Abstract and Introduction

Patients with cirrhosis are immunocompromised and susceptible to infections. Although detection and treatment of spontaneous bacterial peritonitis (SBP) have improved, overall survival rates have not increased greatly in recent decades— infection still increases mortality 4-fold among patients with cirrhosis. Hospitalized patients with cirrhosis have the highest risk of developing infections, especially patients with gastrointestinal (GI) hemorrhage. Bacterial infections occur in 32% to 34% of patients with cirrhosis who are admitted to the hospital and 45% of patients with GI hemorrhage. These rates are much higher than the overall rate of infection in hospitalized patients (5%–7%). The most common are SBP (25% of infections), urinary tract infection (20%), and pneumonia (15%). Bacterial overgrowth and translocation from the GI tract are important steps in the pathogenesis of SBP and bacteremia—these processes increase levels of endotoxins and cytokines that induce the inflammatory response and can lead to septic shock, multiorgan dysfunction, and death. A number of other bacterial and fungal pathogens are more common and virulent in patients with cirrhosis than in the overall population. We review the pathogenesis of infections in these patients, along with diagnostic and management strategies.

Introduction

Cirrhosis is considered an immunocompromised state that leads to a variety of infections, which then account for an approximate 30% mortality.[1] Apart from early recognition and better treatment of spontaneous bacterial peritonitis (SBP) leading to better survival, there has been little improvement in overall survival rates in recent decades: infections still account for a 4-fold increase in mortality among patients with cirrhosis.[2] Hospitalized patients with cirrhosis are at the highest risk of developing infection, especially in those with gastrointestinal (GI) hemorrhage. Bacterial infections occur in 32% to 34% of admitted patients with cirrhosis[3] and in 45% of those with GI hemorrhage.[4] These rates are drastically higher than the usual 5% to 7% overall rate of infection in hospitalized patients.[1] The most common infections are SBP (25% of infections), urinary tract infection (UTI) (20%), and pneumonia (15%).[5] Bacterial overgrowth and translocation from the GI tract are important steps in the pathogenesis of SBP and bacteremia.[6][5] This pathogenic process leads to increased levels of endotoxins and cytokines that trigger an excessive inflammatory host response, a cause for septic shock, multiorgan dysfunction, and death.

Pathogens such as Mycobacterium tuberculosis, Clostridium difficile, Cryptococcus neoformans, Vibrio vulnificus, Yersinia enterocolitica, and Listeria monocytogenes, are more common and virulent in patients with cirrhosis than in the general population. Because of the high morbidity and mortality of infections in cirrhosis, prevention, early diagnosis, and proper management of these infections are necessary to improve survival.

State of Immune Dysfunction in Cirrhosis

Cirrhosis-associated immune dysfunction syndrome (CAIDS) is a multifactorial state of systemic immune dysfunction (Figure 1), which decreases their ability to clear cytokines, bacteria, and endotoxins from circulation. The liver contains 90% of the reticuloendothelial (RE) cells,[7] such as Kupffer and sinusoidal endothelial cells, that are central to clearing bacteria. When radiolabeled E. coli and P. aeruginosa were injected intravenously, 70% and 96% of their populations, respectively, were found in the liver only 10 minutes later.[8] Porto-systemic shunting, whereby blood is increasingly directed away from the liver, and reduced RE cells in patients with cirrhosis, allow less bacteria and endotoxins to be cleared by the liver from circulation.[1][7]
Monocyte spreading, chemotaxis, bacterial phagocytosis, and bacterial killing are significantly reduced in cirrhosis compared with controls. Patients with acute decompensated liver cirrhosis have reduced expression of the antigen presenting HLA-DR molecules on monocytes. This may also result in decreased monocyte activation and cytokine secretion.

In addition to RE system dysfunction, patients with cirrhosis have decreased neutrophil mobilization and phagocytic activity, a phenomenon that correlates with severity of liver disease. The decreased phagocytic activity in cirrhosis has been attributed to reduced activity of tuftsin and phospholipase C. In addition, it has been suggested that hyperammonemia and hyponatremia function synergistically to affect neutrophil cell volume and impair phagocytosis. Neutropenia, typically a result of hypersplenism in cirrhosis, is further exacerbated by shortened neutrophil survival via apoptosis. The Fas/Fas ligand has been implicated in the regulation of apoptosis in neutrophils, but it is unclear how decreased levels of Fas in cirrhosis impact this mechanism.

