Bacterial infections in cirrhosis: A critical review and practical guidance

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Bacterial infection is common and accounts for major morbidity and mortality in cirrhosis. Patients with cirrhosis are immunocompromised and increased susceptibility to develop spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens. Once infection develops, the excessive response of pro-inflammatory cytokines on a pre-existing hemodynamic dysfunction in cirrhosis further predispose the development of serious complications such as shock, acute-on-chronic liver failure, renal failure, and death. Spontaneous bacterial peritonitis and bacteremia are common in patients with advanced cirrhosis, and are important prognostic landmarks in the natural history of cirrhosis. Notably, the incidence of infections from resistant bacteria has increased significantly in healthcare-associated settings. Serum biomarkers such as procalcitonin may help to improve the diagnosis of bacterial infection. Preventive measures (e.g., avoidance, antibiotic prophylaxis, and vaccination), early recognition, and proper management are required in order to minimize morbidity and mortality of infections in cirrhosis.

Key words: Bacteria; Infection; Sepsis; Bacteremia; Liver cirrhosis; Vaccination; Spontaneous peritonitis; Immune dysfunction

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INTRODUCTION
In the past decades, there have been several improvements in the management of cirrhotic patients, such as antiviral therapy and management of portal hypertension and liver transplantation (LT). However, the mortality of infection in cirrhosis is still high and has not changed substantially. Cirrhosis is an immunocompromised state that predisposes patients to spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens. Once infection develops, the excessive response of pro-inflammatory cytokines on a pre-existing hemodynamic derangement in cirrhosis further predispose the development of serious complications such as shock, acute-on-chronic liver failure, renal failure, and death. The incidence of resistant bacteria has continually increased, especially in healthcare-associated settings. Preventive measures, early recognition and proper management are necessary to minimize morbidity and mortality of infections in cirrhosis.

MECHANISM OF INCREASED SUSCEPTIBILITY AND VULNERABILITY TO INFECTION IN PATIENTS WITH CIRRHOSIS

Immune dysfunction in cirrhosis
Patients with cirrhosis are in a state of immune dysfunction, in parallel with a state of excessive activation of pro-inflammatory cytokines, referred to as cirrhosis-associated immune dysfunction syndrome, which predisposes the patient for infections[1-5]. Portosystemic shunting allows less gut-derived bacteria and their products to be cleared from portal circulation by the liver, which contains about 90% of the reticuloendothelial cells in the body[1-5]. Nearly all components of systemic immune response are significantly impaired in cirrhosis, including a decrease in phagocytic activity, a reduction in serum albumin, complement and protein C activities, and an impaired opsonic activity both in serum and ascitic fluid[1-4,6-10]. Genetic polymorphisms of toll-like receptor (TLR) and nucleotide-binding oligomerisation domain 2 (NOD2) genes could be responsible for bacterial translocation (BT) and increase infection risk in cirrhosis by altering the TLR’s ability to bind to lipopolysaccharide or endotoxins[11,12]. Further, cirrhosis-associated immune dysfunction may further complicate by additional factors such as malnourishment[13] and alcohol drinking[14] (Table 1).

BT
BT is the migration of viable native bacteria from gut lumen through systemic circulation via mesenteric lymph nodes (MLN) and portal vein. Although this can be a healthy phenomenon, BT has increased pathologically compromising effects in cirrhosis[15-17]. The diagnosis of BT relies on the isolation of viable bacteria in MLN, while the detection of bacterial DNA in serum or ascitic fluid is proposed as a useful surrogate marker[15-18]. It has been shown that oral administration of radio-labeled

Escherichia coli
(E. coli) to cirrhotic rats revealed the detection of these bacteria not only in the gut lumen but also in the MLN and ascites[19]. Several experimental and clinical studies have suggested that small intestinal overgrowth, increased intestinal permeability, impaired intestinal motility, lack of bile acids, sympathetic overactivity, and local innate and adaptive immunological alterations (e.g., impaired leukocyte recruitment, altered T-cell activation, TLR and NOD2 mutation) are important factors involved in the pathogenesis of BT[11,12,17,20,21].

BT is pathogenetically linked to the development of infections, particularly spontaneous bacterial infections, and other serious complications in cirrhosis[15-17]. Apart from infections, bacterial DNA and bacterial products, such as endotoxin, can translocate to extra-intestinal sites and promote host immunological and hemodynamic responses, which is associated with the development of systemic pro-inflammatory and hyperdynamic circulatory state in cirrhosis[16,18]. The pathological translocation of viable bacteria occurs in the decompensated stage, while the rate and degree of translocating bacterial products also increases in the earlier stages of cirrhosis[19]. Notably, treatment with non-selective beta-blockers has been shown to ameliorate intestinal permeability and reduce BT[20].

