩾ 242 ng/mL in ascitic fluid[27].

The most frequently identified organisms in patients with SBP are gram-negative bacteria (*E. coli*) and gram-positive cocci (streptococcus and enterococcus). Approximately, 30% of isolated gram-negative bacteria are resistant to quinolones and this resistance is higher in patients undergoing norfloxacin therapy[9]. The most frequent causative organisms in community-acquired SBP are gram-negative bacteria, while in nosocomial infections gram-positive organisms are responsible for most infections.

Secondary peritonitis constitutes the main differential diagnosis of SBP, accounting for 5%-10% of all peritonitis in patients with cirrhosis and ascites. This is due to perforation or inflammation of an intra-abdominal organ, and its mortality is much higher than that of SBP (66% *vs* 10%)[28]. Secondary peritonitis must be suspected in patients with inadequate response to therapy or when multiple organisms are identified in the ascitic fluid[29]. A diagnosis of secondary peritonitis is probable when at least two of the Runyon's criteria are present: glucose level < 50 mg/dL; protein concentration > 10 g/L; or lactate dehydrogenase > 225 mU/mL[8]. When secondary peritonitis is suspected, an abdominal computerized tomography should be performed as soon as possible[30].

Other infections in patients with cirrhosis

Urinary tract infections: Urinary tract infections (UTI) in cirrhosis can be asymptomatic or oligosymptomatic, and asymptomatic bacteriuria is frequent[31,32]. The incidence of UTI is higher in cirrhotic patients with indwelling catheters and in women. The most frequent bacteria causing UTI are *E. coli* and *Klebsiella pneumoniae* (*K. pneumonia*). Quinolones are not recommended for the treatment of UTI in areas with a high prevalence of quinolone-resistant enterobacteria, such as Southern Europe. Amoxicillin-clavulanic acid or an oral cephalosporin should be considered in these high-risk patients[33-35].

Pneumonia: Pneumonia is the third most common infection in liver cirrhosis, after SBP and UTI. Community-acquired pneumonia is most frequent, especially in subjects with active alcoholism[36]. Streptococcus pneumonia is the most common causative organism, followed by *anaerobic bacteria* or *Haemophilus influenza*, *K. pneumonia*, *Mycoplasma pneumonia* or *Legionella*[37,38]. The initial treatment of choice should include macrolides combined with one of the following: cefotaxime, ceftriaxone, amoxicillin-clavulanic acid, imipenem or piperacillin-tazobactam. Factors such as tracheal intubation and hepatic encephalopathy may predispose for hospital-acquired pneumonia, mainly caused by gram-negative bacilli and staphylococci. In these cases, the treatment should be adapted to the local epidemiological pattern of resistant bacteria; meropenem or ceftazidime plus ciprofloxacin may be an adequate option. Vancomycin or linezolid should be added in patients with risk factors for methicillin-resistant Staphylococcus aureus (MRSA) (Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage).

Endocarditis: Streptococcus and Staphylococcus aureus are the most common causative organisms.

Skin and soft-tissue infections: Lymphangitis of the lower extremities and abdominal wall are frequent in cirrhotic patients with edema or ascites. The most common etiologic organisms are Staphylococcus aureus and Streptococcus pyogenes, followed by Enterobacteriaceae and anaerobes[39]. Empirical therapy with cloxacillin has been considered the first-choice. Amoxicillin-clavulanic acid or quinolones (i.e., ofloxacin) may be an adequate alternative. Cellulitis is usually treated with a combination of cloxacillin and a third-generation cephalosporin.

TREATMENT OF SBP IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

In practice, third generation cephalosporins have already been established as the standard treatment of SBP[40-42]. However, the efficacy of currently recommended empirical antibiotic therapy is very low in nosocomial infections, including SBP, when compared to community-acquired episodes. Infections caused by multiresistant bacteria have increased nearly 100%, and are associated to a higher incidence of treatment failure, rapid deterioration of liver function and mortality. This change may be associated with the emergence of infections caused by *Enterococcus*

faecium and extended-spectrum β-lactamase-producing Enterobacteriaceae, which are resistant to the current recommended empirical antibiotic therapy. This findings led to the suggestion that nosocomial SBP should be treated with carbapenems or with tigecycline[43].