The decreased phagocytic activity of the innate immune response is confounded by decreased bactericidal and opsonization capacity. Patients with cirrhosis have much lower levels of immunoglobulins IgM, IgG, and IgA in ascitic fluid. Further, C3, C4, and CH50 concentrations are significantly lower in both serum and ascitic fluid, thus leading to diminished bactericidal activity.

Additional aspects of immunodeficiency are complicated by factors such as malnutrition, immunosuppressive medications, and alcohol intake. Chronic and acute alcohol consumption are associated with a decrease in T cells, B cells, natural killer cells, monocytes, and an increase in proinflammatory cytokines.

**Bacterial Translocation**

Bacterial translocation is the migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes. It has also been implicated as a cause of recurrent SBP. Patients with cirrhosis have slowed intestinal motility, which leads to intestinal bacterial overgrowth. This overgrowth, along with portosystemic shunting, enables perpetuation of bacteria and can lead to bacteremia. Further oxidative damage from increased endotoxins, proinflammatory cytokines, and nitric oxide (NO) alter the structure and permeability of intestinal mucosa in cirrhosis. In conjunction with the decreased local and impaired systemic immune function in cirrhosis, decreased gut motility and increased permeability facilitate the spread of intestinal bacteria to extraintestinal sites and predispose patients with cirrhosis to infections.
Sirs, Sepsis, and Cirrhosis

Systemic inflammatory response syndrome (SIRS) is not uncommon in cirrhosis, and sepsis is defined as SIRS in the presence of confirmed bacterial infection (Figure 3). Bacterial derived toxins, such as peptidoglycans from gram-positive bacteria or lipopolysaccharides from gram-negative bacteria, bind to Toll-like receptors which initiate a cascade of cell signaling. Toll-like receptors trigger either nuclear factor fxB or mitogen activated protein kinase, which in turn stimulate the release of NO and proinflammatory cytokines tumor necrosis factor (TNF)-a, interleukin (IL)-6, and IL-1. In SIRS, anti-inflammatory cytokines (IL-10, IL-4, IL-13, prostaglandin E2) are unable to balance the proinflammatory cytokines, also known as a "cytokine storm," resulting in excessive inflammation.
SIRS and cirrhosis are interlinked determinants of survival outcomes. The severity of liver disease determines the development of SIRS, while SIRS leads to variceal bleeding, hepatic encephalopathy, and adversely affects survival.\footnote{33} Certain aspects of cirrhosis can exacerbate SIRS and complicate its diagnosis. Patients with cirrhosis have higher levels of circulating endotoxins that inversely correlate with hepatic deterioration.\footnote{34} After lipopolysaccharide challenge, those with cirrhosis had higher proinflammatory cytokine levels than those without, particularly TNF-α and IL-6.\footnote{35,36} Protein C and high density lipoprotein, protective anti-inflammatory, and antiapoptotic factors are thought to be reduced in cirrhosis.\footnote{37} NO, whose metabolite concentrations are correlated with those of endotoxins, is increased in cirrhosis and is known to contribute to the oxidative stress and worsening vasodilatation of sepsis.\footnote{38,39} Complications of cirrhosis may mask themselves as symptoms of SIRS. For example, hypersplenism may reduce white blood cell count, hyperdynamic circulation may elevate heart rate, and hepatic encephalopathy may cause hyperventilation.\footnote{31} However, these indicators appear to be more exaggerated in patients with cirrhosis. The release of large amounts of cytokines in sepsis intensifies this hyperdynamic state and serves as the link between bacterial infection and renal failure. Renal failure following SBP-related and non-SBP-related bacteremia has been observed in 1 third of patients with cirrhosis and ascites.\footnote{28,30} Altered hemodynamics and widespread inflammation lead to impaired tissue oxygenation, cell necrosis, and apoptosis, and ultimately organ failure. When organ function can no longer sustain homeostasis without intervention, the patient is deemed to have multiple organ dysfunction syndrome, a common result of cirrhosis and severe sepsis.

