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REVIEW

Bacterial infections other than spontaneous bacterial peritonitis in cirrhosis

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Abstract

Cirrhotic patients are immunocompromised with a high risk of infection. Proinflammatory cytokines and hemodynamic circulation derangement further facilitate the development of serious consequences of infections. Other than spontaneous bacterial peritonitis, bacteremia and bacterial infections of other organ systems are frequently observed. Gram-negative enteric bacteria are the most common causative organism. Other bacterial infections, such as *enterococci*, *Vibrio spp.*, *Aeromonas spp.*, *Clostridium spp.*, *Listeria monocytogenes*, *Plesiomonas shigelloides* and *Mycobacterium tuberculosis* are more prevalent and more virulent. Generally, intravenous third generation cephalosporins are recommended as empirical antibiotic therapy. Increased incidences of gram-positive and drug-resistant organisms have been reported, particularly in hospital-acquired infections and in patients receiving quinolones prophylaxis. This review focuses upon epidemiology, microbiology, clinical features and treatment of infections in cirrhosis other than spontaneous bacterial peritonitis, including pathogen-specific and liver disease-specific issues.

Key words: Bacterial infection; Cirrhosis

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INTRODUCTION

Despite the advancement in medical care for patients with advanced liver disease in the past decades, bacterial infections remain very common and account for significant morbidity and mortality (approximately 30%) in these patients[1,2]. Cirrhosis is an immunocompromised state which predisposes the patient to a variety of infections[3]. Once infection occurs, the proinflammatory cytokines and hemodynamic circulation derangement further facilitate the development of serious consequences of infections such as septic shock, multiple organ failure and death[3]. Bacterial infections are commonly caused by gram-negative enteric bacteria; however, a number of uncommon pathogens are also more frequently observed and more virulent in cirrhotic patients. Moreover, these pathogens can present with various clinical syndromes which may be difficult to recognize. Appropriate preventive measurements have been shown to reduce the risk of overall bacterial infections. Early recognition and prompt

management are warranted in order to minimize their complications. The outline of bacterial infection in cirrhotic patients is shown in Figure 1.

EPIDEMIOLOGY

Bacterial infection is responsible for approximately 30%-50% of deaths in cirrhotic patients[1,3-5]. Compared to a 5%-7% infection rate reported in hospitalized patients in general, those hospitalized with cirrhosis have an infection rate of 32%-34%[6,7] and which may be up to 45% in those with gastrointestinal bleeding[8]. The most common bacterial infections are spontaneous bacterial peritonitis (SBP) (25%-31%), urinary tract infection (UTI) (20%-25%), pneumonia (15%-21%), bacteremia (12%) and soft tissue infection (11%)[7,9]. Approximately 75% of bacterial infections in patients with cirrhosis are caused by gram-negative bacteria, e.g. *Escherichia coli, Klebsiella spp.*, *Enterobacter spp.*, *P. aeruginosa, Vibrio spp.*, *Aeromonas spp.*, whereas gram positive comprise 20.2% and anaerobes only 3.2%[10]. However, in cirrhotic patients who had been hospitalized, received quinolones prophylaxis and had invasive procedures, the risk of gram-positive organisms is more frequently encountered (38%-70%)[7,11,12]. In addition, resistant organisms are isolated in up to 64% of hospital-acquired infection and are associated with poor outcomes[12].

PATHOGENESIS AND CONSEQUENCES OF INFECTION IN CIRRHOSIS

State of immune dysfunction in cirrhosis

Cirrhotic patients are in a multifactorial state of local and systemic immune dysfunction[3]. Porto-systemic shunting allows less bacteria and endotoxins to be cleared by the liver from the portal circulation[1]. Systemic reticuloendothelial system function is also significantly impaired[1,3,13]. Cirrhosis is associated with a decrease in bactericidal activity of phagocytic cells, an impaired opsonic activity and a reduction in complement and protein C levels[1,3,13]. In addition, immunodeficiency state can be further complicated by compelling factors such as skin/mucosal problems, malnutrition, alcohol intake and immunomodulatory therapy (Table 1).

Bacterial translocation

Bacterial translocation is defined as the migration of bacteria or bacterial products from the intestinal lumen to mesenteric lymph nodes and other extra-intestinal sites. It has been implicated as the key step in the pathogenesis of SBP and spontaneous bacteremia in cirrhotic patients. The mechanisms of bacterial translocation are complex and not yet completely understood. Immune dysfunction, intestinal bacterial overgrowth and altered intestinal permeability are hypothesized to contribute to the development of bacterial translocation[14]. Gram-negative enteric bacteria, enterococci and other streptococci have been reported to be the most adept at translocating to mesenteric lymph nodes. More recently, it has been linked to the development of the hyperdynamic circulatory state in cirrhosis, characterized by splanchnic and systemic vasodilatation, increased cardiac output and decreased arterial blood pressure[1]. An amplification of bacteria and their products can lead to activation of monocytes, lymphocytes and pro-inflammatory cytokines, which exacerbate the pre-existing hyperdynamic circulation in cirrhosis[1,14].

