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*Review*

# Pathogenesis, diagnosis and therapy of Infections complicating patients with chronic liver disease

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## SUMMARY

**Patients with chronic liver disease represent a susceptible group of the population who manifest numerous complications during the natural course of their disease.**

**As liver disease is considered one of the most common forms of acquired immunodeficiency related to multiple defects in immune defence, infections are one of the main inconveniences associated with high morbidity and mortality. In addition, diagnostic, therapeutic and nursing procedures may influence the critical equilibrium of these patients and predispose to infection. However, the most important predisposed factor is the severity of liver disease and the mortality rate is associated more with the severity than with the etiology of the disease.**

**Infections seen in chronic liver disease include not only spontaneous bacterial peritonitis (SBP) and spontaneous bacterial empyema (SBEM) but urinary tract infections, community or hospital acquired pneumonia, bacteremia, skin and soft tissue infections, endocarditis, and meningitis. Alcoholic subjects are also prone to develop pneumonia and pulmonary or peritoneal tuberculosis. On the other hand, a wide range of infectious sequels, involving almost any organ has been associated with esophageal variceal sclerotherapy (EVS). A significantly shorter series of infectious complications has been related to ligation (EVL).**

**Clinical suspicion of infection should be high in any patient with a deteriorating clinical status, encephalopathy or worsening renal insufficiency, as fever may not present. Since long term prognosis of cirrhotic patients with repeated infectious complications such as SBP and SBEM is poor, survivors should be considered potential candidates for orthotopic liver transplantation.**

**Clinicians' higher index of suspicion of infection, together with the use of more efficient and safer antibiotics, may, for the present at least improve the short term prognosis of this group of patients.**


**Key words:** Chronic liver disease, cirrhosis, spontaneous bacterial peritonitis, spontaneous bacterial empyema, esophageal variceal sclerotherapy, esophageal variceal ligation, other infections

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## 1. INTRODUCTION

Patients with chronic liver disease represent a susceptible group of the population who manifest several complications during the clinical course of their disease.

Infections are one of the most common problems in advanced liver cirrhosis, as in acute or fulminant liver failure, associated with high morbidity and mortality[1,2].

Seeing that infections constitute a potentially reversible cause of acute deterioration of patients with severe liver disease, we should like to emphasize in this review the most important advances in pathogenesis, management and prevention of the more frequent infections complicating chronic liver disease.

## 2. INFECTIONS IN CIRRHOSIS

### *2.1 Factors predisposing to infection in cirrhosis*

The prevalence of bacterial infections in cirrhotic patients is very high. In several studies 30 to 60% of

cirrhotic patients presented with bacterial infection when admitted to the hospital or develop this complication during hospitalization[3] (Table 1).

Cirrhosis may be considered as one of the more common forms of acquired immunodeficiency because of the high frequency of bacterial infections and the associated multiple defects in immune defense.[4] In fact, recently, an increasing body of evidence has been published documenting multiple derangements in defense mechanisms, in both human and animal models.[5-9]

Nevertheless, even the small bowel of normal subjects may be colonized by low number of gram-negative bacilli[10], the concentration of these microorganisms being significantly increased in the jejunal flora of several cirrhotic patients[11] (Figure 1). One of the postulated mechanisms of the intestinal bacterial overgrowth is prolonged intestinal transit as a consequence of altered intestinal motitility.[12] Decreased intestinal IgA or bile salts, conditions that have been observed in patients with cirrhosis, could also favor intestinal bacterial overgrowth in cirrhosis.[13,14]. Intestinal bacterial overgrowth is one of the main mechanisms postulated to promote bacterial translocation. In fact, bacterial translocation of a specific organism is almost always associated with intestinal bacterial overgrowth of the same microorganism.[12]

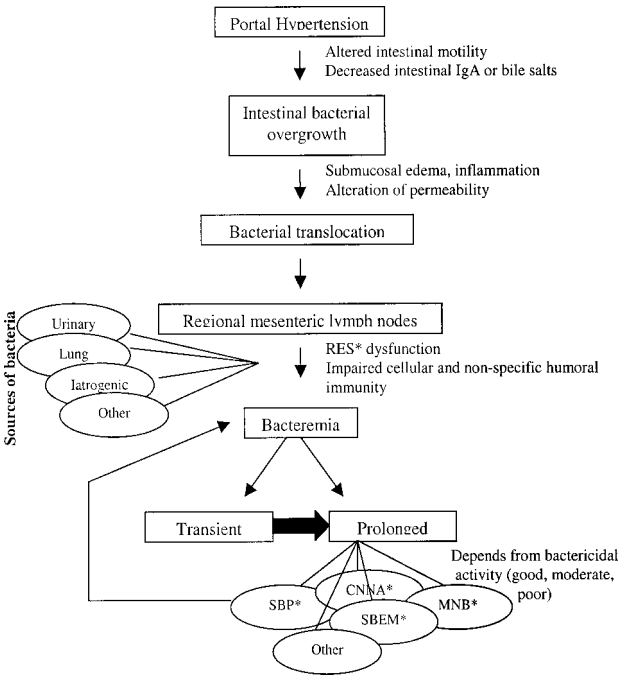
Translocation of bacteria from the gut to extraintestinal sites is considered one of the important pathogenic mechanisms that, under concrete clinical conditions, can satisfactorily explain the high incidence of bacteriemia in cirrhosis. The same mechanism has been postulated in the pathogenesis of gram negative sepsis in the intensive care unit patients with multiple organ failure in the setting of trauma, burn wound sepsis and sepsis associated with cancer chemotherapy.[15] Bacterial translocation is defined by culture positive mesenteric lymph nodes infected with enteric flora.[16] Gram-negative enteric bacteria translocate more frequently than gram positive and gram positives in turn transalocate more frequently than anaerobes.[17]