Appropriate empirical antibiotic therapy is associated with improved survival. In the absence of ascitic fluid cultures, it is important to use broad-spectrum antibiotics, selected according to the type and severity of infection. Epidemiological factors, such as site of acquisition of the infection (nosocomial *vs* community-acquired infections), and previous history of multiresistant infection, must be taken into account[11]. Prevention and treatment of renal failure, sometimes triggered by infection, is of pivotal importance in the treatment of these patients. Therefore, some antibiotics, such as aminoglycosides, should not be used in cirrhosis because of the high risk of renal failure[44].

Treatment of community-acquired SBP

The organisms traditionally associated with community-acquired SBP are gram-negative bacteria, mainly Enterobacteriaceae. This family of bacteria usually shows optimal response to third-generation cephalosporins (e.g. cefotaxime). Amoxicillin-clavulanic acid and ciprofloxacin have shown similar results. Intravenous cefotaxime 2 g/12 h is considered the first-line antibiotic for the empirical treatment of SBP. A 5-d therapy is as effective as a 10 day treatment. Other effective and safe options are *iv* ceftriaxone 1 g/(12-24) h or *iv* amoxicillin-clavulanic acid (1-2) g/(6-8) h[45]. The use of fluoroquinolones (e.g., ciprofloxacin 200 mg/12 h, *iv*) has demonstrated similar efficacy. In patients with uncomplicated SBP (absence of gastrointestinal hemorrhage, severe encephalopathy, septic shock or creatinine > 3 mg/dL), oral ofloxacin (400 mg/12 h) may be an effective alternative. In patients who develop SBP while receiving norfloxacin prophylaxis, quinolones are not recommended and the best alternative is cefotaxime or amoxicillin/clavulanic acid. In SBP it is of crucial importance to assess the response to treatment by performing a follow-up paracentesis two days after initiation of the antibiotic therapy. A reduction in the ascitic fluid PMN count (< 25%), compared with the pretreatment value, is considered treatment failure and indicates the need for modification of the antibiotic treatment according to *in vitro* sensitivity.

Administration of albumin as adjuvant treatment to antibiotics is considered essential in patients with SBP and impaired renal or liver function, in order to prevent worsening of renal function[46-48]. The recommended dose is 1.5 g/kg on day 1 and 1 g/kg on day 3. The concomitant use of albumin decreases the incidence of type 1 hepatorenal syndrome (from 30% to 10%) and reduces mortality (from 29% to 10%), compared with cefotaxime alone. Treatment with albumin is particularly effective in patients with serum bilirubin ⩾ 4 mg/dL or serum creatinine ⩾ 1 mg/dL, while its use in patients without these criteria remains controversial[49]. However, in unselected patients with SBP, even low-dose albumin (10 g/d on day 1 and 3) reduces tumour necrosis factor and interleukin 6 levels in serum and ascites as well as preventing increases in serum nitric oxide induced by SBP[50].

Treatment of nosocomial SBP

Unfortunately, antibiotic therapy fails in 26%-41% of patients with SBP[51]. One of the explanations may be that current guidelines for the treatment of SBP do not distinguish between community-acquired and nosocomial episodes. Recent studies have reported an increasing prevalence of extended-spectrum β-lactamase-producing bacteria and multiresistant gram-positive bacteria such as Enteroccocus faecium or MRSA[52]. In fact, bacteria isolated in nosocomial SBP are frequently resistant to β-lactams (33%-78%), and this is associated with a low success rate in a significant proportion of nosocomial SBP[53-56], which are being treated with third generation cephalosporins, amoxicillin/clavulanic acid or quinolones.

Clinical and research efforts are focused on decreasing rates of mortality, morbidity and healthcare associated costs. The development of bacterial resistance in community-acquired SBP increases the risk of mortality four-fold, since it is usually associated with empirical treatment failure. Therefore, for an optimal treatment of nosocomial infections in patients with cirrhosis, epidemiological factors and patterns of resistance should be considered. Hospitalisation within the previous 3 mo, intensive care treatment, and prior antibiotic treatment, are independent risk factors for the development bacterial multi-resistance[57].