Systemic inflammatory response syndrome and circulatory dysfunction in cirrhosis
Patients with cirrhosis are susceptible to the development of severe infection, septic shock, and organ...
failure[1,2,23]. In cirrhosis, bacterial infection is associated with a dysregulated cytokine response, which transforms helpful responses against infections into excessive, damaging inflammation[1,2,23]. Nitric oxide is strikingly released in cirrhotic patients with sepsis and is a key driver of circulation dysfunction in this setting[23,24]. A pre-existing hyperdynamic circulatory state in patients with advanced cirrhosis predisposes detrimental complications from a sepsis-induced nitric oxide and cytokine storm which subsequently leads to intractable hypotension, insufficient tissue perfusion, multiple organ failure and death[1,3,23].

### Epidemiology and types of infection
Bacterial infection accounts for about 30%-50% death in patients with cirrhosis[3,24,25]. Infections present in 32%-34% of hospitalized patients with cirrhosis, which is 4-5 folds higher than hospitalized patients in general, and is especially higher in those with gastrointestinal bleeding (45%-60%)[26-28].

Common types of infections in patients with cirrhosis include spontaneous bacterial peritonitis (SBP) (25%-31%), urinary tract infection (UTI) (20%-25%), pneumonia (15%-21%), bacteremia (12%), and soft tissue infection (11%)[2,27,29]. The major causative organisms are gram-negative bacteria, e.g., *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., whereas gram positive bacteria, especially *Enterococci* and *Staphylococcus aureus*, comprise about 20% and anaerobes only 3%[30]. Risk factors of infection by gram positive bacteria are recent or current hospitalization, receiving quinolones prophylaxis, and invasive procedures[27,26,30].

Healthcare-associated is defined as infections diagnosed within 48 h of hospital admission in patients with any prior 90-d healthcare contact and nosocomial is defined as infections diagnosed after 48 h of admission.

These infections are increasingly common in cirrhosis, frequently resistant to antibiotics (up to 64%) and are associated with bad outcomes[30]. In a large prospective study of cirrhotic patients with infections (> 650 infectious episodes)[31], multi-resistant bacteria (18%) were isolated in 4%, 14%, and 35% of community-acquired, healthcare-associated, and nosocomial infections, respectively (P < 0.001). The main resistant organism was extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, followed by *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterococcus faecium*[31]. There was a significantly higher incidence of septic shock and death from infections caused by resistant bacteria. Notably, the efficacy of empirical antibiotic treatment was decreased in nosocomial infections (40%), compared to community-acquired and healthcare-associated episodes (83% and 73%, respectively; P < 0.0001), especially in SBP, UTI, and pneumonia (26%, 29% and 44%, respectively)[31]. Due to an increasingly use of broad spectrum antibiotics (ATB), it is speculated that infections with multi-resistant gram-negative organisms and *Enterococci* will be largely more common and more problematic in the near future.

The common types of infections in cirrhosis and suggested empiric therapy are summarized in Table 2[23]. In addition, the common clinical features and risk factors of less common pathogens are summarized in Table 3[32]. It should be noted that the data regarding these less common pathogens derived from case reports and series from various regions of the world, in which the patterns of infection and ATB usage varies among reports. In real-life practice, empirical ATB should be selected based upon types of infection, individual risk factors, and the local epidemiological pattern of resistant bacteria, then narrow-downed according to the culture and ATB susceptibility testing.

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**Table 1** State of immune dysfunction in patients with cirrhosis

| Natural barriers | Fragile, thin and/or edematous skin |
|------------------|-----------------------------------|
|                   | Alteration of GI motility and mucosal permeability |
|                   | Alteration of GI bacterial flora, bacterial overgrowth |
| Hepatic RES activity | Portosystemic shunting |
|                   | Kupffer cells - ↓ number, impaired function |
| Cellular defense mechanisms | RES - ↓ activation, ↓ chemotaxis, ↓ phagocytosis, ↓ production of pro-inflammatory cytokines (IL-1, IL-6, IL-18, TNF-α) |
|                   | PMN - ↓ lifespan, ↓ intracellular killing activity, ↓ phagocytosis, ↓ chemotaxis |
| Serum factors | ↓ Complement levels (C3, C4, CH50) |
|                   | ↓ Opsonic activity |
|                   | ↓ Protein C activity |
| Iatrogenic and treatment-related factors | ↑ GI mucosal ulcersations |
|                   | Frequent hospitalization |
|                   | Immunosuppressive agents (autoimmune hepatitis, post-transplantation) |
|                   | Interferon therapy (viral hepatitis) |
|                   | Proton pump inhibitors |
| Other compelling factors | Malnutrition |
|                   | Alcohol drinking |