**Table 1.** Infections associated with cirrhosis.

| Type | Common causes |
|---|---|
| **Spontaneous bacterial peritonitis** | Escherichia coli, Klebsiella species, Streptococcus species Enterococcus species. Infrequently anaerobic organisms |
| **Spontaneous bacterial empyema** | E. coli |
| **Urinary tract** | Gram-negatives |
| **Community acquired pneumonia** | Streptococcus pneumonia, Hemophilus influenzae, Klebsiella, Mycoplasma pneumoniae, Legionella species, Peptostreptococcus, Bacteroides melaninogenicus, Fusobacterium nucleatum |
| **Hospital acquired pneumonia** | Gram negatives and staphylococci |
| **Bacteremia** | Escherichia coli, Klebsiella pneumoniae, Aeromonas hydrophila, Staphylococcus aureus, Streptococcus group |
| **Pulmonary or peritoneal tuberculosis** | Mycobacterium tuberculosis |
| **Lymphangiitis of lower extremities or cellulites** | Gram-positives and Gram-negatives |
| **Endocarditis** | Streptococcus pneumonia, Escherichia coli, Staphylococcus aureus |
| **Meningitis** | Streptococcus pneumonia, Escherichia coli, Listeria monocytogenes |

Recently, experimental studies reported an alteration of intestinal permeability in cirrhotic animal models with ascites that permits the translocation of bacteria from intestinal lumen to extra intestinal sites, including regional mesenteric lymphnodes, and then to the bloodstream.[15,18-20] Portal hypertension may produce structural changes in the bowel mucosa. The submucosa becomes markedly edematous and inflamed, which permits the rupture of the intestinal permeable barrier and thus favours bacterial translocation. In consequence, bacteria that escape the immunologic mechanisms of the regional lymph nodes would reach the efferent lymphatic vessels and through the thoracic duct, enter the systematic circulation.[18,19]

It's interesting that in cirrhotic animal models with ascites found a high rate of bacterial translocation (reported from 56% to 80%) to mesenteric lymph nodes.[15,18] Bacterial translocation significantly increases, according to the Child-Pugh classification, and is reduced




*RES: reticuloendothelial system, SBP: spontaneous bacterial peritonitis, SBEM: spontaneous bacterial empyema, MNB: monomicrobial nonneutrocytic bacterascites CNNA: Culture negative neutrocytic ascites.

**Figure 1.** Mechanisms involved in the pathogenesis of infections in cirrhosis.

to the level of non-cirrhotic patients by selective intestinal decontamination.[21]

Furthermore, acute hemorrhage in portal hypertensive rats promotes bacterial translocation to mesenteric lymph nodes. This experimental finding syggests that a frequent event in cirrhotic patients, such as hypovolemia due to gastrointestinal hemorrhage by variceal hemorrhage, for example, may secondarily increase the possibility of bacterial infection of enteric origin.[20] Variceal bleeding is a frequent complication of patients with cirrhosis and portal hypertension, with associated mortality for each bleeding episode, ranges from 30-50%.[22] Among cirrhotic patients with acute gastrointestinal bleeding, 20% have ascitic fluid infection at the time of admission to the hospital and another 30 to 40% may develop intra or extraperitoneal infection during hospitalization.[23] Bacterial infections are frequently recognized in up to 66% of patients with cirrhosis and gastrointestinal bleeding within the second week.[85] They have been associated with failure to control bleeding, with early rebleeding as well as increased mortality.[24,25] The mortality rate of the infected patients with bleeding reported is about 30-40%.[110,3]

The strong relationship between bacterial infections and bleeding in cirrhotic patients may be attributed to the invasive diagnostic and therapeutic procedures,[85] increased intestinal bacterial translocation,[7] transient depression of the reticuloendothelial system function caused by hypovolemia[7] and deficiency of complement levels.[22]

On the other hand, the increase in systemic circulation of the lipopolysaccharide component of the outer wall of gram negative bacteria (endotoxinemia), during bacterial infection could be an important trigger for bleeding. High concentrations of endotoxin have been detected in the portal and systemic circulation of patients with chronic liver disease.[26] Endotoxin exerts its effects through the synthesis of endothelin and nitric oxide with ensuing inhibition of platelet aggregation and as a powerful activator of hyperfibrinolysis.[27,28] Furthermore, during bacterial infection, the induction by endotoxin of endothelin and possibly vasocostrictive cyclo-oxygenase products results in increase in portal pressure and the contraction of hepatic stellate cells with further deterioration of intrahepatic vascular resistance.[27] Thus the aberration of primary haemostasis at the level of varix and the changes in portal pressure gradient could, in combination, trigger the initiation of variceal hemorrhage.

The use of immediate prophylactic antibiotics during acute bleeding episodes has been shown to reduce the frequency of bacterial infection.[22,29,82,84,85]

Although bacterial translocation occurs as a spontaneous event with increased incidence in patients with distal intestinal obstruction, inflammatory bowel disease, and in those with surgical trauma, the prevalence and the clinical significance of bacterial translocation in cirrhotic patients remains to be clarified with further investigation.[30]

In conclusion bacterial translocation to extraintestinal sites may be mediated by one or more of these three principal mechanisms a) alteration of the normal gut flora resulting in bacterial overgrowth b) impaired host defenses and c) physical damage to the intestinal mucosa. In patients with cirrhosis, some bacteria can escape the filter of regional mesenteric lymph nodes and directly reach ascitic fluid, leading to spontaneous bacterial peritonitis (SBP), or to blood, leading to spontaneous bacterial systemic reaction or sepsis.