Carbapenems are the most effective option for nosocomial infections in areas with a high prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae. Tigecycline may be a potential alternative, although recent studies have showed increased mortality related to its low clinical efficacy and it should not, therefore, be recommended as first-line therapy in the general population[58]. Penicillin used in combination with β-lactamase inhibitors (e.g., piperacilin-tazobactam) may be an adequate alternative. However, the most appropriate antibiotic treatment in any particular case should be selected according to the results of the relevant microbiological studies.

PROPHYLAXIS OF SBP IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

In patients with cirrhosis at high risk of SBP (low protein ascites and advanced liver dysfunction or impaired renal function), norfloxacin administration decreases the 1-year probability of developing this infection and hepatorenal syndrome, and moreover increases 3-mo and 1-year survival[29]. However, recent studies suggest that norfloxacin is not now as affective as it was in the past, possibly due to the development of quinolone-resistant bacteria in the fecal flora of patients receiving long-term prophylaxis. Thus, to prevent antibiotic resistance and to make these strategies cost-effective, antibiotic prophy-

laxis must be restricted to those patients at a very high risk of bacterial infections. Since the gut appears to be the main source of bacteria in SBP, a selective intestinal decontamination by elimination of gram-negative bacilli (mostly responsible for infections in cirrhosis) should be performed.

Primary prophylaxis in patients with gastro-intestinal bleeding

Cirrhotic patients with upper gastrointestinal bleeding are at high risk (25%-65%) of bacterial infections, particularly SBP, during the first 7 d after the bleeding episode. Moreover, bacterial infections increase the risk of early re-bleeding[59]. An increase in portal pressure and changes in hemostasis induced by infection have been suggested as possible mechanisms[60,61]. A beneficial effect of antibiotic prophylaxis on control of bleeding and prevention of re-bleeding has been reported[62]. Current guidelines recommend antibiotic prophylaxis in patients with cirrhosis and gastrointestinal bleeding regardless of the presence of ascites[9]. A meta-analysis of five trials comprising 534 cirrhotic patients with variceal haemorrhage, demonstrated that antibiotic prophylaxis for 4 to 10 d significantly reduced the occurrence of SBP and septicaemia, and improved short-term survival[63]. Similar results were seen in a more recent meta-analysis of twelve trials comprising a total of 1241 patients with cirrhosis and gastrointestinal bleeding, in which antibiotic prophylaxis significantly decreased the incidence of bacterial infections, re-bleeding, length of hospitalisation and mortality. Prophylaxis benefits were observed irrespective of the antibiotic used, although they were stronger with cephalosporins, quinolones and quinolones plus beta-lactams[64]. The use of antibiotic prophylaxis as secondary prevention of variceal bleeding may reduce the incidence of early re-bleeding, mainly in the first seven days after the first haemorrhage[65].

Currently, the recommended antibiotics are mainly oral quinolones (norfloxacin 400 mg *bid* for 7 d) or intravenous cephalosporins (ceftriaxone 1 g/d for 7 d). Norfloxacin is a poorly absorbed quinolone with antibacterial activity against gram-negative bacteria, which is simple to administer and has low cost. The main complication of long-term norfloxacin prophylaxis is the occurrence of infections by quinolone-resistant organism, which are usually susceptible to third-generation cephalosporins. This fact and the lack of efficacy of norfloxacin against gram-positive or anaerobic organisms, may explain the superiority shown by intravenous ceftriaxone over oral norfloxacin in a randomized controlled trial on patients with variceal bleeding and advanced cirrhosis (characterized by at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin > 3 mg/dL)[66]. Invasive procedures used in patients with cirrhosis and haemorrhage are a risk factor for infections caused by gram-positive bacteria. Intravenous administration seems to be more appropriate than oral intake in patients with active upper bleeding who have vomits and very rapid intestinal transit. Intravenous ceftriaxone should, therefore, be used in the prophylaxis of bacterial infections in patients with advanced cirrhosis and upper gastrointestinal bleeding, whereas patients with less severe liver disease may be given oral norfloxacin or an alternative oral quinolone.