Adapted from Bunchorntavakul C, Chavalitdhamrong D. *World J Hepatol* 2012; 4: 158-168. RES: Reticuloendothelial system; GI: Gastrointestinal; IL: Interleukins; TNF: Tumor necrosis factors; PMN: Polymorphonuclear cells.
Table 2 Types of infection and suggested empirical antibiotic therapy in patients with cirrhosis

| Types of infection            | Common responsible bacteria | Suggested empirical antibiotic |
|-------------------------------|-----------------------------|--------------------------------|
| SBP, spontaneous bacteremia, SBE | Enterobacteriaceae          | 1st line: Cefotaxime or ceftriaxone or BL-BI IV |
|                               | *S. pneumonia*              | Options: Ciprofloxacin PO for uncomplicated SBP; carbapenems IV for nosocomial infections in areas with a high prevalence of ESBL. |
|                               | *S. viridans*               | BL-BI may prefer in those with suspicious for enterococcal infection 5. |
| Pneumonia                     | Enterococci                 | Community-acquired: ceftriaxone or BL-BI IV + macrolide or levofloxacin IV/PO |
|                               | *S. pneumonia*              | Nosocomial and health care-associated infections: Meropenem or cefazidime IV + ciprofloxacin IV (IV vancomycin or linezolid should be added in patients with risk factors for MRSA) |
|                               | *H. influenzae*             | |
|                               | *M. pneumoniae*             | |
|                               | *Legionella spp.*           | |
|                               | Enterobacteriaceae          | |
|                               | *P. aeruginosa*             | |
|                               | *S. aureus*                 | |
| Urinary tract infection       | Enterobacteriaceae          | 1st line: Ceftriaxone or BL-BI IV in patients with sepsis. Ciprofloxacin or cotrimoxazole PO in uncomplicated infections. |
|                               | *E. faecalis*               | Options: In areas with a high prevalence of ESBL, IV carbapenems for nosocomial infections and sepsis (+ IV glycopeptides for severe sepsis); and nitrofurantoin PO for uncomplicated cases. |
|                               | *E. faecium*                | |
| Skin and soft tissue infections | *S. aureus*                | Community-acquired: Ceftriaxone + cloxacillin IV or BL-BI IV |
|                               | *S. pyogenes*               | Nosocomial: Meropenem or cefazidime IV + glycopeptides IV |
|                               | Enterobacteriaceae          | |
|                               | *P. aeruginosa*             | |
|                               | *Vibrio vulnificus*         | |
|                               | Aeromonas spp.              | |
| Meningitis                    | *S. pneumoniae*             | Community-acquired: Cefotaxime or ceftriaxone IV + vancomycin IV |
|                               | Enterobacteriaceae          | Ampicillin IV should be added if *L. monocytogenes* is suspected. |
|                               | *L. monocytogenes*          | Nosocomial: Meropenem + vancomycin IV |
|                               | *N. meningitidis*           | |

Adapted from Fernandez J, Gustot T. J Hepatol 2012; 56 (Suppl 1): S1-12. 1Quinolones should not be used in patients submitted to long-term norfloxacin prophylaxis or in geographical areas with a high prevalence of quinolone-resistant Enterobacteriaceae; 2Risk factors for *Enterococci*: Quinolone prophylaxis, hospital-acquired infection; 3Risk factors for MRSA: Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage; 4Risk factors for *L. monocytogenes*: Hemochromatosis, detection of gram-positive bacilli/coccobacilli in cerebrospinal fluid. BL-BI: Beta-lactam/beta-lactamase inhibitors (e.g., amoxicillin/clavulanic acid, ampicillin/sulbactam, and piperacillin/tazobactam); MRSA: Methicillin-resistant *Staphylococcus aureus*; ESBL: Extended spectrum beta-lactamases; SBP: Spontaneous bacterial peritonitis; SBE: Spontaneous bacterial empyema; IV: Intravenous; S. pneumoniae: Streptococcus pneumoniae; S. viridans: Streptococcus viridans; H. influenzae: Haemophilus influenzae; M. pneumoniae: Mycoplasma pneumoniae; P. aeruginosa: Pseudomonas aeruginosa; S. aureus: *Staphylococcus aureus*; E. faecalis: Enterococcus faecalis; E. faecium: Enterococcus faecium; S. pyogenes: Streptococcus pyogenes; L. monocytogenes: *Listeria monocytogenes*; N. meningitidis: *Neisseria meningitidis*.