The clinical consequences of blood or ascitic fluid colonization depend on their capacity to kill bacteria.[31]

Abnormalities in immune response, including a decrease in reticuloendothelial system activity, have been reported in cirrhotic patients. Approximately 90% of this defense system is located within the liver (Kupffer cells and other sinusoidal cells) and because of its intravascular location is considered as the main defense mechanism of the organism.[11] A marked depression of the hepatic reticuloendothelial system fraction phagocytic activity in cirrhotics is expressed clinically with the development of bacteremia and/or spontaneous bacterial peritonitis. In contrast these infections do not occur in patients with normal reticuloendothelial system function.[7]

The impairment in reticuloendothelial system activity is more evident in patients with more advanced liver cirrhosis and is associated with a short survival time.[7,32] A decrease in maximum removal capacity is associated with higher probability of spontaneous bacterial peritonitis and poorer clinical prognosis.[32]

The pathogenesis of the decreased phagocytic activity of reticuloendothelial system is not clear in patients with advanced liver injury. In surgical, trauma and burn patients the failure in systemic host defense is, in part, mediated by a deficiency in a circulating opsonic $\alpha_2$ surface binding glycoprotein or plasma fibronectin. The role of fibronectins in organ and microvescicular integrity, especially in septic injured patients, seems to be very important.[33]

In most cirrhotic patients the intrahepatic shunting of blood, which escapes the phagocytic action of reticuloendothelial system cells located in the sinusoids[7,32] and the decrease serum concentration of complement and fibronectin, plays an important role in the decrease of their reticuloendothelial system activity.[11] Furthermore, serum fibronectin levels are probably an independent prognostic factor of survival in cirrhotic patients.[34]

Monocytes have been considered to be a component of the monocyte macrophage system, which includes, among others, Kupffer cells. In patients with cirrhosis liver monocyte function as determined by their phagocytic and bactericidal activity, is significantly decreased.[35] Similarly decreased is also their metabolic activity. On the other hand an impairment of the splenic macrophage Fcγ receptors has also been described in alcoholic cirrhotic and in patients with primary biliary cirrhosis.[36,37] Macrophage Fcγ receptors are important in the host defense, since they participate in the clearance of IgG coated microorganisms.[36]

Cirrhotic patients appear to have a normal or enhanced specific humoral activity. A significantly high titer of antibodies against microorganisms, for example against the common enterobacterial cell wall, was detected in cirrhotics compared with healthy control subjects. This finding indicates that advanced liver injury is associated with an immune response to intestinal bacteria that escape into systemic circulation.[38]

By contrast the non-specific humoral immunity, as expressed by serum bactericidal and opsonic activities and serum levels of complement and fibronectin, seems to be depressed in cirrhosis.[39] The ability of polymorphonuclear cells to destroy bacteria is only moderately impaired in advanced cirrhosis[6], so other factors such as intra ascitic activity, are more probably responsible for the occurrence of infections in these patients. Lower chemoattractant and opsonic activity in cirrhotic ascites is inversely correlated with the risk of developing bacterial infection.[40] Opsonic activity of ascitic fluid correlates directly with the serum concentration of defense substances including immunoglobulins and complement.[41]

The concentration of the third component of complement ($C_3$) in ascitic fluid appears to have the best predictive value for bacterial infections[6], although this finding is not confirmed by all performed studies[42] (Table 2). More interesting is that the total ascitic fluid protein is in relationship with its opsonic activity. In general, it is considered that patients with $C_3$ level <13mg/dL and/or protein concentration below 1gr/dL in ascitic fluid have an increased risk ofr developing SBP in comparison with those with greater concentrations.[9,40,43,44] Diuresis of cirrhotic ascites increases the total protein concentration and its opsonic activity and this mechanism may help to prevent SBP.[45]

Other factors, such as total bilirubin level of >2.5mg/dL, seem to be an independent factor for the development of SBP.[42]

**Table 2.** Predisposing factors for spontaneous bacterial peritonitis (SBP)

| |
|---|
| • Severity of the underling liver disease (Child – Pugh class C) |
| • Ascitic fluid total protein concentration <1gr/dl |
| • Ascitic fluid $C_3$ level <13mg/dl |
| • Total bilirubin level of >2.5mg/dL or >3.2 mg/dl |
| • Low platelet count (<98000/mm$^3$) |
| • Gastrointestinal bleeding |
| • Previous spontaneous bacterial peritonitis episodes |
| • Urinary, respiratory tract or other source of infection |
| • Iatrogenic factors (e.g. urinary bladder, intravascular catheters) |

In addition to measures that are well known to predispose to infection, such as the placement of intravenous or urethral catheter, several cirrhotic patients under diagnostic and therapeutic procedures which carry a high risk of inducing bacterial infection. In these patients, between 4 and 20% of all bacteremic episodes may be caused by intravascular catheters.[23] Patients who require esophageal tambonade for bleeding varices are prone to develop aspiration pneumonia.[46]

Diagnostic or therapeutic abdominal paracentesis or endoscopy are associated with very low risk of bacterial infection.[47,48] Post-endoscopy bacteremia is usually transient with no clinical consequences.[47] However, among hospitalized patients, the two main independent risk factors for the development of bacterial infection are gastrointestinal bleeding and low serum albumin levels.[49]

Almost 70% of patients who develop SBP are Child-Pugh class C, with the remainder being class B. So the most important predisposing factor for bacterial infections in cirrhotic patients is the severity of liver disease and the mortality rate is associated more with the severity than with the etiology of the disease.[23,50]

