Infections in Cirrhosis

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Abstract

Purpose of review Patients with cirrhosis are at high risk of developing serious infections. Bacterial infections remain the most common cause of morbidity and mortality in these patients. This review is focused on the prevalence of infections in those with cirrhosis, including multidrug-resistant (MDR) pathogens, pathogenesis of infection-related acute-on-chronic liver failure (ACLF), current treatment recommendations, and prophylactic strategies in patients with cirrhosis.

Recent findings Recent epidemiological studies have noted an emerging prevalence of MDR bacterial infections and associated with poor prognosis, and a high rate of treatment failure and mortality. Therefore, new recommendations on empirical antibiotic use based on epidemiological data have been developed in order to improve outcomes.

Summary Spontaneous bacterial peritonitis (SBP) and urinary tract infection (UTI) are the most frequent infections followed by pneumonia, cellulitis, and bacteremia, while pneumonia carries the highest risk of mortality. The incidence of MDR bacterial infections has been increasing, especially in healthcare-associated settings. Second infections that develop during hospitalization, multiple organ failures, and high MELD score are associated with poor survival. Preventive measures, early diagnosis, and adequate treatment of infections are essential key concepts in minimizing morbidity and mortality in patients with cirrhosis.

Introduction

Infections, predominantly bacterial in nature, are not uncommon in patients with cirrhosis and these are associated with high morbidity and mortality [1]. In these patients, infections are a consequence of multiple pathophysiological mechanisms such as gut dysbiosis, increased bacterial translocation,
portosystemic shunting, cirrhosis-associated immune dysfunction (CAID), liver dysfunction, and genetic factors [2, 3]. The most frequent infections are spontaneous bacterial peritonitis (SBP) and urinary tract infection (UTI) while pneumonia, cellulitis, and bacteremia are not uncommon [4]. Community-acquired bacterial infections account for about 30% of all infections followed by healthcare acquired in approximately 30% and nosocomial infections in 35–40% [5, 6]. Recent epidemiological data has shown that the incidence of multidrug-resistant (MDR) bacteria is increasing, especially in healthcare-associated settings [6, 7]. MDR bacteria-associated infections have the worst prognosis and are associated with higher rates of treatment failure, septic shock, and high mortality [4–6]. Preventive measures, early diagnosis, and adequate treatment of infections are potentially decreasing morbidity and mortality.

Epidemiology and MDR infections

Among hospitalized patients with cirrhosis, infections account for 25–35% of all admissions and this is 4–5-fold higher rate of infections than in those without cirrhosis [6, 8]. Bacteria remain the most common pathogens with a prevalence of about 25–46% in patients hospitalized for acute decompensated cirrhosis [9–11] which then increases the probability of death by approximately 4-fold, reaching 30% at 1 month and 63% at 1 year [12, 13]. Enterobacteriaceae and non-enterococcal streptococci are the major causes of spontaneous infection in cirrhosis [4, 5].

MDR organisms (MDROs) are pathogens which are resistant to at least one agent in ≥ 3 of the main antibiotic families, including β-lactams. Examples of MDROs are extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL), non-fermentable gram-negative bacilli such as Pseudomonas aeruginosa, Stenotrophomonas maltophilia or Acinetobacter baumannii, methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE) [4]. Nowadays, MDR infections are increasing not only in the hospitals but also in the communities [14•]. The prevalence of MDROs differs among various geographic regions and with higher rates in nosocomial (23–39%) and healthcare-associated settings (14–41%) rather than in community-acquired infections (0–16%) [4, 6, 7]. ESBL-producing Enterobacteriaceae are more predominant isolates in South Europe and Asia, while VRE infections are frequently encountered in the USA and Latin America [14•].

In the recent multicenter intercontinental prospective study “Global study” (2015–2016) of hospitalized patients with cirrhosis across the world (n = 1302), the most common infections were SBP (27%), UTI (22%), and pneumonia (19%). Nine hundred fifty-nine microorganisms were isolated (58% gram-negative, 38% gram-positive, 4% fungi). The global prevalence of MDR infection was 34%. Risk factors for MDROs were an infection in Asia (OR = 2.79) particularly in India, or in South America (OR = 2.23); the use of antibiotics within 3 months before hospitalization (OR = 1.92); the category of infection (nosocomial [OR = 2.65], healthcare-associated [OR = 1.62]); and the site of infection (pneumonia [OR = 3.20], UTI [OR = 2.48], skin/soft tissue infection [OR = 2.92]) [15•]. Further, MDR infections were associated with a lower rate of response to empirical antibiotic treatment (40 vs 68%; p < 0.001), higher incidence of shock (27
Pathogenesis of bacterial infections

Cirrhosis, being an immunomodulatory deficiency state, predisposes such patients to infections through multiple mechanisms (Fig. 1). Bacterial overgrowth and intestinal barrier dysfunction can result in bacterial translocation [18]. Genetic variants in those with cirrhosis have been noted to be associated with an increased risk and severity of infections. Multifactorial pathogenetic mechanisms can cause excessive inflammatory response and thus induce circulatory dysfunction, acute decompensation, and eventual development of acute-on-chronic liver failure (ACLF).