Systemic inflammatory response syndrome and sepsis in cirrhosis

Cirrhotic patients are prone to develop sepsis, septic shock, sepsis-induced organ failure and death[3,15]. In cirrhosis, bacterial infection is accompanied by an imbalanced cytokine response, which converts responses that are normally helpful against infections into excessive, detrimental inflammation[3,15]. The pathophysiology of the exaggerating inflammatory response in cirrhotic patients has been postulated. In the early stage of sepsis, bacteria and their products, particularly lipopolysaccharides, activate toll-like receptor-4, which induces the release of pro-inflammatory cytokines[5,15]. Nitric oxide (NO), a key mediator contributing to a circulation compromised in septic patients, is markedly released in infected cirrhotic patients[5,15].

A pre-existing hyperdynamic circulatory state predisposes devastating consequences from a sepsis-induced NO and cytokine storm which eventually leads to refractory hypotension, inadequate tissue perfusion, multiorgan failure and death[1,5,15]. Additional factors, such as relative adrenal insufficiency[16], beta-blockers[17], low levels of protein C and high-density lipoprotein, may further adversely complicate the course of sepsis in cirrhosis[3].

Clinical consequences and prognosis of infections in cirrhosis

Bacterial infection in cirrhotic patients is associated with poor clinical outcomes (up to 4-fold mortality)[2]. The mortality rate of sepsis in cirrhotic patients is approximately 26%-44%[2,13].

A recent analytical review of 11 987 cirrhotic patients suggested several clinical predictors of death after infection, such as advanced liver disease, presence of shock and/or organ failure (particularly kidneys), gastrointestinal bleeding, encephalopathy, hepatocellular carcinoma and nosocomial acquisition[2]. Patients who survived a significant episode of infection are still at high risk of death (up to 30%) within 1 year[2].

Acute renal dysfunction following infections has been observed in 27%-34% of patients with advanced cirrhosis[18-20]. Thus, it is a strong independent risk of death in these patients with a 40%-50% mortality rate[2,19,20]. Several risk factors for the development of renal failure in cirrhotic patients with bacterial infections include advanced liver disease[19-21], pre-existing renal insufficiency[21], inadequate circulatory volume[19], low baseline cardiac output[22], lack of resolution of infection[20] and not receiving early albumin infusion[18]. Renal failure that does not respond to albumin infusion in the setting of

Table 1 Immune dysfunction in cirrhotic patients

Natural barriers	Fragile, thin and/or edematous skin
	Alteration of gastrointestinal motility, mucosal permeability and bacterial flora
	↑ Gastrointestinal mucosal ulcerations
Hepatic RES activity	Portosystemic shunting
	Kupffer cells – ↓ number, impaired function
Cellular defense mechanisms	RES – ↓ activation, ↓ chemotaxis, ↓ phagocytosis, ↓ production of pro-inflammatory cytokines
	PMN – ↓ lifespan, ↓ intracellular killing activity, ↓ phagocytosis, ↓ chemotaxis
Serum factors	↓ Complement levels (C3, C4, CH50)
	↓ Opsonic activity
	↓ Protein C activity
Iatrogenic and treatment-related factors	Invasive procedure and catheters
	Medications: immunosuppressive agents, proton pump inhibitors
Other compelling factors	Malnutrition
	Alcohol drinking

RES: Reticuloendothelial system; PMN: Polymorphonuclear neutrophil.

bacterial infection without septic shock was recently considered hepatorenal syndrome (HRS)[23]. Sepsis-related renal failure and HRS can persistently progress despite the resolution of infection, thus needing further special interventions[18].

Bacterial infections can precipitate a rapid deterioration of liver functions and encephalopathy which is associated with poor short-term prognosis[1,15]. Pulmonary complications are increasingly common in cirrhotic patients. Acute respiratory distress syndrome may develop as a result of exaggerated systemic inflammatory response syndrome (SIRS) in severe sepsis which leads to higher mortality[24]. Aspiration is common in encephalopathic patients. Prognosis of cirrhotic patients who were intubated were dismal, with a 33%-60% mortality rate[25].

The effects of sepsis on coagulation cascades are more complex in cirrhosis. Patients with advanced cirrhosis are associated with thrombocytopenia and low clotting factors (e.g. factor V, Ⅶ, X and prothrombin). The consumption of coagulation factors and the enhanced fibrinolytic activity by sepsis-induced inflammatory cytokines leads to a further worsening of pre-existing coagulation and platelet abnormalities[5,15,26]. Presence of bacterial infection in patients with variceal bleeding is independently associated with failure to control and early recurrent bleeding[27]. Antibiotic prophylaxis in cirrhotic patients with variceal hemorrhage decreases infections, rebleeding and mortality[28] (Figure 2).