### *2.2 Spontaneous bacterial peritonitis (SBP)*

*SBP* has been defined as a bacterial infection of ascitic fluid that presents a positive bacterial culture for a single organism and ascitic fluid polymorphonuclear cell count ≥250 cells /mm$^3$, in absence of a surgically treatable intraabdominal source of infection.[23,51]

It was recognized by Conn in 1964.[51] Although SBP has been described as occurring in different clinical settings, such as in patients with ascites due to acute liver failure[52], in nephrotic syndrome,[51] in patients with cardiac ascites[53] (less common), or in diseases accompanied by high ascitic fluid total protein levels, such as peritoneal carcinomatosis,[54] the most frequent underlying disease in which SBP develops is cirrhosis.[51] Its incidence in cirrhotics varies from 8 to 31% during a single hospitalization.[23,55-57]

On the basis of the characteristics of ascitic fluid analysis (polymorphonuclear count and culture) different variants of ascitic fluid infection have been described and their clinical course evaluated. Diagnostic paracentesis should be performed on hospital admission in all cirrhotic patients with ascites and on hospitalized patients when they develop a) local symptoms or signs suggestive of peritoneal infection (abdominal pain, rebound tenderness) b) systemic signs of infection (fever, leukocytosis) c) hepatic encephalopathy or rapid impairment of renal function.[58]

Despite the use of sensitive methods, ascites cultures are negative in 30% to 60% of patients with clinical manifestations suggestive of SBP and increased ascite polymorphonuclear. However the greatest sensitivity for the diagnosis of SBP is reached with a cutoff of 250 cells /mm$^3$ and the greatest specificity with a cutoff of 500 polymorphonuclear /mm$^3$. It is worthy of note that in patients with bloody ascites (red blood count >10000/ mm$^3$) a correction factor of 1 polymorphonuclear per 250 red blood cells has been proposed, since this is the maximum expected ratio of polymorphonuclear to red blood cells normally presented in peripheral blood.[58]

*Culture negative neutrocytic ascites (CNNA)* is diagnosed when the ascitic fluid polymorphonuclear count is ≥250 cells /mm$^3$ with negative ascitic fluid culture. The other possible causes of neutrocytic ascites, such as previous antibiotic treatment, hemorrhage into the ascitic fluid, hepatocellular carcinoma, peritoneal carcinomatosis or tuberculosis and pancreatitis should be excluded.[59]

*Monomicrobial nonneutrocytic bacterascites (MNB)* is characterized by ascitic fluid polymorphonuclear count of less than 250 cells /mm$^3$ with a positive ascitic fluid culture for a single microorganism.[60] Spontaneous resolution of bacterascites occurs in 62 to 82% of cases. The underling liver disease is usually less severe in patients with bacterascites than in those with SBP. Among patients with asymptomatic MNB the colonization is usually resolved without antibiotic therapy.[60-62]

*Secondary bacterial peritonitis.* Although secondary peritonitis represents less than 10% of ascitic fluid infections in cirrhotic patients, it should be considered in any patient with neutrocytic ascites.[51] It is diagnosed in cases with ascitic fluid positive cultures (usually polymicrobial) and polymorphonuclear count ≥250mm$^3$ due to surgically treatable intraabdominal source of infection (e.g. perforated gut, perinephric abscess). Perforative peritonitis should be suspected when ascitic fluid infection is polymicrobial and ascitic fluid analysis shows two or more of the following criteria: total protein >1gr/dL, glucose <50mg/dL, and LDH >225 U/mL (or higher than the upper limit of the normal for serum).[63,64]

*Polymicrobial bacterascites* is characterized by polymorphonuclear count of ascitic fluid less than 250 cells /mm$^3$ and gram stein or culture demonstrate multiple organisms.[65] It is usually the consequence of a needle perforation of the gut during a diagnostic or therapeutic paracentesis.[23]

The majority of SBP episodes (60 to 72%) are caused by aerobic gram-negative enteric bacteria.[66,67] Escherichia coli is the infecting organism in almost half of them, followed by Klebsiella species in 13% of cases. Gram positive coci represent a frequency of 29%, with the Streptococcus species in 19% and Enterococcus species in 5% of all episodes.[67] Although the colon flora is predominately anaerobic, isolation of an anaerobic organism is an infrequent event (5%)[67], probably because ascites has too high an oxygen tension to permit anaerobic growth.[68]

The factors that predispose to the development of ascitic fluid infection are (Table 3) the severity of liver disease, the serum total bilirubin level >2,5 mg/dl, ascitic fluid total protein <1gr/dl, urinary tract infections, iatrogenic factors, such as urinary bladder and intravascular catheters, and previous spontaneous bacterial peritonitis episodes.[9,23,32] In a recent publication, the investigators identified two parameters as high serum bilirubin (>3.2 mg/dl) and low platelet count (<98000/mm$^3$), independently associated with higher risk of developing SBP.[69]

Although 87% of patients appear to be symptomatic at the time of diagnosis the clinical manifestations are often subtle, such as low changes in mental status[60]. The most frequently observed symptoms are fever (62-69%) and abdominal pain (59-64%)[23,70]. Most patients manifest diffuse abdominal pain which is often accompanied by rebound tenderness. Rigid abdomen, in contrast to common impression, is infrequent in these patients even if bowel perforation occurs[23]. Other clinical features frequently observed are hepatic encephalopathy (44-54%), abdominal tenderness (49%) diarrhea (7-32%) ileus (5-30%), shock (8-21%), hypothermia (17%).[23,70]