Gut microbiota and bacterial translocation

Intestinal bacterial overgrowth (IBO), common in patients with cirrhosis, could be a consequence of slow intestinal transit due to decreased bowel motility, low secretion of gastric acid and bile acids, and local intestinal immunological dysfunction. This can lead to gut barrier dysfunction and bacterial translocation into the systemic circulation. The ensuing excessive inflammatory response can trigger multiple organ failure.

[Diagram of the Pathogenesis of bacterial infections in cirrhosis]

Fig. 1. Pathogenesis of bacterial infections in cirrhosis. (Modified from [1, 4, 11, 16, 17]) IBO, intestinal bacterial overgrowth; RES, reticuloendothelial system; NO, nitric oxide; AKI, acute kidney injury; ACLF, acute on chronic liver failure; HE, hepatic encephalopathy; RAI, relative adrenal insufficiency; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome.
defects [19]. High production of nitric oxide (NO) inducing vasodilatation and portal hypertension may further facilitate bacterial overgrowth [18, 20–22]. IBO can then result in bacterial translocation (BT) and liver inflammation [4]. BT is defined as the migration of microorganisms or bacterial endotoxins from the intestinal lumen to the mesenteric lymph nodes or systemic circulation. The most common bacteria involved in BT are derived from the family of Enterobacteriaceae (E. coli, Klebsiella spp., etc.), Enterococci, and Streptococci spp. These multiple mechanisms can cause a wide range of clinical manifestations, including hemodynamic instability, high proinflammatory cytokine levels, development of severe or recurrent infections, ACLF, hepatic encephalopathy, and hepatorenal syndrome (HRS), and these associated with poor prognosis [18]. Data from 181 patients in The North American Consortium for Study of End-Stage Liver Disease (NACSELD) cohort showed that dysbiosis of the intestinal microbiota in hospitalized patients with cirrhosis (particularly changes in Proteobacteria constituents; e.g., Enterobacteriaceae, Campylobacteraeae, and Pasteurellaceae) associates with increased risk of extra-hepatic organ failure, ACLF, and death [23].

**Increased intestinal permeability**

In cirrhosis with portal hypertension, the microcirculation in the intestinal mucosa is disturbed with loosening of tight junctions (TJ) between epithelial cells resulting in impairment of mucosal integrity which can facilitate BT [21, 24]. Secreted mediators that limit the direct contact of intestinal bacteria with the epithelial surface and are shown to be deficient in cirrhosis include immunoglobulin A [25], biliary lipids [26], and antimicrobial peptides [4, 27]. This also results in impaired mucus secretion which then facilitates bacterial penetration [18].

**Genetic predisposition and immune dysfunction**

Cirrhosis is associated with an immunodeficiency state and the designated “cirrhosis-associated immunodeficiency dysfunction (CAID)” concept includes two entities: (1) immunodeficiency which affects both innate and adaptive immune systems and (2) a state of persistent but inadequate activation of immune system leading to production of proinflammatory cytokines and systemic inflammation. Pathogen-associated molecular patterns (PAMPs) from enteric bacterial organisms and damage-associated molecular patterns (DAMPs), originating from the host tissue upon injury, bring into pattern recognition and activation of immune cells causing systemic inflammation [16]. Further, genetic polymorphisms of immunity pathways may lead to variation in immune responses and infection susceptibilities. Genetic variations coding for pattern recognition receptors (PRR), especially NOD2 and TLR2 variants causing impairment of innate host defense mechanisms, have been associated with SBP susceptibility, and markers of impaired intestinal permeability with higher systemic inflammation in patients with cirrhosis [4, 28].