Therefore, in patients with upper gastrointestinal bleeding, antibiotic prophylaxis is considered essential. In patients with less severe liver disease norfloxacin may be given, whereas in those with severe liver disease ceftriaxone is the prophylactic antibiotic of choice. Timing of antibiotic administration is also important and prophylaxis should be started from admission, ideally before or immediately after endoscopy[67]. Local bacterial resistance profile and treatment costs, are other factors to consider in the selection of antibiotics.

Primary prophylaxis in patients with ascites

Primary prophylaxis in cirrhotic patients with ascites, but without gastrointestinal bleeding, is controversial. A recent meta-analysis including seven trials comparing antibiotic prophylaxis to no intervention or placebo, showed that the relative risk of SBP and mortality was lower in patients treated with antibiotics (RR 0.2; 0.11 to 0.37) than with no treatment or placebo (RR 0.6; 0.43 to 0.87)[16]. However, these findings must be taken with caution because of the low methodology quality of most of the trials and the likely existence of systematic bias in the trials included. Given the increasing emergence of resistant bacteria and the limited validity of these results, antibiotic prophylaxis in all patients with ascites without bleeding should not be recommended until we have more conclusive evidence.

However, it is well known that the risk of SBP in patients with ascites depends on ascitic fluid protein concentration, since it has been shown that low protein concentration (< 10-15 g/L) is a risk factor, and the incidence is greater in those with advanced liver disease. Several independent studies and meta-analysis have assessed this issue[68-71]. In a placebo-controlled trial on patients with protein ascitic levels < 15 g/L and advanced liver failure or impaired renal function, norfloxacin (400 mg/d) reduced the 1-year probability of developing SBP and improved the 3-mo survival, although at 1 year the difference in survival was not significant[29]. Similarly, a placebo-controlled trial on patients with ascites protein < 15 g/L and moderate liver failure, showed that prophylaxis with ciprofloxacin for 12 mo improved the 1-year survival. However, there was no significant difference between groups in the occurrence of SBP or other infections[72]. A recent meta-analysis of these three trials supports the efficacy of quinolones in these settings, since it demonstrates significant preventive power for SBP and mortality[18]. A previous meta-analysis, which aimed to assess the effect of antibiotic prophylaxis in the prevention of SBP and survival, showed similar results. It included eight studies comprising 647 patients with cirrhosis at risk for developing SBP. In seven of the eight studies the

mean ascitic fluid protein level was < 15 g/L. Criteria for defining advanced liver disease included Child-Pugh scores > 9, bilirubin levels > 2.5 mg/dL, and impaired renal function. The analysis showed that prophylaxis improved short-term survival and reduced the incidence of infections, including SBP[73]. These results suggest that primary prophylaxis has a great impact in the clinical course of patients with low ascites protein content and advanced cirrhosis, and may reduce the incidence of SBP and improve survival. Nevertheless, studies in patients with low ascitic fluid protein but without severe liver disease, have failed to show significant effect of norfloxacin on survival or in the occurrence of SBP[74].

To the light of these studies, patients with protein ascitic levels < 15 g/L and severe liver disease or renal impairment should be considered for long-term prophylaxis with norfloxacin (400 mg/d), particularly those patients awaiting liver transplantation, because antibiotic prophylaxis may increase the applicability of this procedure. The optimal duration of primary antibiotic prophylaxis has not been established. Oral ciprofloxacin is a valid alternative to norfloxacin. In patients with low protein concentration in ascitic fluid, but with mild or moderate liver disease, antibiotic prophylaxis is not currently recommended[9].