**Table 3.** Recommendations on treatment of spontaneous bacterial peritonitis (SBP)

- Empiric antibiotic treatment must be started as soon as possible, especially when the polymorphonuclear count in ascitic fluid is greater than 250 cells/mm$^3$
- Cefotaxime is currently considered the first antibiotic of choice in the empiric treatment of SBP (minimum dose 2gr/12h, minimum duation 5 days)
- In patients with uncomplicated SBP[58] and not under quinolone prophylaxis, oral ofloxacin
- Cefotaxime appears to be the most adequate antibiotic regimen for patients developing SBP while under quinolone prophylaxis
- Patients with hypersensitivity to beta-lactam can be treated with quinolone[58]

However clinical sings of severe intrabdominal infections such as ileus and shock are less frequently described in more recent series than in the past probably due to increased awareness of this complication and its earlier diagnosis.[51]

The early prescription of antibiotics can improve survival of patients with a suspected episode of SBP.[55,71] Empiric antibiotic treatment must be started as soon as possible, especially when the polymorphonuclear count in ascitic fluid is greater than 250 cells/mm$^3$. Non-treated SBP may progress to numerous lethal complications, including septic shock, progressive circulatory and renal deterioration and renal failure.[51]

In the past, the usual treatment for patients with SBP was a combination of antibiotic regimens including a β lactam plus an aminoglycoside. However, these therapeutic regimens were associated with a relatively low efficacy and the aminoglycoside nephrotoxicity limits their usefulness.[72,73]

Cefotaxime, a third generation cefalosporin is currently considered the first antibiotic of choice in the empiric treatment of SBP. The antibiotic coverage for anaerobic bacteria, as also the coverage for Pseudomonas or Staphylococcus is not essential[66]. Cefotaxime as monotherapy can achieve resolution of infection in 85% of patients with SBP compared to 56% of patients who receive ampicillin plus tobramicin.[74] Two randomized, controlled trials assessing the optimal dosage of cefotaxime have reported that the dose of 2.0 gr cefotaxime given intravenously every 8 or 12 hours presented similar effectiveness with the same intravenous dose of the drug given every 6 hours.[75,76]

The duration of antibiotic therapy has also been evaluated. 5 days of therapy has been shown to be as effective as a long course (10 days).[77] Treatment with cefotaxime produces sterilization of ascitic fluid culture with a single dose in 86% of patients with SBP and rapid decrease in ascitic fluid neutrophil count to normal values.[63]

The rate of resolution of SBP with other cefalosporins, such as ceftriaxone and cefonicid, ceftizoxime, ceftazidime, has been found to be very high, with no significant differences as compared to that reported with the use of cefotaxime.[51,58]

Non-cefalosporin drugs have been used in the treatment of SBP with varying success. In comparative studies aztreonam was less effective than cefotaxime in the treatment of SBP, archiving resolution of the infection in 56% of patients but amoxicilline plus

clavulanic acid (1gr every 6 hours) was as effective as cefotaxime in 85% of episodes of SBP with no significant side effects.[78,79]

Recent investigations suggest that SBP may be treated by oral administration of quinolones such pefloxacin or ofloxacin (rate of infection cure 84.4%). These antibiotics are highly effective against most bacteria responsible for bacterial peritonitis, are almost completely absorbed after oral administration (except norfloxacin), diffuse rapidly to the ascitic fluid and have low incidence of side effects[80,81] (Table 3).

In base of earlier publications routine follow up paracentesis is not necessary if patient has a typical clinical response to antibiotic treatment so follow up paracentesis after 48 hours is required only if the patient presents abnormal clinical evolution or is suspected secondary peritonitis.[63] On contrary according the recommendations of a recent consensus meeting the response to antibiotic treatment should be assessed by periodically evaluating symptoms and sings of infection and at least one follow up paracentesis after 2 days of antibiotic therapy to determine the polymorphonuclear count in ascitic fluid.[58]

Several groups of patients with cirrhosis such those with low (<1 g/dl) ascitic fluid protein levels, those survived from a previous episode of SBP, those with gastrointestinal bleeding are at high risk to develop a recurrent episode of SBP. Prophylactic measures not only reduce the risk of recurrence but also improve the survival of this group of patients. A recent meta-analysis demonstrated that in cirrhotic patients with gastrointestinal bleeding the antibiotic prophylaxis significantly increased the mean percentage of patients free of infection, bacteremia or SBP and significantly increased the short term survival rate. General long-term measures including improvement in nutrition and general status of the patient, aggressive treatment of localized infections, reducing the risk of development of gastrointestinal bleeding or ascites may appear useful in the preventing of SBP.[23,82]

Because most episodes of SBP are caused by organisms usually present in the intestinal flora, selective intestinal decontamination has been considered an alternative measure in preventing infection. Norfloxacin 400 mg/day orally has been reported to successfully prevent SBP in patients with prior ascitic fluid infection.[83] During gastrointestinal hemorrhage intestinal decontamination with oral norfloxacin 400mg b.i.d per os or via nasogastric tube for 7 days markedly reduced the incidence of SBP or spontaneous bacteriemia in these patients.[84] Systemic antibiotic therapy with ofloxacin 400 mg/day also seems to be effective in preventing bacterial infection in cirrhotic patients with gastrointestinal hemorrhage.[85]