**Infection and ACLF**

In those with cirrhosis, ACLF, a unique condition, can evolve following bacterial infections and the presentation is characterized by acute hepatic
decompensation and multi-organ failure. A large multicenter prospective study of 1343 patients hospitalized from acute decompensation of cirrhosis “CANONIC study” (in the context of EASL-CLIF Consortium) established a definition and categorized grading which defines short-term mortality (ACLF grades 1–3, mortality 22% to 77%) [29, 30]. In this study, bacterial infection was the most common identifiable precipitating factor for ACLF (33%), followed by active alcoholism (25%). Among bacterial infections, SBP and pneumonia were the most frequent sites of infection associated with ACLF. Severity of infection, such as sepsis or septic shock, also correlated with ACLF. The presence or types of precipitating events were not related to mortality, but prognosis depended more on the numbers of organ failures (OFs). In this context, the presence of OFs assessed by the CLIF-SOFA or the CLIF-C OF scores was associated with 28-day and 90-day mortality and it has been suggested that ACLF grading be determined to assess mortality in hospitalized patients with cirrhosis and ACLF. During hospitalization, the majority of patients have been noted to achieve Grade 3 ACLF within the first week. Therefore, the next assessment, since admission, of ACLF grade at days 3–7 with a new scoring system “CLIF-C ACLF score” is suggested as it has a significantly higher predictive accuracy than MELD, MELD-Na, and Child-Pugh-Turcotte score at all main time points after ACLF diagnosis; it has a significantly higher area under the receiver operating curve (AUROC) for prediction of 28-day and 90-day mortality [30].

While again noting a spectrum of infections, a prospective multicenter study in 507 patients with cirrhosis hospitalized with an infection across the USA and Canada (NACSELD consortium database) [31, 32] has noted some differences when compared with the EASL-CLIF consortium. The most frequently encountered infections were UTI (28.5%) and SBP (22.5%) while other infections included spontaneous bacteremia (13.2%), skin/soft tissue (12.2%), respiratory (9.9%), miscellaneous (9.6%), and C. difficile (4.1%). Nosocomial infections, often due to drug-resistant organisms, were found as first infections in 15.8%, and were frequently related to in-hospital procedures, and the use of medications (antibiotics, proton pump inhibitor, or SBP prophylaxis). Most commonly, the infections were due to gram-positive organisms (32.9%), followed by gram-negative (26.8%), and fungi (17.6%); no organisms were isolated in 22.7% [32••]. Thus, the current epidemiological pattern is of the majority being non-SBP infections, domination by gram-positive organisms, and large proportion of nosocomial infections. In addition, second infections developed during hospitalization were encountered in 21.6% of the patients (UTI 32%, respiratory infections 25%, and SBP 12.5%), and were also associated with poor survival. Some of the hospitalized patients with bacterial infection developed OFs (1-OF 37%, 2-OFs 10%, and 3-OFs 10%). Poor predictors found to be associated with development of ACLF were nosocomial infections, high baseline MELD, low mean arterial pressure (MAP), and non-SBP infections. Independent predictors of poor 30-day survival were I-ACLF (a simple bedside tool, defined as ≥2 OFs: shock, grade III–IV HE, ventilation, renal replacement therapy), second infections, high admission MELD, high white blood cell count, and low albumin [32••]. Similar to the CANONIC study, the numbers of OFs were found to be an important predictor of overall survival in those with ACLF. In liver transplant–listed patients, in the NACSELD experience, there was a 42% risk of delisting/death within a 6-month period following
an episode of infection due to multiple organ failures, making it likely the main reason for delisting/death among liver transplant–listed patients [33].

**Spontaneous bacterial peritonitis**

### Clinical and prevalence

The prevalence of SBP in outpatients is 1.5–3.5% and ranges from 10 to 30% in hospitalized patients with cirrhosis [34]. Fifty percent of cases have evidence of SBP at the time of hospital admission while the rest are acquired during hospitalization [35]. Symptoms include abdominal pain, vomiting, and diarrhea and patients may also have signs of peritonitis or signs of systemic inflammation: fever, leukocytosis, tachycardia, or shock. SBP can be asymptomatic in about a third of the patients [36]. Therefore, diagnostic paracentesis should be performed in all patients with cirrhosis and ascites without delay at hospital admission and/or in patients with gastrointestinal bleeding, shock, signs of systemic inflammation, worsening of liver or renal function, and hepatic encephalopathy [37]. Hospital mortality after a first episode of SBP has ranged from 10 to 50% and 1-year mortality from 31 to 93% [38].