Secondary prophylaxis in patients with prior SBP

The probability of survival at 1 year after an episode of SBP is about 30%-50%[75], with a cumulative recurrence rate at 1 year of 70%. Therefore, after one episode of SBP, liver transplantation must be considered. In all patients with a prior episode of SBP it is essential to initiate long-term antibiotic prophylaxis. For secondary prophylaxis, the evidence is strongest for norfloxacin (400 mg/d), since its use after an episode of SBP has been shown to reduce the recurrence from 70% to 20%[76]. This prophylactic strategy results in a substantial cost saving by avoiding resource utilization associated with treatment[77]. Intermitting antibiotic therapy schedules have been suggested as secondary prophylaxis, however this strategy may select resistant flora more rapidly and should, therefore, be avoided.

In these settings prophylaxis should be instituted after the completion of treatment for acute SBP and continued until liver transplantation or disappearance of ascites. The development of bacterial resistance is a potentially harmful complication of long-term antibiotic therapy, and it is greater with longer duration of antibiotic administration. In patients who develop resistance to quinolones, trimethoprim/sulfamethoxazole has been suggested as an alternative to norfloxacin[78]. However, there is a high rate of SBP caused by trimethoprimsulfamethoxazole resistant Gram-negative bacteria (44%-72%), suggesting that this antibiotic is not a suitable alternative to norfloxacin[79,80]. Data supporting the use of trimethoprim/sulfamethoxazole are weak, while its side effects are potentially dangerous and probably under-reported[81]. There are no data to support discontinuation of prophylaxis with quinolones in patients who develop infection due to quinolone-resistant bacteria. Antibiotic cycling or combined treatment regimes have been proposed to reduce the risk of emerging resistant bacteria, but there are no data supporting this strategy.

Probiotics, a non-antibiotic and safe therapy, may decrease bacterial translocation, since it has been reported that they can correct bacterial overgrowth, stabilize mucosal barrier function and decrease bacterial translocation in experimental conditions[82-84]. However *Lactobacillus* failed to reduce bacterial translocation and ascitic fluid infection in an animal model[85,86]. Further studies in patients with cirrhosis are needed to define the possible role of probiotics in SBP prophylaxis.

It has been suggested that acid-suppressive therapy with proton pump inhibitors (PPIs), which is widely used in patients with cirrhosis, may increase the risk of bacterial infections, since they cause bacterial overgrowth in the small intestine and increase intestinal permeability[87-92]. Several studies, including a meta-analysis[93] of four studies involving a total of 772 patients[94-98], found significant association between PPI and the development of SBP in patients with cirrhosis (odds ratio 2.77, 95%CI: 1.82-4.23). However, a recent study suggests that even though PPIs may be a contributing factor, the predominant factor determining infection risk is the stage of the liver disease[99]. Bajaj *et al*[100] identified PPI use as a risk factor for Clostridium Difficile Associated Disease (CDAD) in hospitalized patients with cirrhosis, which is associated with higher mortality, length of stay and costs. However, the relation between PPI use and CDAD has not been confirmed in other populations of patients with impaired immunity[101]. Therefore, more studies are needed to verify this association.

CONCLUSION

Bacterial infections in cirrhosis are common, accounting for significant mortality. Patients with decompensated cirrhosis have more frequent episodes of infection than those with compensated liver disease. Spontaneous bacterial peritonitis is the most common infection in these patients. The development of cirrhosis is associated with impairment in the immune system, which worsens over time, and with disease progression. Risk factors associated with development of infections in cirrhosis are severe liver failure, variceal bleeding, low ascitic protein level and prior episodes of SBP.

Identification of risk factors for SBP is important to develop optimally targeted safe and cost-effective strategies for its prevention. Improvements in survival are achieved with early diagnosis and prompt antibiotic treatment. Empirical antibiotics should be started immediately following the diagnosis of SBP and the first line antibiotic treatment is third-generation cephalosporins. The concomitant administration of albumin decreases the frequency of hepatorenal syndrome and improves survival.

Antibiotic prophylaxis should be used in cirrhotic

patients hospitalized with an episode of gastrointestinal haemorrhage, ascites and a prior history of SBP. Patients with protein ascitic levels < 15 g/L and severe liver disease or renal impairment should be considered for long-term antibiotic prophylaxis. Patients who recover from SBP have to be considered for liver transplantation, since they have a poor long-term survival.

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