**Biomarkers of bacterial infection in cirrhosis**

It is crucial, but often difficult to make an early diagnosis of bacterial infections in cirrhosis due to non-specific manifestations, which are indistinguishable from other non-infectious causes of systemic inflammatory response syndrome (SIRS) and the symptoms of liver deterioration. Therefore, serum biomarkers that are sensitive, reliable and inexpensive are being pursued in order to improve the diagnosis of bacterial infection in the setting of cirrhosis. General inflammatory markers, such as C-reactive protein (CRP, synthesized by the liver), ferritin (synthesized by the liver) or white blood cells (WBC), lack specificity for bacterial infections. Procalcitonin (PCT) is potentially a more specific marker for bacterial infection. PCT is produced by nearly all tissues in response to endotoxin or mediators released in response to bacterial infections [interleukin (IL)-1b, tumor necrosis factor-alfa, and IL-6]. It highly correlates with the severity of bacterial infections and may be helpful to distinguish bacterial infections from viral infection or other non-infectious causes.[20]

In the meta-analysis included 10 diagnostic studies (1144 cirrhotic patients and 435 bacterial infection episodes), PCT displayed an area under the curve of 0.92, a sensitivity of 0.79, and a specificity of 0.89 in diagnosing bacterial infection.[21] The pooled sensitivity estimates were 79% for PCT and 77% for CRP tests, whereas the pooled specificity were higher for both PCT (89%) and CRP tests (85%)[22]. The results were consistent when stratified to patients with SBP or patients with systemic infection. The authors suggested that the PCT test can be used as a rule-in diagnostic tool (positive likelihood ratio 7.38), CRP test can be used as a rule-out diagnostic tool (negative likelihood ratio 0.23) in patients without signs of infection.[23]. However, the diagnostic accuracy of CRP in the detection of bacterial infections decreased in setting of advanced liver disease. The combination of CRP and PCT may slightly improve the diagnostic accuracy of bacterial infection[24].

**SBP**

**Epidemiology and clinical features of SBP**

SBP is common and quite unique in patients with cirrhosis. The prevalence of SBP in cirrhotic patients with ascites admitted to the hospital ranges from 10%-30%;
Increased incidence 50% of TB peritonitis cases in the United States had; Increased incidence of MRSA carriage and infection Increased incidence High mortality (30% in bacteremia) Diabetes Risk factors; Increased incidence Increased incidence Remarks; Alcoholic Increased incidence, especially extrapulmonary forms (> High mortality (20%-60%), especially when worsening of pre­existing ascites, although these symptoms of SBP include fever, abdominal pain, and worsening of pre-existing ascites, although these symptoms may be absent in up to one-third of cases.

Therefore, diagnostic paracentesis is recommended to perform in all cirrhotic patients with ascites at the time of admission and/or in case of gastrointestinal (GI) bleeding, shock, signs of inflammation, hepatic encephalopathy, worsening of liver or renal function. The hospital mortality for SBP ranges from 10%-50% depending on various factors. Predictors for poor prognosis in SBP include older age, higher Child-Pugh scores, nosocomial origin, encephalopathy, elevated serum creatinine.
and bilirubin, ascites culture positivity, presence of bacteria, and infections with resistant organisms. Notably, the modifiable factors to reduce morbidity and mortality in SBP include prompt diagnosis, proper first-line ATB treatment and prevention of subsequent renal failure. SBP is one of the important prognostic landmarks in the natural course of cirrhosis as the overall one-year mortality rate after a first episode of SBP are 30%-93% regardless of its recurrence.

**Diagnosis of SBP**

The diagnosis of SBP is relied on the cell count of the ascitic fluid, determined either by microscope or appropriate automated cell counters, and bacterial culture. Ascitic fluid culture is important and ascites culture positivity, presence of bacteria, and infections with resistant organisms. Notably, the modifiable factors to reduce morbidity and mortality in SBP include prompt diagnosis, proper first-line ATB treatment and prevention of subsequent renal failure. SBP is one of the important prognostic landmarks in the natural course of cirrhosis as the overall one-year mortality rate after a first episode of SBP are 30%-93% regardless of its recurrence.