Relative adrenal insufficiency is common in patients with septic shock and is associated with hemodynamic instability, renal failure, and increased mortality.\footnote{40} It is diagnosed in approximately 70% of septic shock patients with cirrhosis and is believed to be linked to their impaired cortisol synthesis and decreased high density lipoprotein levels.\footnote{41,42} The use of hydrocortisone in patients with septic shock remains controversial\footnote{41,43,44}, however, a recent randomized trial found its use to be associated with an increase in shock relapse and GI bleeding.\footnote{45}

### Infections in Cirrhosis

#### Gastrointestinal Bleeding-associated Infections and Prophylaxis

GI bleeding is associated with an increased incidence of infection, and approximately 17% to 45% of cases lead to an episode of SBP or bacteremia.\footnote{46} Conversely, the presence of infection has been found to increase the risk of early bleeding.\footnote{47,48} Goulis et al.\footnote{49} hypothesize that bacterial endotoxins stimulate hepatic stellate cell contraction and endothelial NO production, which then increase sinusoidal pressure and inhibit platelet aggregation, respectively.

Patients who present with acute episodes of GI bleeding require short-term antibiotic prophylaxis regardless of the presence of...
ascites. Most infections are caused by gram-negative bacteria and are preventable with selective decontamination by quinolones.[50] Long-term SBP prophylaxis with norfloxacin has resulted in quinolone-resistant gram-negative bacteria and an increased prevalence of gram-positive bacteria.[3] Therefore, third-generation cephalosporins, which target both gram-negative and gram-positive bacteria, are preferred prophylactic strategies. In patients with advanced cirrhosis, 1 g of intravenous (IV) ceftriaxone for 7 days after bleeding was found to be more effective in preventing bacterial infections than oral norfloxacin.[51] Prospective randomized trials and a recent Cochrane Database review found antibiotic prophylaxis to significantly reduce rates of infection, rebleeding, and mortality.[62,54]

Based upon the "endotoxin-induced sinusoidal pressure" hypothesis,[49] antibiotic decontamination may lower the risk of rebleeding via reduction of endotoxin levels and subsequent portal pressure. Nonsselective beta blockers, commonly used to lower portal hypertension and prevent initial variceal hemorrhage, can also serve to decrease bacterial translocation during an acute hemorrhage. A recent meta-analysis[55] found evidence that beta blockers increase gut motility and reduce translocation, thereby reducing the incidence of infection. A study by Che-larescu et al.[56] in the postsurgical setting found propranolol to reduce infections from 42% to 15%. However, the use of beta blockers in patients with refractory ascites may limit the compensatory increase in cardiac output and increase vulnerability to complications such as septic shock and renal failure.[57,58]

Prokinetic agents may also reduce dysmotility and bacterial translocation. Prophylaxis with norfloxacin and cisapride was found to significantly reduce the rate of SBP compared with norfloxacin alone.[59] There is some evidence to suggest that the use of probiotics promotes the growth of gram-positive bacteria at the expense of gram-negative bacteria,[60] but it has yet to been shown to benefit patients with cirrhosis.[61,62] Given the increasingly negative implication of gram-positive bacteria in infections, replacing gram-negative bacterial populations may be of little use.

### Spontaneous Bacterial Peritonitis: Diagnosis, Treatment, and Prevention

The prevalence of SBP in patients with cirrhosis and ascites admitted to the hospital ranges between 10% and 30%; approximately half of cases are present at the time of hospitalization and half develop during the hospitalization.[63] The in-hospital mortality rate from SBP is approximately 32%.[64] The majority of these infections are caused by *E. coli, Klebsiella spp.*, other Enterobacteriaceae, *P. aeruginosa, enterococci*, and streptococci (Table I).[65]

The current recommendation is to perform a diagnostic paracentesis in all patients with ascites at the time of hospital admission and in those who manifest symptoms of peritoneal infection, systemic signs of infection, hepatic encephalopathy, or rapid impairment in renal function while hospitalized.[63,64] The diagnosis cutoff of SBP is a polymorphonuclear (PMN) count of 250 cells/mm³ while the highest specificity is reached at 500 cells/mm³.[63]