### Diagnosis

The diagnosis of SBP is defined by ascitic neutrophil count of $\geq 250$ cells/mm$^3$ with a positive ascitic fluid bacterial culture without the evidence of intra-abdominal, surgically treatable source of infection [39]. The methods for estimating neutrophil count include manual count by microscopy, automated count by flow cytometry, or leukocyte esterase reagent strips (LERS), although the last one is not recommended for rapid screening test due to low sensitivity (45%) [37, 40]. While a positive ascitic fluid culture is not essential for the diagnosis of SBP, ascitic and blood culture should still be performed before starting antibiotics as organisms can be isolated in 40–60% of cases [5, 8]. Levels of ascitic fluid lactoferrin (AFLAC) have been noted to be elevated in SBP. In a prospective study conducted at tertiary centers (218 ascites samples/148 patients) using a cut-off level of 242 ng/mL, the sensitivity and specificity for diagnosis of SBP were 95.5% and 97%, respectively [41]. Another prospective study from South Korea (182 patients) noted a sensitivity of 95.8% and specificity of 74.4% at a cut-off level of 51.4 ng/mL [42]; however, further validation studies are still needed for it to be recommended in clinical practice. Another newly established in situ hybridization method for detecting the phagocytized bacterial DNA in ascites from SBP patients ($n = 51$) demonstrated a sensitivity of 91% and specificity of 100%; the results were provided in a day [43].

Secondary peritonitis is another differential diagnosis of peritonitis that should be considered when multi-organisms are encountered on ascites culture, and also when there is growth of anaerobes, fungi, very high ascites neutrophil counts, or in those with inadequate response to therapy. Runyon’s criteria are as follows: $\geq 2$ ascitic parameters (ascitic glucose $< 50$ mg/dL, protein $> 10$ g/L, LDH $> \text{normal serum levels}$) are helpful in considering this entity and with a sensitivity of 67% and specificity of 90%. Prompt abdominal CT and early surgical consideration should be pursued [35, 39].
Management of SBP

Empirical antibiotic must be started immediately after the diagnosis of SBP and nephrotoxic drugs should be avoided. Choice of empirical antibiotic(s) depends on the type of infection, individual risk factors, and the bacterial epidemiology in a particular global region. For community-acquired SBP, the recommended first-line antibiotic treatment is a third-generation cephalosporins given intravenously for a duration of 5–7 days [37••]. For healthcare-associated and nosocomial SBP, piperacillin/tazobactams are recommended in areas with low prevalence of MDROs. Carbapenem is the antibiotic of choice in regions where there is a high prevalence of ESBL-producing Enterobacteriaceae, and it should be used in combination with glycopeptides or daptomycin or linezolid in areas with high prevalence of gram-positive MDR bacteria (Table 1). Extensive drug resistance (XDR) bacteria, defined by a non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pan-drug resistance (PDR) bacteria defined by a non-susceptibility to all agents in all antimicrobial categories [46], may require combination of antibiotics including highly nephrotoxic agents such as vancomycin or aminoglycosides where, if used, plasma levels need to be monitored. Prompt de-escalation based on bacterial susceptibility is highly recommended in order to minimize evolution of a resistant strain [37••]. Failure of treatment should be suspected if clinical symptoms worsen or there is inadequate reduction of leukocyte response (less than 25% of ascitic neutrophil count in 48 h).

Intravenous 20% albumin (1.5 g/kg at diagnosis of SBP followed by 1 g/kg on day 3), in combination with antibiotics, significantly reduced renal impairment (from 33 to 10%) and reduced mortality (from 29 to 10%). Albumin infusion is especially effective in patients with total bilirubin of > 4 mg/dL, blood urea nitrogen > 30 mg/dL, or serum creatinine > 1 mg/dL [44, 47].

Prophylaxis of SBP

Three high-risk groups of patients with cirrhosis should be considered for use of prophylaxis to prevent SBP and they include those with acute gastrointestinal bleeding, advanced cirrhosis with low protein ascites (primary prophylaxis), and previous history of SBP (secondary prophylaxis) (Table 2).