**Management of SBP**

Empirical ATB should be given promptly to all cirrhotic patients with ascites PMN counts > 250 cells/mm² in clinical settings that suggestive for ascitic fluid infection (culture results are often unavailable at this time). The choice of empirical ATB should be based on the origin of infection, individual risk factors for resistant organism and local microbial epidemiology. In general, the suggested initial treatments of community-acquired SBP are third-generation cephalosporins (mostly preferred), amoxicillin-clavulanate or quinolones (Table 2). These empirical ATB should be given intravenously for a duration of 5-10 d. In countries with low rate of quinolone-resistant *Enterobacteriaceae*, oral quinolones may be used for uncomplicated SBP, as defined by cases without shock, ileus, GI bleeding, hepatic encephalopathy (grade II) or renal impairment (creatinine > 3 mg/dL). In nosocomial SBP, use of the antibiotics recommended above can be associated with unacceptable failure rates because resistance to third-generation cephalosporins (23%-44%) and quinolones (38%-50%) are increasingly reported.

Notably, the incidence of SBP causing by with gram-positive and resistant bacteria (mainly ESBL-producing
Diagnosis paracentesis

- Cell count, protein, albumin
- C/S (10 mL ascites in hemo C/S bottle)

PMN ≥ 250 /mm³

- ATB is recommended, while awaiting culture result
- IV albumin for high risk patients

PMN < 250 /mm³

- C/S negative
- CNNA
- Treat as SBP
- Morbidity and mortality
- Approximately SBP
- Approximately 35% turn to SBP later

- C/S positive
- SBP
- C/S: Multiple organisms
- Secondary peritonitis should be suspected

- C/S: Multiple organisms
- MNB
- Poly microbial bacterascites

FU paracentesis is recommended

- FU paracentesis is recommended
- Low morbidity
- Majority from traumatic tap (bowel entry)
- Clinical FU ± ATB is recommended

Radiological ± surgical evaluations

Figure 2  Algorithm for the management of cirrhotic patients with suspicious for ascitic fluid infection (adapted from Bonnel et al[1]. Clin Gastroenterol Hepatol 2011; 9: 712. With permission). PMN: Polymorphonuclear cells; SBP: Spontaneous bacterial peritonitis; ATB: Antibiotics; CNNA: Culture-negative neutrocytic ascites; MNB: Monobacterial non-neutrocytic bacterascites; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; ALP: Alkaline phosphatase; ULN: Upper limit of normal; FU: Follow-up; C/S: Culture.

bacteria and multi-resistant gram-positive bacteria such as Enterococci or MRSA) has been increasingly reported in the healthcare associated and especially in nosocomial settings[37,57]. In patients with typical presentation and clinical improvement after ATB, a repeat of paracentesis is not necessary to assess for resolution of SBP[1,37,40,41]. However, in cases with questionable diagnosis or in those who did not satisfactorily improve with ATB, repeated paracentesis should be performed to document the response of treatment[37,40]. If the PMN count does not reduce by at least 25% after 2 d of ATB, changing treatment and/or reevaluation for other possible cause(s) of symptoms should be considered[37,59].

Renal impairment develops in 30%-40% of SBP cases and is a strong predictor of death during hospitalization[38,40,60]. The use of intravenous albumin (1.5 g/kg within 6 h of SBP diagnosis followed by 1 g/kg on day 3) in conjunction with intravenous (IV) antibiotic was found to reduce the incidence of renal impairment from 33% to 10% and mortality from 29% to 10%[61]. Notably, albumin infusion was particularly effective in patients with baseline serum creatinine ≥ 1 mg/dL, blood urea nitrogen ≥ 30 mg/dL or bilirubin ≥ 4 mg/dL[39,61]. Unfortunately, albumin infusion in high-risk SBP has been underutilized, even in the United States, with > 50% of cases did not follow the guidelines[62]. It is unclear whether crystalloids or artificial colloids could replace albumin in this setting[39,41,63].

Prophylaxis of SBP

After recovering from SBP, the rate of recurrence is around 43% at 6 mo and 69% at 1 year[46]. Therefore, secondary prophylaxis of SBP should be given indefinitely or until LT[37,40,61,64]. Intermittent dosing of prophylactic ATB may select resistant flora, thus daily dosing is preferred[37,40].

Primary prophylaxis of SBP is justified for patients with high risk for developing SBP. A meta-analysis of ATB prophylaxis in cirrhotic patients with GI hemorrhage (5 RCT; n = 534) revealed 32% reduction of infections including SBP and/or bacteremia (P < 0.001) and 9% increase in survival (P = 0.004)[28]. Further, a subsequent meta-analysis of 8 oral antibiotic trials (n = 647) demonstrated 72% reduction in mortality at 3 mo; only 6 patients were additionally treated in order to prevent another death[65]. Oral norfloxacin is often utilized for primary prophylaxis in most settings, however IV ceftriaxone has been shown to be more effective than oral norfloxacin in patients with particularly advanced cirrhosis[66] (Table 4).