#### Table 1. Pathogens Causing Infections and Unique Features in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Common clinical syndrome</th>
<th>Special comments</th>
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</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
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<tr>
<td><em>E. coli</em>, <em>Klebsiella spp.</em>, and <strong>other gram-negative enteric bacteria</strong></td>
<td>SBP, bacteremia, UTI</td>
<td>Increased resistance in patients taking prophylactic quinolones and in nosocomial infections</td>
</tr>
<tr>
<td><strong>Vibrio vulnificus</strong></td>
<td>Soft tissue infection, bacteremia</td>
<td>Increased incidence in cirrhosis, particularly hemochromatosis</td>
</tr>
<tr>
<td><strong>Vibrio cholera (non-o1)</strong></td>
<td>Diarrhea, septicemia</td>
<td>Increased incidence and morbidity in advanced cirrhosis (mortality 24%)[11]</td>
</tr>
<tr>
<td><strong>Vibrio parahemolyticus</strong></td>
<td>Diarrhea, septicemia</td>
<td>Increased morbidity</td>
</tr>
<tr>
<td><strong>Aeromonas spp.</strong></td>
<td>Soft tissue infection, bacteremia</td>
<td>Increased incidence and morbidity in cirrhosis</td>
</tr>
<tr>
<td><strong>Yersinia spp.</strong></td>
<td>Septicemia, hepatosplenic abscesses, peritonitis</td>
<td>Increased incidence in cirrhosis and iron overload state</td>
</tr>
<tr>
<td><strong>Listeria monocytogenes</strong></td>
<td>Septicemia, meningitis, peritonitis</td>
<td>Increased incidence in cirrhosis, particularly hemochromatosis</td>
</tr>
<tr>
<td><strong>Plesiomonas shigelloides</strong></td>
<td>Septicemia, meningitis, soft tissue infection</td>
<td>Increased incidence in cirrhosis and iron overload state</td>
</tr>
<tr>
<td><strong>Clostridium spp.</strong></td>
<td>Septicemia, soft tissue infection, peritonitis</td>
<td>Increased incidence and morbidity of *C. perfringens in cirrhosis (mortality 54%–65%)[11]</td>
</tr>
<tr>
<td><strong>Clostridium difficile</strong></td>
<td>Antibiotic-associated diarrhea and colitis</td>
<td>Increased incidence (may be related to the common use of antibiotics and PPI in patients with cirrhosis)[12]</td>
</tr>
<tr>
<td><strong>Organism</strong></td>
<td><strong>Clinical Manifestations</strong></td>
<td><strong>Diagnostic Findings</strong></td>
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<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Soft tissue infection, septicemia, endocarditis</td>
<td>Increased incidence in cirrhosis, particularly hospitalized patients</td>
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<td></td>
<td></td>
<td>Increased MRSA nasal carriage</td>
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<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Septicemia, pneumonia, meningitis</td>
<td>Increased incidence and morbidity</td>
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<tr>
<td></td>
<td></td>
<td>Pneumococcal vaccine is recommended in patients with cirrhosis (vaccine efficacy has been validated in alcoholic cirrhosis)</td>
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<tr>
<td><em>Streptococcus group B</em></td>
<td>Septicemia, peritonitis, skin and soft tissue infection</td>
<td>Increased incidence</td>
</tr>
<tr>
<td><em>Enterococcus spp.</em></td>
<td>SBP, septicemia, UTI, biliary tract infection, endocarditis</td>
<td>Increased incidence and morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality rate approximately 25% (up to 50% in endocarditis form)</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em> (TB)</td>
<td>Pulmonary TB, extrapulmonary TB, esp. peritonitis, disseminated TB</td>
<td>Higher incidence, more virulent, and more extrapulmonary forms in cirrhosis compared to non-cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk for multi-drug resistance TB</td>
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<tr>
<td>Fungi</td>
<td>Cryptococcus neoformans</td>
<td>Peritonitis, meningitis, disseminated cryptococcosis</td>
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<tr>
<td></td>
<td></td>
<td>Increased incidence in advanced cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality rate up to 70%</td>
</tr>
<tr>
<td>Fungi</td>
<td>Candida spp.</td>
<td>Biliary tract infection, septicemia</td>
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<tr>
<td></td>
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<td>Identified in the bile up to 44% of PSC patients with cholangitis</td>
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Up to 65% of patients with clinical evidence of SBP and increased ascites have negative cultures, but inoculation of 10 mL of ascitic fluid in aerobic and anaerobic culture bottles at the bedside has improved sensitivity to approximately 80%. Recent applications of culture-independent methods have attempted to improve screening outcomes. Several types of leukocyte esterase reagent strips have been evaluated in the diagnosis of SBP and have demonstrated sensitivity and specificity ranging between 45% and 100% and 81% to 100%, respectively. A recent study demonstrated an esterase strip calibrated to an ascitic fluid PMN count >250 cells/mm³ to be a good bedside screening tool. Preliminary application of molecular analysis to identify bacterial DNA has yielded promising results that may replace culture techniques in the future.