Gastrointestinal bleeding

Forty-five to 66% of patients with cirrhosis and with an upper gastrointestinal bleeding developed bacterial infection within 7 days of the bleeding episode [4, 51, 52]. Antibiotics administration can decrease the incidence of infection to 10–20% [51, 53], and has also been associated with a reduction in rebleeding rate, and improved survival [52]. Oral norfloxacin (400 mg/12 h for 7 days) is the gold standard prophylaxis; however, patients with advanced cirrhosis (≥ 2 of the following: ascites, severe malnutrition, encephalopathy, or jaundice) should receive intravenous ceftriaxone (1 g/day for 7 days). A randomized controlled trial (RCT) comparing oral norfloxacin and intravenous ceftriaxone in advanced cirrhosis with gastrointestinal hemorrhage showed that the probability of developing possible infections (33% vs 11%, p = 0.003), proven infections (26% vs 11%, p = 0.03), and spontaneous bacteremia/SBP (12% vs 2%, p = 0.03) is significantly higher in patients receiving oral norfloxacin [53].
| Type of infection                     | Common bacteria                                      | Recommended empirical antibiotics                                                                 | Nosocomialb and Healthcare-associated infectionsc |
|--------------------------------------|------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------|
| SBP and spontaneous bacteremia       | *E. coli*, *K. pneumoniae*, *S. pneumoniae*, *S. viridans* | First-line therapy: IV 3rd generation cephalosporins (e.g., cefotaxime, ceftriaxone) Other options: - IV ciprofloxacin or oral ofloxacin (in uncomplicated SBP)* - Piperacillin/tazobactam in high rates of bacterial resistance countries. | Low prevalence of MDR Piperacillin/tazobactam High prevalence of MDR Meropenem+/-glycopeptide# |
| Urinary tract infections             | *E. coli*, *K. pneumoniae*, *E. faecalis*, *E. faecium* | Uncomplicated infection:** Oral ciprofloxacin or co-trimoxazole Sepsis: IV 3rd generation cephalosporins or piperacillin/tazobactam | Uncomplicated infection: Fosfomycin or nitrofurantoin Sepsis: Low prevalence of MDR Piperacillin/tazobactam High prevalence of MDR Meropenem+/-glycopeptide# |
| Pneumonia                            | *S. pneumoniae*, *H. influenzae*, *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *S. aureus* | - Piperacillin/tazobactam or - Ceftriaxone + macrolide or - Levofloxacin or - Moxifloxacin | Low prevalence of MDR Piperacillin/tazobactam High prevalence of MDR Meropenem or ceftazidime + levofloxacin +/- glycopeptide or linezolid should be added in patients with risk factors for MRSA § |
| Skin and soft tissue infections       | *S. aureus*, *S. pyogenes*, *E. coli*, *K. pneumoniae*, *P. aeruginosa* | - Piperacillin/tazobactam or - 3rd generation cephalosporins + oxacillin | Meropenem or ceftazidime + oxacillin or glycopeptide# |

*SBP* Spontaneous bacterial peritonitis, IV intravenous, *MDR* Multidrug resistance, *MRSA* methicillin-resistant *Staphylococcus aureus*
*aCommunity-acquired infection defined as infection diagnosed within 48 hours of hospitalization and did not fulfill the criteria for HCA infection
*bNosocomial infection defined as infection diagnosed after more than 48 hours of hospital stay
*cHealthcare-associated (HCA) infection defined as infection diagnosed within 48 hours of hospitalization in patients with any of the following criteria: (1) had attended a hospital or a hemodialysis clinic, or had received intravenous chemotherapy during the 30 days before infection; or (2) were hospitalized for at least 2 days, or had undergone surgery during the 180 days before infection; or (3) had resided in a nursing home or a long-term care facility [45]
*dIn patients without prior exposure to quinolones, vomiting, shock, hepatic encephalopathy ≥ grade II, or serum creatinine > 3 mg/dL
**IV vancomycin or teicoplanin in areas with a high prevalence of MRSA and vancomycin-susceptible enterococci. Glycopeptides should be replaced by linezolid or daptomycin in areas with a high prevalence of vancomycin-resistant enterococci
§high risk for MRSA: ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.
Primary prophylaxis

Primary prophylaxis with norfloxacin 400 mg/day is recommended in patients with advanced cirrhosis (Child-Pugh score ≥ 9 and serum bilirubin ≥ 3 mg/dL) and low ascitic protein (< 1.5 g/dL) with either impaired renal function (serum creatinine ≥ 1.2 mg/dL or blood urea nitrogen ≥ 25 mg/dL) or hyponatremia (serum sodium ≤ 130 mEq/L). An RCT evaluated norfloxacin prophylaxis versus no intervention in high-risk patients of developing SBP and HRS, and noted that norfloxacin demonstrated improvement in the 3-month (94% vs 62%; p = 0.003) and 1-year survival (60% vs 48%; p = 0.05), and significantly reduced the 1-year probability of developing SBP (7% vs 61%; p < 0.001) and HRS (28% vs 41%; p = 0.02) [54]. In addition, ciprofloxacin 500 mg/day for 12 months has also been shown to improve 1-year survival (86% vs 66%; p < 0.04) [55].