In cirrhotic patients with low ascitic fluid protein < 1.5 g/dL, the risk of developing a first episode of SBP is 13%-45% at 1 year[32,39]. However, several studies evaluating primary prophylaxis of SBP with norfloxacin in this setting yielded heterogeneous results[69]. Notably, a well-designed, randomized, controlled trial conducted in patients with severe liver disease and ascites protein < 1.5 g/dL without prior SBP demonstrated that norfloxacin (400 mg/d) reduced the development of SBP (from 61% to 7%) and improved survival at 1 year (from 48% to 60%)[67]. Notably, primary prophylactic ATB for SBP should be considered only for selected patients with
advanced cirrhosis and ascitic fluid protein < 1.5 g/dL since more liberal use of these ATB in long-term would lead to subsequent infection by resistant bacteria as well as *Clostridium difficile*-associated diarrhea (Table 4).

### Table 4 Vaccinations and other preventive measures for bacterial infections in patients with cirrhosis

| Avoidance                                                                 | Recommended yearly for all patients with chronic liver disease |
|--------------------------------------------------------------------------|---------------------------------------------------------------|
| Raw/uncooked foods, especially seafood                                   | Recommended for all cirrhotic patient                        |
| Close contact to at-risk animals or sick people                          | Booster dose after 3-5 yr                                     |
| Wound exposure to flood or seawater                                      |                                                               |
| Vaccination[70]                                                          |                                                               |
| Influenza                                                                |                                                               |
| Pneumococcal (polysaccharide)                                            |                                                               |
| Hepatitis A                                                              | Recommended for all non-immune, cirrhotic patient, 2 injections 6-12 mo apart |
| Hepatitis B                                                              | Recommended for all cirrhotic patient without serological markers of HBV (e.g., negative HBsAg, anti-HBs, and anti-HBc antibodies) |
| Therapeutic interventions for infection[32,41]                           | 3 injections (at month 0, 1 and 6)                            |
| Anti-HBs should be checked 1-2 mo after the last dose                    | Anti-HBs should be checked 1-2 mo after the last dose         |
| Patients with advanced cirrhosis should receive 1 dose of 40 μg/mL (Recombivax HB) administered on a 3-dose schedule or 2 doses of 20 μg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2 and 6 mo | |
| Other vaccines, e.g., Td, Tdap, MMR, varicella                         | Recommendations are as same as general adult population       |
| Prophylactic antibiotics                                                 |                                                               |
| Secondary prophylaxis for SBP[30,41]                                     | Recommended for all cirrhotic patients who recovered from SBP |
| Norfloraxin 400 mg PO daily                                              |                                                               |
| Primary prophylaxis in GI bleeding[16,41]                                | Recommended for all cirrhotic patients with GI hemorrhage    |
| Norfloraxin 400 mg PO twice daily or ceftriaxone 1 g IV daily for 7 d   |                                                               |
| Primary prophylaxis in patients with low ascitic fluid protein[23,32]   | IV ceftriazone is preferred, in patients with advanced cirrhosis as defined by the presence of at least two of the following: Ascites, severe malnutrition, encephalopathy or bilirubin > 3 mg/dl. |
| Prophylaxis before undergoing endoscopic and surgical procedures        | Alternatives: TMP/SMX 1 double-strength tablet or ciprofloxacin 500 mg PO daily |
| Prophylactic antibiotics are recommended for the moderate-high risk invasive endoscopic or surgical procedures (choice of antibiotics should be individualized) | Recommended for all cirrhotic patients with ascitic fluid protein < 1.5 g/dL and at least one of the following is present: Serum creatinine > 1.2 mg/dL, blood urea nitrogen > 25 mg/dL, serum sodium < 130 mEq/L or Child-Pugh > 9 points with bilirubin > 3 mg/dL. |
| Prophylactic antibiotics are not routinely recommended for diagnostic endoscopy, elective variceal band ligation or sclerotherapy, and abdominal paracentesis | |

HBV: Hepatitis B virus; SBP: Spontaneous bacterial peritonitis; Td: Tetanus-Diphteria; Tdap: Tetanus-Diphteria-Pertussis; MMR: Measles/Mumps/Rubella; GI: Gastrointestinal; TMP/SMX: Trimethoprim/sulfamethoxazole; PO: Per oral; IV: Intravenous.

### Consequences of bacterial infections in cirrhosis

Bacterial infections in cirrhosis are associated with poor outcomes (increased mortality about 4 folds).[47]. Both short- and long-term mortality rates of sepsis in cirrhotic patients are very high; 26%-44% of patients die within 1 mo after infection and another one-third die in 1 year.[4,47]. The clinical predictors of death during or following infection are advanced liver disease, nosocomial origin, gastrointestinal hemorrhage, encephalopathy, liver cancer, presence of shock and organ failure (especially renal failure).[4,47].