Selective intestinal decontamination with oral norfloxacin (400 mg/day) has proved effective in the prevention of SBP in cirrhotic patients with ascites and low protein concentration in ascitic fluid.[86,87] Quinolone-resistant SBP constitutes an emergent problem in long-term norfloxacin prophylaxis with trimothoprim-sulphamethoxazole not being a valid alternative.[88] The development of bacterial resistance to quinolones has very important clinical consequences because: a) cross resistance between norfloxacin and other quinolones has been showed[89] b) the development of quinolone resistant bacterial stains is significantly associated with previous administration of primary or secondary quinolone prophylaxis[90] c) resistant bacteria could cause more severe infections in patients on prophylaxis[91,92] d) patients submitted to antibiotic prophylaxis could develop infections caused by bacteria also resistant to antibiotics most commonly used to treat infections in cirrhotic patients including beta-lactams[89] e) the development of bacterial resistance might decrease the effectiveness of this method of prophylaxis[51,93] f) it could result in changes in the spectrum of bacteria (e.g. staphylococcal infections) causing SBP and other infections[94]. However in recent studies it was observed that empiric antibiotic treatment when an infection is suspected in cirrhotic patients on prophylaxis with norfloxacin can be the same as in patients without prophylaxis (cefotaxime or amoxiciline-clavulanic acid)[95,96]. But cefotaxime appears to be the most adequate antibiotic regimen for patients developing SBP while under quinolone prophylaxis, as resistance to amoxiciline-clavulanic acid has already been reported.[58,96] On the other hand, quinolones should not be used in such patients.[96]

The continuous schedule of oral norfloxacin is useful to prevent the recurrence of SBP in cirrhotic patients but the emergence of norfloxacin-resistant E Coli suggests the probable need for stricter indications of continuous prophylaxis in order to minimize the emergence of resistant bacteria.[97] In fact, continuous prophylaxis should be restricted to highly selected groups of patients at high risk of infection, closely monitored for the development of bacterial resistant.

The survival expectancy after one episode of SBP has been reported to be very short, with a 1 year and 2 year

probability of survival of 30-50% and 25-30% respectively. Since survival seems to be higher after liver transplantation, all patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation.[58]

### *2.3 Spontaneous bacterial empyema (SBEM)*

Cirrhotic hydrothorax is characterized by the presence of large pleural effusion (>500ml) in cirrhotic patients, with or without ascites, in the absence of primary pulmonary or cardiac disease. At a reasonable estimate, the prevalence would appear to be 4% to 6% and perhaps up to 10% in patients with advanced liver disease.[98-101]

SBEM is the bacterial colonization of a pre-existing sterile hydrothorax without any concomitant pneumonia. It seems to be a frequent complication (13%) of cirrhotic hydrothorax and it could be expected to appear in 1% to 2% of hospitalized cirrhotic patients with ascites. Almost half of the cirrhotic patients with SBEM also have spontaneous bacterial peritonitis.[102]

A postulated mechanism for the development of pleural effusion in patients with cirrhosis consists of the transfer of peritoneal fluid directly via defects in the tedious portion of diaphragm from the abdominal cavity to the pleural space. The unidirectional flow of fluid from the abdomen to the chest and the evidence of pressure gradient between the two cavities may explain the development of this complication.[98] Where diagnostic doubts exists regarding the cause of effusion in a patient with ascites, intraperitoneal injection of technetium Tc 99m sulf colloid may be used to demonstrate the communication between the two cavities.[98,103,104]

The most frequent causative organisms are Gram negative bacilli particularly E. coli. The mechanism of pathogenesis seems to be the same as that of SBP. The infection of the fluid in the thoracic cavity as an effect of spontaneous bacteremia or the passage of infected ascites from the abdomen through the diaphragm are mechanisms that have been suggested.[102,105-107]

SBEM should be suspected when fever and dyspnea develop in a patient with or without previous known hydrothorax.[106]

Diagnosis of SBEM is based on laboratory findings in pleural fluid similar to those in ascitic fluid of SBP, mainly an increase in the polymorphonuclear count. As criteria for the diagnosis of SBEM, the presence of a positive pleural fluid culture and a poly-morphonuclear count greater than 250 cells /mm$^3$ are emphasised , while in the case of patients with negative culture and a compatible clinical course, the existence pleural fluid polymorpho-nuclear count > 500 cells/mm$^3$. The diagnosis can be estabilished after the exclusion of human immuno-deficiency virus infection, parapneumonic infections with chest radiogram or computed tomography scan and if the patient has not be treated with variceal sclerotherapy during the previous week.[67,106]

Recommended therapy consists of parenteral antibiotics, usually a third generation cefalosporin (e.g. cefotaxime 4gr/24h for minimum duration 5 days), without the need of pleural drainage. Generally, in the treatment of SBEM the same antibiotic schedule used empirically in SBP is followed because the organisms isolated are similar in both types of infection.[102,106] As criteria of response to therapy, the relief of clinical symptoms and the improvement in chest radiogram could be used.

Selective intestinal decontamination with norfloxacine appears to be effective in preventing the recurrence of infection. However, its effectiveness may decrease with time because of the selection of resistant strains. Thus, quinolones should not be used in patients undergoing selective intestinal decontamination with norfloxacine who develop a severe infection.[108]

Criteria for chest tube insertion are frank pus or pH <7.1 plus glucose levels <40 mg/dl. Chest tube placement can lead to massive protein and electrolyte depletion resulting in an unfavourable clinical course for the patient.[98,102,108,109]

In conclusion, SBEM is a frequent complication in cirrhotic patients with hydrothorax and should be considered as an indication for liver transplantation, independently of SBP.

### *2.4 Other infections*

Other infections seen in chronic liver disease include not only SBP and SBEM but urinary tract infections community or hospital acquired pneumonia, bacteremia, skin and soft tissue infections, endocarditis and meningitis. Alcoholic subjects are prone to develop pneumonia and pulmonary or peritoneal tuberculosis. A wide range of infectious sequels has also been associated with esophageal variceal sclerotherapy (EVS) but a significantly smaller series of infectious complications has been related to ligation (EVL).