Bacterascites and secondary peritonitis are unique conditions of SBP that require specific guidelines for identification and therapy. It is identified by a positive ascitic fluid culture and an ascitic PMN <250 cells/mm³. The differentiation between SBP and secondary peritonitis, i.e., bacterial peritonitis caused by perforation or acute inflammation of organs, can be quite difficult. Secondary peritonitis, though only accounting for 4.5% of all peritonitis cases in cirrhosis, should be suspected in any of the following situations: (1) lack of a response to antibiotic therapy; (2) 2 or more organisms isolated (particularly anaerobes or fungi); (3) the presence of at least 2 of the following in ascitic fluid: glucose <50 mg/dL, protein >1 g/dL, lactic dehydrogenase greater than normal serum levels. With intestinal perforation, secondary peritonitis may also be suspected if chorioembryonic antigen >5 ng/mL or alkaline phosphatase >240 U/L. After diagnosis of a cause of secondary peritonitis with a radiological study such as magnetic resonance imaging or computed tomography scan, patients should receive antibiotic therapy and undergo surgical evaluation. Because it is often a monobacterial infection with an associated white blood cell response, SBP is defined as culture positive. However, a variant of it called culture-negative neutrocytic ascites can be encountered and has similar clinical outcomes (Figure 4).
The current standard for treatment of SBP is with a minimal dose of 2 g of intravenous cefotaxime every 12 hours for 5 days.\textsuperscript{[80,81]} In those with clinical improvement, a repeat of paracentesis is not necessary to assess for resolution of SBP. Equally effective alternative therapies include cephalosporins (ceftriaxone, ceftazidime, ceftizoxime), amoxicillin-clavulanic acid, and quinolones (ciprofloxacin, ofloxacin, levofloxacin) for beta-lactam hypersensitive patients.\textsuperscript{[31],[63,82]} When clinical signs of infection have improved, replacing IV cephalosporin with oral ciprofloxacin to complete the course of therapy may be more cost-effective.\textsuperscript{[83]} Patients taking quinolones as prophylaxis should be aware of treatment failure because of antibiotic resistance or enterococcal infection. If clinical improvement and a sufficient drop in neutrophil count in ascites (<25% of initial value) are not observed by day 3 of treatment, a switch of antibiotic therapy should be considered while the patient is evaluated for secondary peritonitis.

Renal impairment develops in approximately 1 third of all SBP patients and is a strong predictor of mortality during hospitalization.\textsuperscript{[27]} The activation of the cytokine cascade and NO production in cirrhosis and SBP negatively impact renal function.\textsuperscript{[28,84]} The use of intravenous albumin (1.5 g/kg body weight within 6 hours of SBP diagnosis followed by 1 g/kg body weight on day 3) in conjunction with cefotaxime was found to reduce the incidence of renal impairment from 33% to 10% and mortality from 29% to 10%.\textsuperscript{[28]} Albumin increases mean arterial volume, binds TNF-\(\alpha\) and NO to counteract the inflammatory response of infection, and removes toxins from circulation.\textsuperscript{[84–86]} These infusions are most effective in patients with baseline creatinine >1.0 mg/dL and total bilirubin >4.0 mg/dL.\textsuperscript{[28,87]} A recent pilot study by Cartier et al.\textsuperscript{[88]} suggests polygeline (Gelafundin 4%; B Braun Medical AG, Cnssier, Switzerland), a cheaper plasma expander, as a reasonable alternative to albumin.