The suggested strategies for the management of cirrhotic patients with severe sepsis are discussed in depth in other articles[23,32,68,69]. Broad spectrum empirical ATB[70] and fluid resuscitation, with either colloids or colloids (albumin, gelatins or hydroxyethyl starches), should be promptly initiated and followed an early goal-directed therapy approach (stepwise emergent resuscitation with predefined goals to keep mean arterial pressure ≥ 65 mmHg, central venous pressure between 8-12 mmHg, central venous oxygen saturation ≥ 70% and urine output ≥ 0.5 mL/kg per hour)[23,32,68,69]. Resuscitation with crystalloids requires more fluid to attain the same targets and results in more edema, particularly in cirrhotic patients with hypoalbuminemia.[32,40]. The benefit of resuscitation with albumin in non-cirrhotic patients with sepsis has been reported[71]. However, the role of albumin infusion for sepsis other than from SBP in cirrhosis is still unclear. The RCT from Spain found beneficial effects on renal and circulatory functions with a potential benefit on survival[72]. Conversely, more recent RCT from France reported that albumin delayed the onset of renal failure, but did not significantly improve 3-mo renal failure and survival rates. Thus, pulmonary edema developed in 8% of patients in the albumin group[73]. Norepinephrine and dopamine have been considered as the first-choice vasopressor agents in patients with septic shock[23,32,68,69]. Cirrhotic patients with septic shock are often associated with vascular hyporeactivity to these vasopressor agents. Thus, inotropic drugs are not generally effective since they already present high cardiac outputs[23,32,68]. Relative adrenal insufficiency is common (51%-77%) in cirrhotic patients with septic shock, however the effects of corticosteroids on such patients' outcomes...
are unclear[23,32,68]. Therefore, stress dose corticosteroid is currently recommended only for patients with vasopressor-unresponsive septic shock[23,32,68]. Blood sugar should be maintained in the range of 140-180 mg/dL[69].

Acute kidney injury following infections develop in 27%-34% of patients with advanced cirrhosis[2,61,74,75], and is a strong predictor of death (40%-50% mortality)[47,74,75]. Risk factors for infection-induced renal failure include advanced liver disease[74,76], pre-existing kidney disease[76], hypovolemia or low cardiac output[42,75], unresolved infection[74] and not receiving prompt albumin infusion[61]. It should be noted that most studies that reported poor survival in patients with infection-induced renal failure have defined renal failure as a serum creatinine level of > 1.5 mg/dL. Recently, the International Ascites Club and the Acute Dialysis Quality Initiative group proposed that acute kidney injury (AKI) in cirrhosis should be redefined as an increase in serum creatinine level of 0.3 mg/dL in less than 48 h or a 50% increase in serum creatinine level from a stable baseline reading within the previous 6 mo, irrespective of the final serum creatinine level[77,78]. This new definition was then evaluated and found to accurately predict 30-d mortality in patients with cirrhosis and infection (10-fold higher among those with irreversible AKI than those without AKI)[79]. Renal failure during infection (without septic shock) that does not respond to albumin infusion is considered hepatorenal syndrome[80].

Bacterial infection can trigger a rapid deterioration of liver functions in patients with cirrhosis and it is one of the most common precipitating cause of ACLF, which represents > 30% of the cases[3,23,81]. The most common sites of bacterial infection are ascites and lungs[81]. Moreover, infections were the second most common cause of death at 28 d among patients with ACLF (28%), behind multiple organ failure without septic or hypovolemic shock (44%). However, there was no difference in 28 d mortality among ACLF patients with or without the bacterial infection at admission (37% and 33%, respectively)[81]. Independent predictors of poor survival in patients with bacterial infections and ACLF were presence of organ(s) failure, second infections, admission values of high MELD, low blood pressure, leukocytosis, and low albumin[83].

Pulmonary complications are commonly observed in cirrhotic patients with infections. Aspiration is common in encephalopathic patients. Acute respiratory distress syndrome is increasingly seen in cirrhosis that may develop is association with exaggerated SIRS in severe sepsis[84]. Prognosis of cirrhotic patients with respiratory failure is poor, with a mortality rate up to 33%-60%[69,85]. Additionally, sepsis-induced cytokines can further worsen pre-existing coagulation and platelet abnormalities in patients with cirrhosis[7,24].

Prevention measures
Preventive measures must be emphasized to all patients with cirrhosis and prophylactic ATB is suggested for those who are at high risk of developing infections (Table 4)[2]. Notably, antibiotic prophylaxis has been associated with the development of multi-drug resistant bacteria and C. difficile infection. Therefore it should be judiciously used in those patients with proper indications.