Secondary prophylaxis

Secondary prophylaxis with norfloxacin 400 mg/day is advised in patients who had experienced an episode of SBP. In an RCT study performed in patients who had a previous episode of SBP, the long-term use of norfloxacin 400 mg/day reduced the 1-year probability of SBP recurrence from 68 to 20% [35, 56]. However, there is no clear recommendation on the duration of the prophylactic antibiotics, but ideally they should continue until liver transplantation (LT) or death. For those who are on rifaximin as a preventive intervention for recurrent hepatic encephalopathy, there is no recommendation on either primary or secondary prophylaxis of SBP. Prospective studies are necessary to evaluate the benefits and adverse effects of combined norfloxacin and rifaximin therapy [37••]. A downside of the long-term use of antibiotic prophylaxis is the emergence of resistant bacteria as noted in a prospective study which reported a higher prevalence of quinolone-resistant organisms in patients with cirrhosis receiving long-term norfloxacin prophylaxis (85% vs 47% receiving placebo; p = 0.0001) [6]. As of now, non-antibiotic prophylaxis (e.g., pre/probiotics, fecal microbiota transplantation) are undergoing investigation [14•].

Infections other than SBP

Urinary tract infection

UTI is a common bacterial infection and is the second most frequent infection after SBP and it accounts for 12–29% of infectious complications in decompensated cirrhosis [57]. Most of the isolated organisms (70–80%) are gram-negative bacteria such as E. coli and K. pneumonia. UTI can be asymptomatic and asymptomatic bacteriuria can also be encountered at high frequency. This could possibly be related to the frequently found residual urinary volume and vesical dysfunction in those with cirrhosis [58, 59].

Empirical antibiotics for community-acquired UTI in those with cirrhosis include intravenous third-generation cephalosporins or piperacillin/tazobactam if there is associated sepsis, and oral quinolones or trimethoprim-
sulfamethoxazole in uncomplicated UTI. Quinolones are not recommended as first-line treatment in those already on long-term norfloxacin prophylaxis [5] (Table 1). Several studies have found that nosocomial-acquired UTIs are associated with the presence of a urinary catheter around 63–75% [60, 61], other risks such as performance of urological procedure during admission are also associated with catheter-associated urinary tract infections (CAUTIs) (OR 1.17; 95%CI 1.11–1.22; p < 0.001) [62]. Common microorganisms isolated from CAUTIs are Enterococcus spp., E. coli, and P. aeruginosa which can be multidrug-resistant strains [63–65]. Additionally, in patients with cirrhosis, urinary catheterization during an admission was found associated more with MDR bacterial infections than non-MDR (32% vs 10%; p = 0.0001) [6]. This brings to the concern of catheter withdrawal as soon as possible for patients with cirrhosis in order to prevent CAUTIs.

### Pneumonia

In the hospitalized patients with cirrhosis, pneumonia carries the highest risk of mortality than other infections (HR = 2.95 (2.05–4.25)) [66]. Development of pneumonia is associated with a more severe form of community-acquired pneumonia (CAP), and may be associated with bacteremia, multi-lobar involvement, impaired consciousness, renal failure, and septic shock (overall mortality 7.4% vs 14.4%; p < 0.024) [67]. The risk of hospital-acquired pneumonia (HAP) is increased in the setting of hepatic encephalopathy and tracheal intubations. The most common pathogen for CAP pneumonia in those with cirrhosis is still Streptococcus pneumoniae, and similar to patients without cirrhosis. The predominant pathogens for HAP pneumonia are gram-negative bacilli and staphylococci, and which is also associated with high mortality [66, 68]. Empirical antibiotic use in cirrhosis with HAP pneumonia consists of an intravenous anti-pseudomonal cephalosporin or carbapenem, plus fluoroquinolone, and/or glycopeptide in high-risk patients for MRSA organisms (Table 1).

### Skin and soft tissue infection

The most common causative organisms for cellulitis are gram-positive bacteria (group A streptococci and Staphylococcus aureus) but gram-negative organisms (include E. coli, Klebsiella spp., P. aeruginosa, Aeromonas spp., Vibrio spp.) are also frequently reported in those with cirrhosis [69]. Necrotizing fasciitis caused by gram-negative bacteria tends to have concurrent bacteremia and initially present with septic shock [70]. High awareness for this manifestation is necessary for early surgical intervention in order to decrease morbidity and mortality. Empirical treatment is highly effective in community-acquired skin and soft tissue infection (SSSI), and in only one third with nosocomial SSSI [71]. Broad-spectrum antibiotics such as third-generation cephalosporins in combination with oxacillin, or piperacillin-tazobactam, should be promptly initiated. (Table 1).