When treated effectively, recovery from SBP is seen in approximately 90% of patients and 30-day survival is in at least 80%.\textsuperscript{[63]} For patients who fail treatment, hospital mortality ranges from 50% to 80%.\textsuperscript{[89]} The rapid deterioration of liver function in SBP patients makes for generally poor long-term prognosis after an episode of SBP. Franca et al.\textsuperscript{[90]} found the 1-year survival rate to be 28.5%. The recent shift in microbial etiology of SBP toward cefotaxime-resistant strains may complicate survival by delaying infection resolution.
Patients recovering from an episode of SBP should be given antibiotic prophylaxis. In those without antibiotic prophylaxis, the rate of recurrence of SBP is 43% at 6 months, 69% at 1 year, and 74% at 2 years after the initial episode. Gines et al[91] found that 400 mg per day oral norfloxacin reduced recurrence of SBP from 68% to 20%. The use of 500 mg ciprofloxacin per day, rather than the 750 mg once per week dosage previously suggested, is known to be effective. Intermittent dosing of prophylactic antibiotics may select resistant flora, therefore daily dosing is preferred. For patients intolerant to quinolones, daily double-strength oral trimethoprim/sulfamethoxazole is an effective alternative. [95,96] The current time scale for long-term prophylaxis is indefinite.

Patients with advanced cirrhosis and low protein ascites may be candidates for primary prophylaxis against SBP. In a randomized controlled trial, patients with low protein ascites levels (<1.5 g/dL) with advanced liver failure or impaired renal function who received norfloxacin prophylaxis had a significantly decreased probability of SBP, hepatorenal syndrome, and mortality.

Other Infections in Cirrhosis

Urinary Tract Infection

UTI occurs in approximately 15% to 20% of hospitalized patients with cirrhosis; it is twice as frequent in patients with cirrhosis compared with matched controls.[13,99] Women have a 4 times higher rate of bacteriuria than men.[99] Gram-negative bacilli, such as *E. coli* and *Klebsiella* spp., are the primary causative agents. Notably, bacteriuria is not associated with an increased risk of sepsis, SBP, or other infections often seen in patients with cirrhosis.[99] Although more frequent among those with cirrhosis, UTI does not consistently correlate with the severity of liver disease and is more strongly associated with gender and diabetes.[99–101] The high incidence of UTI in cirrhosis remains unexplained. Bercoff et al[102] cite the increased bladder postvoid residual volume as an explanation, however, this finding was not supported in a subsequent study.[99] Treatment of UTI with quinolones is effective in approximately 95% of cases.[99]

Pneumonia

Pneumonia is the third leading cause of infections in patients with cirrhosis.[1,50] Pulmonary clearance of pneumococci was significantly decreased in a rat model of cirrhosis, most likely as a result of decreased complement levels.[103] Community-acquired pneumonia (CAP) is most often caused by *S. pneumoniae* and *H. influenzae.*[104] *S. aureus,* *M. pneumoniae,* *M. catarrhalis,* *C. pneumoniae,* *Klebsiella* spp., and *Legionella* spp. have also been implicated as causes of CAP. The risk of bacteremia in CAP is increased in patients with cirrhosis.[105] Further, procedures such as tracheal intubation and esophageal tamponade put patients with cirrhosis at risk of hospital-acquired pneumonia.[106] In the presence of comorbidities such as cirrhosis, treatment is ideal with IV beta-lactam plus macrolide or IV antipneumococcal quinolones.[104] Pneumococcal vaccination is recommended in patients with cirrhosis.[104,107]

Soft Tissue Infections

Chronic edema and increased bacterial translocation predispose patients with cirrhosis to soft tissue infections, which constitute approximately 11% of infections.[108] Both gram-positive (*S. aureus,* group A *Streptococci*) and gram-negative bacteria (*Klebsiella* spp., *Aeromonas* spp., *V. vulnificus*) are common causes of soft tissue infections. Cellulitis is the most frequently observed skin infection in patients with cirrhosis and has a recurrence rate of 20%.[109] Necrotizing fasciitis, a rare but severe form of soft tissue infection, is predominately caused by gram-negative bacteria.[110] Unlike the general population, necrotizing fasciitis in those with cirrhosis rarely develops from an obvious portal of entry in the extremities, thereby suggesting a potential pathway of bacterial translocation and bacteremia leading to soft tissue infections.[110,111] Broad spectrum antibiotic treatment is necessary for proper management of soft tissue infections, and surgical intervention for deep infections may be needed.