Active immunization against hepatitis A and B viruses, influenza and pneumococcus are recommended since these preventable infections carry accompanied by higher morbidity and mortality in patients with cirrhosis (Table 4)[86-88]. Both cellular and humoral immune responses are suboptimal in cirrhosis, particularly in the advanced stage, which can be associated with inadequate post-vaccination antibody response, as well as loss of immunogenicity in the long-term[86-88]. Therefore, it is important to address immunization needs in patients with chronic liver disease or compensated cirrhosis early on, when immunizations are most effective.

Although there is no clear recommendation whether we can safely utilize live and attenuated vaccines in patients with cirrhosis, inactivated or killed-type vaccinations are generally preferable[86-88]. The incidence and severity of Streptococcus pneumoniae infections are increased in patients with cirrhosis[89-92]. Pneumococcal vaccination is less effective in patients with cirrhosis, with a further decline in protective antibodies after LT[93]. It is therefore recommended with booster doses every 5 years[86-88]. Incidence of seasonal flu is not obviously increased in cirrhosis; however, influenza may precipitate liver decompensation[86,87,94]. Influenza vaccine is well-tolerated and effective in cirrhotic patients, despite a mildly decreased immunogenicity[95,96]. All other vaccinations recommended for general adult population are also indicated in patients with cirrhosis as the Centers for Disease Control and Prevention recommendation for adults[97].

Proton pump inhibitors and the risk of infections in cirrhosis
Proton pump inhibitors (PPIs) have been widely used in patients with cirrhosis (sometimes over-utilized)[98]. Patients with cirrhosis have high prevalence of gastroduodenal mucosal lesions[99,100] and are associated with increased mortality rate from peptic ulcer bleeding (adjusted OR = 3.3; 95%CI: 2.2-4.9)[101]. However, clear evidence for a protective role of PPIs in cirrhosis is limited.

A state of gastric acid suppression induced by PPIs, particularly in long-term users, is known to be associated with small bowel bacterial overgrowth, alteration of gut flora and reduction of gastrointestinal motility[102-104]. By these effects, PPIs may enhance BT and possibly increase the risk of various infections in patients with cirrhosis. In addition, impairment of neutrophil function caused by PPIs has also been reported[105-107]. There have been several studies, including case-control, retrospective and prospective cohorts, and meta-analyses, suggesting that PPIs are associated with increased risk of bacterial infections, such as SBP, bacteremia, Clostridium difficile-associated diarrhea, and enteric
infections, in patients with cirrhosis\textsuperscript{108-115}. However, the association between PPIs and infections in cirrhosis remains somewhat controversial since many studies have reported conflicting results\textsuperscript{116-118} (Table 5). Though randomized controlled studies are required to draw firm conclusions whether or not PPIs increase infections in cirrhosis, PPI should be used only if clinically indicated.

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| Ref. | Design | n | Results |
|------|--------|---|---------|
| Campbell et al\textsuperscript{108} | Case-control | 116 | NS for SBP (OR = 1.05; 95%CI: 0.43-2.57) |
| Bajaj et al\textsuperscript{109} | Case-control | 83230 | PPI use were significantly higher in those with CDAD (74% vs 31%, P = 0.0001) |
| Bajaj et al\textsuperscript{110} | Retrospective, propensity-matched | 1268 | † Serious infections (HR = 1.66; 95%CI: 1.31-2.12) |
| de Vos et al\textsuperscript{111} | Case-control | 102 | PPI were more frequently used in SBP patients than in controls, but did not influence prognosis of SBP |
| Min et al\textsuperscript{112} | Retrospective cohort | 1554 | † SBP (HR = 1.39; 95%CI: 1.057-1.843) |
| Manderfer et al\textsuperscript{113} | Retrospective | 607 | PPI neither predisposes to SBP (HR = 1.38; 95%CI: 0.63-3.01) or other infections (HR = 1.71; 95%CI: 0.85-3.44) |
| Terg et al\textsuperscript{114} | Prospective | 770 | PPI therapy was not associated with a higher risk of SBP and other infections |
| Merli et al\textsuperscript{115} | Cross-sectional | 400 | † Bacterial infections (OR = 2; 95%CI: 1.2-3.2) |
| O’Leary et al\textsuperscript{116} | Prospective | 188 | † Infections: CDAD and SBP (OR = 2.94; 95%CI: 1.39-6.20) |

NS: Not significance; SBP: Spontaneous bacterial peritonitis; PPI: Proton pump inhibitor; CDAD: Clostridium difficile associate disease.
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