Urinary tract infections are the most frequent complication in cirrhosis (12% to 29%) and are a major risk factor for the development of bacteremia.[3,110,111] As

in non-cirrhotic patients, the use of indwelling urinary catheters predispose to the development of urinary infection. Asymptomatic bacteriuria is quite common. In the majority of cases, urinary tract infections are caused by Gram-negative bacilli (i,e E. coli). The incidence is markedly higher in female than in male patients.[112-114] In women patients with primary biliary cirrhosis, a higher susceptibility to bacteriuria has been reported[112], although this finding has not been confirmed by other investigators.[114] A direct correlation probably exists between the presence of tense ascites and the development of infection. In addition, in the group of patients with alcoholic cirrhosis, the progress of infection is related to incomplete bladder emptying.[115]

In cirrhotic patients community acquired pneumonia is a relatively frequent complication (7% to 23%).[3,110] The causes of community acquired pneumonia in cirrhotics include infection from Streptococcus pneumonia, Hemophilus influenzae, Klebsiella, Mycoplasma and Legionella species and anaerobes (mostly Pepto-streptococcus, Bacteroides melaninogenicus and Fusobacterium nucleatum). A macrolide or a quinolone (levofloxacin), along with cephalosporin, are recommended for antibiotic treatment. However hospital acquired pneumonia is predominantly caused by gram negative organisms and staphylococci. Most cases of pneumonia occur after the aspiration of oropharyngeal contents into the lungs. Other risk factors include gastroentestinal bleeding, upper GI endoscopy and ascites. Empiric treatment with cefipime is a reasonable first choice with the addition of clindamycin if aspiration pneumonia is possible.[11,116,117]

Bacteremia has been reported to occur in 4% to 9% of patients with cirrhosis. Its incidence is significantly higher in patients with decompensated (20%) rather than compensated (1%) liver disease and is associated with poor prognosis.[117,118,119] Despite this, the incidence of bacte-remia is reported to be 3.4 – 28/1000 in hospital admissions in non-cirrhotic patients with estimated average of about 1%, in cirrhotics much higher incidence, from 3.5% to 11%, has been reported.[120]

Severe cirrhosis (according to Child-Pugh classification) has higher rates of bacteremia (A:3%, B: 23%, C: 48%) with overall mortality rate from 37 to 59%. Gram negative bacteremia appears in approximately 76% of patients. The most common microorganisms detected were Escherichia coli, Klebsiella pneumoniae and Aeromonas hydrophilia. Bacteremia with Gram positive bacteria occurs in 21% of patients with predominance of Staphylococcus aureus and the streptococcus group.[120] Unusual pathogens have been reported as causes of primary bacteremia in cirrhotic patients (nontyphoidal Salmonella, Vibrio Vulnificus, Bartonella quintana). Vibrio Vulnificus can cause bacteremia and sepsis, often with accompanying cutaneous lesions after ingestion of contaminated shellfish.[121] Sources of bacteremia include the gut (primary bacteremia) due to portosystemic shunting of blood which allows portal blood to reach the systemic circulation, the urinary and respiratory tracts and intravascular devices (secondary bacteremia). In cases of bacteremia, meningitis and endocarditis should be considered.

Soft tissue infections such as lymphangitis of lower extremities or cellulitis of lower extremities or abdominal wall caused by Gram-positive cocci or Gram-negative bacilli respectively are quite frequent in cirrhotic patients with ascites and generalized edema.[3,11,116,122]

When patients with end stage liver disease present acute deterioration of their clinical status, bacterial endocarditis should be considered, especially in those who have had prior invasive procedures that increase the risk of bacteriemia[123]. In a retrospective study, the incidence of endocarditis was 0.34% in patients with cirrhosis compared to 0.1% in patients without cirrhosis, but other investigators have not confirmed these results.[124,125] It is still not clear whether the aortic or mitral valve is predominantly infected. The pathogens of infective endocarditis also differ in the various studies with S. pneumonia, E. coli and S. aureus encountered with great frequency.[117,123] As potential sources of infection, upper gastrointestinal bleeding, pneumonia, SBP, heart catheterization, abdominal abscess, TIPS placement and hip replacement have been recognized.[123,126] The prognosis of endocarditis in cirrhotic patients is usually poor.[123]

Meningitis is relatively uncommon in patients with cirrhosis. However, its incidence may be underestimated because of the similarity of clinical manifestations of meningitis and encephalopathy. Pneumoniococci, E coli, and L. monocytogenes are the most frequently detected organisms. Mortality seems to be much higher in alcoholics than in non-alcoholic patients.[117]

Alcoholism is perhaps the most important predisposing factor for the development of pneumonia.[117] In alcoholics with active disease, Streptococcus pneumonia appears to be the causative organism in most cases of lower respiratory tract infection.[127] However a significant number of cases of pneumonia are caused by anaerobic

bacteria or Hemophilus influenzae or by Gram-negative bacilli, particularly Klebsiella pneumo-niae.[11] The prognosis and mortality of pneumonia are adversely affected by alcohol abuse. Nevertheless, the extent of liver disease and leukopenia has a greater impact on prognosis than alcoholism itself.[117]

Alcoholic subjects are also prone to develop pulmonary or peritoneal tuberculosis. It is not clear if the environment of their living or the underlying hepatic disease predispose to these infections.[11,127] In patients with low grade fever, high protein ascitic fluid and lymphocyte elevation the possibility of peritoneal tuberculosis should be considered. Diagnosis usually requires laparoscopic investigation.[116] Extrapulmonary tuberculosis should be managed according to the principles and the drug regimens outlined for pulmonary tuberculosis with usually good response to antituberculous treatment.[128,129,130] However, as standard antitubercular drugs are meta-bolized in the liver, there is a risk of increased hepato-toxicity in patients with underling chronic liver disease,[131,132] so alternative therapeutic schemas based on drugs with antitubercular activity and exclusive renal clearance such as ofloxacine, should be considered.[133]

A wide range of complications, involving almost every organ, have been associated with EVS. The most common complications of EVS tend are clinically insignificant, whereas the most serious of them to be relatively infrequent.[134] A large variety of infectious complications related to EVS, including bacteremia,[135-142] meningitis,[143] subdural empyema,[144] perinepfric and cerebral abscess,[144,145] endocarditis[146] and bacterial peritonitis[147,148-150] have been reported.