Endocarditis

Approximately 10% of infectious endocarditis (IE) cases have cirrhosis as an underlying condition.[112] IE is a concern for hospitalized patients with cirrhosis because of the increased risk of bacteremia associated with invasive procedures (transjugular intra-hepatic portosystemic shunt, upper endoscopy, etc.). Valve disorders are present in approximately 60% of patients with cirrhosis who have IE.[112] Gram-positive bacteria such as *S. aureus,* β-hemolytic streptococci (*S. agalactiae,* *S. pyogenes*), and enterococci (*E. faecalis,* *E. faecium*) are the most commonly isolated organisms.[112,113] Depending on the organism, a minimum of 4 weeks of antibiotic therapy is recommended.[114] Patients with advanced liver cirrhosis have high surgical mortality rates,[115] therefore surgical management of IE is reserved for selected patients who do not respond to medical therapy.

Tuberculosis

The incidence and virulence of *Mycobacterium tuberculosis* infections are increased in patients with cirrhosis.[116] In a cohort of tuberculosis (TB) patients with liver cirrhosis in Denmark, the 30-day case fatality rate was 27.3% and the 1-year case fatality rate was 47.7%.[116] TB patients with liver cirrhosis show extrapulmonary involvement,[117] such as TB peritonitis, more frequently. Compared with SBP, TB peritonitis is present in less advanced cirrhosis and is characterized by lower white blood cell count in ascites, higher proportion of mononuclear leukocytes, higher protein concentration, and higher levels of adenosine deaminase activity in ascites.[118] Though adenosine deaminase level analysis is useful in the detection of TB peritonitis in patients without
Cirrhosis, the presence of cirrhosis reduces its sensitivity to 30%.[119] Laparoscopic biopsies provide definitive diagnosis of TB peritonitis by revealing multiple whitish nodules scattered over the peritoneum.[118,120] Patients with TB and cirrhosis respond well to anti-TB therapy, however they face a greater risk of hepatotoxicity.[117]

**Clostridium difficile** *Clostridium difficile* is an increasingly prevalent hospital-acquired infection that affects patients with cirrhosis. A recent study of over 80,000 patients with cirrhosis found patients with *C. difficile-associated* disease to have higher mortality and longer length of stay than those without infection.[121] Antibiotics and proton pump inhibitors were independently associated with *C. difficile* infection. Thus it is recommended that antibiotic prophylaxis be limited to patients at highest risk of developing SBP and that proton pump inhibitors be used selectively.[122]

**Drug-Resistant Infections**

Nosocomial infections account for a significant proportion of infections in patients with cirrhosis and an increasing number of these infections are caused by antibiotic-resistant and gram-positive pathogens. Approximately 37% to 64% of bacterial infections, either nosocomial or in the context of antibiotic intervention in an outpatient setting, have been found to be multidrug-resistant.[3,123,124] Gram-negative isolates in SBP, such as *E. coli* and *K. pneumoniae*, are being encountered with increasing rates of resistance.[125] Gram-positive pathogens are increasingly common in patients with cirrhosis.[125] Methicillin-resistant *S. aureus* has been noted to account for 24.8% of nosocomial SBP.[125] *E. faecalis* and *E. faecium* have been isolated in nearly 10% to 24% of infections in the setting of cirrhosis and are associated with 25% mortality rate.[3,125,126] Approximately a third of enterococcal bacteremia cases demonstrate vancomycin resistance and are associated with twice the mortality rate of nonresistant strains.[127,128]

**Fungal Infections**

Cirrhosis increases susceptibility to *Cryptococcus neoformans*, an encapsulated fungus that is typically associated with human immunodeficiency virus-infected patients.[129,130] Liver cirrhosis is an underlying condition in approximately a third of non-human immunodeficiency virus cryptococecal cases and is a stronger independent predictor of 30-day mortality than those with acquired immunodeficiency syndrome.[131] Though uncommon, *C. neoformans* may infect ascites and cause spontaneous cryptococcal peritonitis. Unlike SBP, spontaneous cryptococecal peritonitis presents itself with elevations in lymphocyte count and, because of late detection, has a very high mortality rate (~70%).[132] The pathogenesis of cryptococcal peritonitis may be via direct percutaneous inoculation during para-centesis, GI bleeding, or bacterial translocation.[130,133] Candida infections can also be encountered particularly in patients with primary sclerosing cholangitis (PSC). *Candida* species have been identified in 44% of bile samples in PSC patients, particularly those with dominant strictures.[134,135] A high prevalence of biliary candidiasis exists, however, the effect of antifungal therapies on treatment outcomes for recurrent cholangitis remains unknown.