### Fungal infections

Fungal infections can be another cause of treatment failure in patients with cirrhosis, especially in patients who are hospitalized in intensive care units [72] or with alcoholic hepatitis [73]. A study in hospitalized patients with cirrhosis and with a culture-positive infection during 2008–2014 (n = 185) noted an approximate 10% rate of fungal infections (8 (4.3%) combined bacterial and fungal
infection, and 11 (6%) fungal infection only). In the fungal infection group, spontaneous fungal peritonitis (SFP) with positive ascitic fluid culture was in 58% (n = 11/19) and fungemia (positive blood culture) without SFP was in 42% (n = 8/19). Most fungal infections were due to Candida spp., with C. albicans and nearly all Candida species were sensitive to amphotericin B, fluconazole, and voriconazole. Nine (47.4%) of the fungal infections were nosocomial infections and seven (36.8%) were healthcare-associated [74]. Mortality rates at 1 month and 6 months were 57.9% and 89.5%, respectively, which were significantly higher than those with bacterial infections. Fungal infections may occur with or without bacterial infections, but often are in those with impaired renal function (creatinine 1.6 vs 1.1 mg/dL; p = 0.034) and in healthcare-associated/nosocomial settings (100% vs 28.3%; p = 0.007). Ascitic fluid characteristics cannot distinguish SFP from SBP. Therefore, hemoculture, ascitic fluid culture for fungi, and empiric use of anti-fungal agents may be considered in those patients with cirrhosis and with nosocomial infections who are not responding to empirical antibiotics therapy [74]. In the NACSELD cohort (n = 2743), 134 patients (12.7% of infected patients) had evidence of fungal infections, all of which were nosocomial. The rate of fungal infections did not correlate with the etiology of cirrhosis. A multi-variable analysis noted that diabetes, acute kidney injury, ICU admission, and admission bacterial infection were associated with fungal infections (AUC = 0.82). Further, fungal infections were associated with ACLF and poor 30-day survival [75].

In patients with alcoholic hepatitis, the STOPAH trial demonstrated a higher rate of infections in prednisolone-treated patients than in the non-prednisolone group (13% vs 7%; p = 0.002) [76]. A recent meta-analysis of 1062 patients with severe alcoholic hepatitis (528 steroids treated) found no difference in infection rates between those treated and untreated with corticosteroids. However, fungal infections were higher among those who received corticosteroids (8/528 vs 1/534; p = 0.02) [77]. Invasive aspergillosis is another frequent complication seen in those with severe alcoholic hepatitis and carries high mortality; thus, systemic and periodic screening for opportunistic pathogens in such patients is recommended [78].

### Vaccination

Immunization against influenza, pneumococcus, and hepatitis A and B is recommended in patients with chronic liver disease. Inactivated or killed-type vaccinations are more preferable than live attenuated vaccinations in patients with cirrhosis [79]. Yearly inactivated influenza vaccination should be provided to every chronic liver disease patient due to its safety and effectiveness in protection.

Pneumonia accounts for 15–20% of infections in cirrhosis which also carries the highest 30- and 90-day mortality rate among other sources of infections [66]. The higher incidence and greater severity of pneumonia from Streptococcus pneumoniae in those with cirrhosis argues for the administration of pneumococcal vaccine to all adult (> 18 years old) patients with cirrhosis and with booster dose after 65 years old (Table 2).

Superimposed infection with hepatitis A or B in patients with chronic liver disease or cirrhosis is associated with increased morbidity and mortality [80, 81]. As immunogenicity to vaccinations has correlated inversely with the degree of hepatic decompensation [82], early immunization against hepatitis A and B prior to the
Table 2. Antibiotics prophylaxis and vaccinations in patients with cirrhosis. (Modified from [4, 48••, 49, 50])

| Prophylactic antibiotics | Recommendations |
|--------------------------|-----------------|
| Gastrointestinal bleeding | - Oral norfloxacin (400 mg/12 h for 7 days) |
| Primary prophylaxis of SBP: | - Patients with advanced cirrhosis (≥ 2 of the followings: ascites, malnutrition, encephalopathy or jaundice): IV ceftriaxone (1 g/day for 7 days) |
| Patients with low protein ascites (<1.5 g/dL) with advanced cirrhosis (Child-Pugh score ≥ 9 and serum bilirubin ≥ 3 mg/dL) and/or renal dysfunction (serum creatinine ≥ 1.2 mg/dL or BUN ≥ 25 mg/dL or serum sodium ≤ 130 mEq/L) | - Oral norfloxacin 400 mg/day or ciprofloxacin 500 mg/day until liver transplantation or death |
| Secondary prophylaxis of SBP | - Oral norfloxacin 400 mg/day until liver transplantation, death, resolution of ascites, or improvement into a compensated status |