Although bacteremia has been documented in association with sclerotherapy, the clinical consequences of the event are still controversial. In prospective studies, the frequency of bacteremia after upper endoscopy with sclerotherapy ranges from 0 to 53%.[135,136,138-141,144,151] It is also not clear whether bacteremia is higher after elective or emergency EVS,[141,152,153] both of which have an additional source of bacteremia as a result of the introduction of microorganisms via the sclerotherapy needle[138] or contaminated water solution.[151]

The microorganisms frequently isolated were alpha-hemolytic Streptococcus, Staphylococcus epidermidis, S aureous, and diphtheroids.[135-142] Most likely these microorganisms consist of oropharyngeal and skin flora and tend to have entered the circulation system to produce transient bacteremia.

EVS, on an emergency basis seems to carry a significantly higher risk of developing bacterial peritonitis than patients treated electively or prophylactically. The calculated risk of developing peritonitis with elective EVS amounts to 0.5% and following emergency EVS to 3%.[154] The mainly pathogens isolated include Klebsiella pneumoniae, streptococcus sanguis, Enterococcus, Streptococcus group B, Staphylococcus aureus, Escherichia coli, Citrobacter freundii.[147-150] It is notable that the microorganisms isolated in patients with post sclerotherapy bacterial peritonitis are not different from those causing SBP. Probably, in most cases with post sclerotherapy bacterial peritonitis the bacteria traslocate through the intestinal wall. EVS on an emergency basis can carry a significantly higher risk of developing bacterial peritonitis. This strongly suggests that the clinical condition of the patient during EVS could determine the risk of this complication. Hypotensive periods during EVS, due to sedatives or tissue hypoxia caused by bleeding episodes, may contribute more than the screrotherapy itself to the translocation of bacteria though the bowel wall.[154,20,84]

The incidence of both transient bacteremia and infectious sequels in patients with acute variceal bleeding was over 10 times lower after EVL than after EVS.[155,156] Probably mechanical strangulation of varices by EVL using small elastic "o" rings, may obliterate the submucosal venous channels and thereby diminish the entrance of bacteria to the blood stream.[156] Gram positive skin and oropharyngeal microorganisms, such as Streptococcus pyogenes, Staphylococcus epidermidis, Staphylococcus aureus and Dipheroid species, have been isolated immediately after EVL.[157] Despite the reported significant risk of asymptomatic bacteremia and bacterial peritonitis after EVL, the clinical significance of these complications remains doubtful. The peritonitis does not seem to be related to the bacteremia, as patients who have bacteremia do not always develop peritonitis and vice versa.[157,158]

The clinical significance of bacteremia after EVS is low since it is transient, even if, in clinical practice, the reduction of the incidence of bacteremia is often attempted through the prophylactic administration of anti-biotics.[153,159,160] Prophylactic antibiotics before EVS or EVL should be reserved for patients with valvular heart disease, prosthetic valves or previous endocarditis, in children who have previously undergone splenectomy,[159] and in patients with Child's C class cirrhosis, with recent history of variceal bleeding, a past history of bacterial peritonitis or a co morbid immuno-suppressive

condition[157]. Enteral decontami-nation could be useful in reducing the incidence of late episodes of infection.[29]

Since patients with episodes of SBP and SBEM are recognized as potential candidates for orthotopic liver transplantation it is worthy of note that the influenza virus could cause significant hepatic decompensation in patients with end stage liver disease who are on a waiting list for liver transplantation. Additionally in transplanted patients, the risk of direct damage or allograft reinfection is substantial. Vaccination remains the main preventive tool against influenza, since 92% to 95% of liver transplant recipients have been reported to be adequately protected by the vaccine.[161,162]

Patients with severe liver disease also have increased morbidity and mortality due to S. pneumoniae infections. Therefore patients evaluated for liver transplantation routinely receive pneumococcal vaccination.[163] But although the initial response to the 23-valent pneumococcal vaccine is good, serum antibodies decline rapidly during the fist 6 months after vaccination, so the determination of the optimal timing for vaccination to maximize its protective effect is very important in this group of patients.[164]

## 3. CONCLUSION

Bacterial infections are common in the susceptible group of patients with chronic liver disease. Because of the frequent infectious complications and the multiple derangements in the defense mechanisms, advanced liver disease might be considered as a form of acquired immunodeficiency. Therefore, in the absence of a local source of infection, such as in cases of SBP and SBEM, an infection may evolve silently in to bacteremia, sepsis and death.

Mortality seems to be related to the severity of the underlying liver disease. Prompt diagnosis and early therapeutic intervention with intravenous broad spectrum antibiotics may slightly decrease the mortality, but which continues to be very high. Prophylactic antibiotics reduce the frequency of infection but do not seem to improve long term survival.

However, the routine use of paracentesis in clinical practice, clinicians higher index of suspicion of infection and the effort to clarify the diagnostic criteria of infection in advanced liver disease, the recognition of SBP and SBEM as indication for liver transplantation, simultaneously with the use of better and safer antibiotics may improve, at least for the present, the short term prognosis of this group of patients.

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