**Specific Liver Disease-related Infections**

Iron overload state impairs cell-mediated response and enhances growth of various pathogens such as *E. coli, Vibrio spp.*, and *Listeria monocytogenes*.[136] Recent evidence suggests that decreased levels of hepcidin, an iron-regulator hormone with antimicrobial activity, serve as the link between liver disease and these infections.[137] Patients with hemochromatosis face a 30-fold greater risk of acquiring *V. vulnificus*, a bacterium acquired through ingestion of contaminated raw oysters.[138] *V. vulnificus* sepsicemia has a 50% to 60% case mortality rate in patients with liver disease and 7% to 22% mortality for localized wound infection.[138,139] *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*-s, 2 gram-negative bacilli transmitted zoonotically, infect via systemic or portal vein bacteremia to cause hepatic abscesses with up to a 56% mortality rate.[140–142]

PSC is a risk factor for ascending cholangitis, which is associated with up to a 16% mortality rate.[143,144] Generally, ascending cholangitis is relatively uncommon unless the biliary tree has been manipulated by endoscopic retrograde cholangio-pancreatography. The most common infections after endoscopic retrograde cholangiopancreatography are caused by gram-negative bacteria such as *E. coli*, *Klebsiella spp.*, and *Enterobacter spp.*.[143,144] However, if cholangitis occurs without any intervention, the presence of stones, dominant strictures, or cho-langiocarcinoma should be considered. In a study of explanted livers with PSC, bacteria were isolated in approximately 60% of cases.[145] The most common bacteria isolated were alpha-hemo-lytic streptococci, enterococci, and staphylococci. Though the etiology of PSC is largely unknown, bacterial infection of the bile ducts with dominant stenoses has been implicated in the progression of the disease.[146]

**Summary**

Patients with cirrhosis are in a multifactorial Immuno-compromised state which predisposes them to a higher risk of infection. *Bacterial* infections, particularly SBP and bacteremia, are an important cause of morbidity and mortality in these patients. Gram-negative enteric bacteria appear to be the most common causative organisms. However, other unusual *bacteria*, and fungi are also frequently observed and more virulent in patients with cirrhosis relative to those without liver disease. Moreover, these pathogens can present with various clinical syndromes that may be difficult to recognize. The relationship between immune dysfunction and infection in cirrhosis has been extensively investigated. *Bacterial* translocation appears to be an important step, which accounts for the increased levels of endotoxins, cytokines, and NO; these play a critical role in the development of an excessive inflammatory response and hyperdynamic circulatory state of cirrhosis. As hepatic function deteriorates and portal...
hypertension progresses, overt infection is more likely to develop and subsequently can evolve to sepsis, leading to consequences such as septic shock, multiorgan failure, and death.

Early diagnosis and proper management of infections in patients with cirrhosis are necessary. Generally, intravenous third generation cephalosporins are recommended as empiric antibiotic therapy for most cases of SBP and bacteremia. However, the risk of resistant organisms and unusual pathogens should be kept in mind, especially in patients with cirrhosis who are receiving quinolone prophylaxis or have hemochromatosis as an etiology of liver disease. Auxiliary therapy with intravenous albumin can significantly reduce morbidity and mortality in SBP patients who are at high risk of developing renal failure. The importance of preventive strategies cannot be underscored. Patients with cirrhosis admitted with GI hemorrhage benefit from short-term antibiotic prophylaxis, whereas long-term oral prophylaxis is recommended in those who have recovered from SBP. Despite recent advances in understanding of the mechanisms of infection in patients with cirrhosis, the outcomes of those patients with severe infections still remain poor. Further studies into mechanisms, diagnostic approaches, and potential preventive strategies are needed to improve the management of infections in patients with cirrhosis.

References


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Conflicts of interest
The authors disclose no conflicts.

Abbreviations used in this paper
CAP, community-acquired pneumonia; GI, gastrointestinal; IE, infectious endocarditis; IL, interleukin; IV, intravenous; NO, nitric oxide; PMN, polymorphonuclear; PSC, primary sclerosing cholangitis; RE, reticuloendothelial; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response syndrome; TB, tuberculosis; TNF, tumor necrosis factor; UTI, urinary tract infection.