Vaccinations

| Vaccinations | Recommended annually in all chronic liver disease patients |
|--------------|----------------------------------------------------------|
| Inactivated influenza | Recommended in all chronic liver disease patients |
| Pneumococcal vaccine (2 types) | - Administer 1 dose of PPSV23 at 19-64 years. |
| 1) 13-valent pneumococcal conjugate vaccine (PCV13) | - Administer 1 dose of PCV13 at ≥ 65 years old. This dose should be given at least 1 year before PPSV23. |
| 2) 23-valent pneumococcal polysaccharide vaccine (PPSV23) | - Administer 1 final dose of PPSV23 at ≥ 65 years old. This dose should be given at least 1 year after PCV13 and at least 5 years after the most recent dose of PPSV23. |
| Hepatitis A | Recommended for all chronic liver disease patients without serologic marker of HAV exposure (anti-HAV total) |
| - Administer 1 dose at 0 and 6–12 months (Havrix) Or 1 dose at 0 and 6–18 months (Vaqta) |
| Hepatitis B | Recommended for all chronic liver disease patients without serological markers of HBV (negative HBsAg, negative anti-HBs) |
| - In adult ≥ 20 years old : | |
| - Administer 1 dose of 10 μg/mL (Recombivax HB) at 0, 1, 6 months | |
| Or 1 dose of 20 μg/mL (Engerix-B) at 0, 1, 6 months | |
| Patients who cannot achieve seroconversion especially with more advanced cirrhosis may benefit from a high-dose or double-dose (40 μg) strategy. | |
| - 1 dose of 40 μg/mL (Recombivax HB) at 0, 1 and 6 months or | |
| - 2 doses of 20 μg/mL (Engerix-B) at 0, 1, 2 and 6 months | |
| Other vaccines (e.g. Td, Tdap, Zoster, HPV, MMR, varicella) | In chronic liver disease: recommended as same as general adult populations. |
| | In advanced cirrhosis: live attenuated vaccinations (e.g. Zoster, MMR, varicella) cannot yet be comfortably recommended. |

*IV intravenous, SBP spontaneous bacterial peritonitis, BUN blood urea nitrogen, HBV hepatitis B virus, Td tetanus-diphtheria, Tdap tetanus-diphtheria-pertussis, HPV human papilloma virus, MMR measles/mumps/rubella*
stage of hepatic decompensation is the optimal strategy. Hepatitis A vaccination in patients with decompensated cirrhosis had low seroconversion rates of about 49–66% [79, 83, 84], and thus this group of patients may benefit from post-vaccination serologic testing to evaluate response. Similarly, hepatitis B vaccination has been noted to be safe and with high seroconversion rates in patients with mild to moderate chronic liver disease, but has reduced efficacy in advanced chronic liver disease and in those who underwent liver transplantation [85–87]. Weight and age of the patients are also factors associated with the response rate. Thus, patients with chronic liver disease should be vaccinated before the onset of advanced fibrosis or cirrhosis if possible by conventional hepatitis B vaccination series. Although patients with cirrhosis may benefit from a high-dose or double-dose (40 μg) strategy (68% response rate) [88] than standard doses (16–20% response rate) [89–91], it remains controversial. As such, a double-dose vaccination is only recommended in other immunocompromised status (e.g., HIV, hemodialysis, on chemotherapy or hematopoietic stem-cell transplant) [50]. However, from our perspective, patients with cirrhosis who do not achieve seroconversion (Anti-HBs ≥ 10 mIU/mL) following a vaccination course may benefit from a second double-dose (40 μg) regimen (Table 2).

Disappointingly, vaccination rates in patients with cirrhosis remain suboptimal. A retrospective study of the trends in vaccination between 2004 and 2013 (n = 17,990) found only 19.8%, 7.7%, and 11.0% of patients receiving a pneumococcal, hepatitis A, and hepatitis B vaccine, respectively, in the same or the following year of cirrhosis diagnosis [92]. Adherence by patients and physicians to vaccination guidelines are of paramount importance in order to reduce morbidity and mortality from vaccine-preventable diseases in patients with cirrhosis.

Compliance with Ethical Standards

Conflict of Interest
Sirina Ekpanyapong, MD, declares that she has no conflict of interest.
K. Rajender Reddy, MD, declares that he has no conflict of interest for this work.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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