ORGAN-SPECIFIC INFECTIONS

Urinary tract infection

UTI is the second most common bacterial infection in cirrhosis after SBP[7]. In cirrhotic patients, the prevalence of bacterinuria is 16%-18%, which is twice as frequent as matched controls[29,30] and which may be attributed to increased bladder post-void residual volume in cirrhotic patients[31]. Notably, bacterinuria is not consistently associated with an increased risk of sepsis[29]. Several predisposing factors for UTI have been suggested, including advanced liver disease, urinary catheter and female sex[13,29,30]. As in non-cirrhotic individuals, the common pathogens are gram-negative bacilli and coagulase-negative staphylococcus[29,30]. Treatment with cephalosporins or quinolones is generally effective. Notably, a high prevalence of resistant bacteria has recently been reported, not only in hospital-acquired (69%), but also community-acquired UTI (22%)[32].

Pneumonia

Pulmonary infections are common in cirrhotic patients. The causative organisms of community-acquired pneumonia appear to be the same as in general adults[33]. Compared to non-cirrhotic, cirrhotic patients with community-acquired pneumonia are more frequently associated with bacteremia, multi-lobar involvement, impaired consciousness, renal failure, septic shock and death (overall mortality 7.4% *vs* 14.4%, $P < 0.024$)[34]. Excessive alcohol intake can further impair pulmonary host defense and increase the risk of oropharyngeal aspiration[35]. Careful monitoring and empirical treatment with intravenous beta-lactams plus macrolides or intravenous antipneumococcal quinolones is recommended[33]. The risk of hospital-acquired pneumonia is increased in cirrhosis, particularly in the setting of gastrointestinal hemorrhage, tracheal intubation and encephalopathy. Thus, it is associated with resistant organisms and dreadful outcomes[7,12]. Empirical antibiotics for cirrhotic patients with hospital-acquired pneumonia should include intravenous antipseudomonal cephalosporins, carbapenams or piperacillin-tazobactam, plus ciprofloxacin or levofloxacin, and vancomycin or linezolid[36].

Bacteremia

Bacteremia without particular organ-specific source is increasingly common in cirrhosis and can be arbitrarily divided into 2 entities: (1) primary or spontaneous bacteremia; and (2) secondary bacteremia. True primary bacteremia shares the same initial step of pathogenesis as SBP, whereby bacteria flora in the gut lumen translocate into

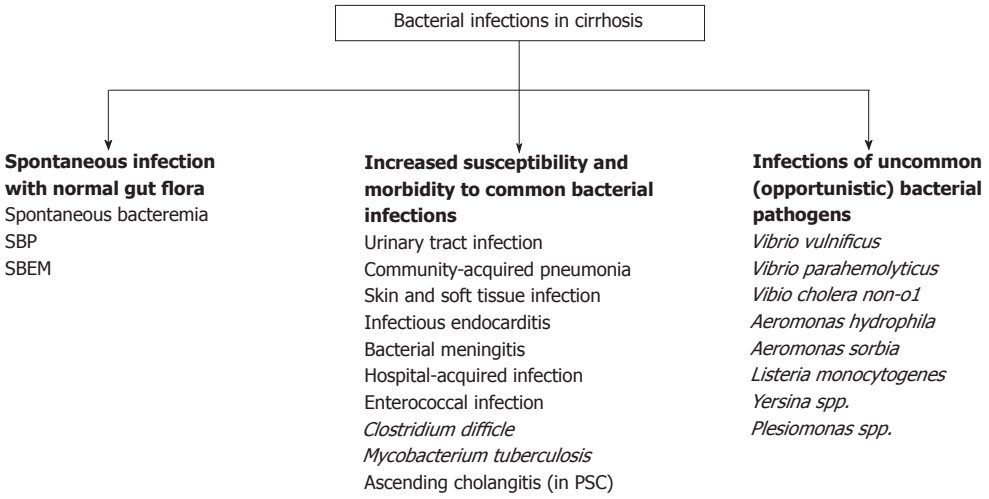

Figure 1 The outline of bacterial infection in cirrhotic patients. SBP: Spontaneous bacterial peritonitis; SBEM: Spontaneous bacterial empyema; PSC: Primary sclerosing cholangitis.

the bloodstream. It is generally encountered in the setting of advanced cirrhosis and is often caused by gram-negative enteric bacilli, enterococci and *Streptococcus spp.*[7,11].

Secondary bacteremia, in which pathogens come from an exogenous source, can be observed either in community-acquired settings, such as gastrointestinal bleeding, wound exposure and food-borne, or in healthcare-associated settings, such as transarterial chemoembolization[37], transjugular intrahepatic portosystemic shunt[38], therapeutic endoscopy[39] and intravenous catheters[7]. The causative organisms are largely dependent on the origin of bacteremia. Bacteremia and/or SBP occur in 17%-45% of patients following an episode of gastrointestinal bleeding[8] and, like those patients with primary bacteremia, the causative organisms are typically gram-negative enteric bacteria. Bacteremia associated with invasive procedures is commonly caused by *S. aureus* and *S. epidermidis*[7,11]. Notably, methicillin-resistant *S. aureus* (MRSA) was reported in up to 35% of nosocomial bacteremia in cirrhotic patients[11]. Although relatively uncommon, several case reports and case series have reported cases of severe community-acquired bacteremia in cirrhotic patients caused by *Vibrio spp.* and *Aeromonas spp.* without obviously localized infection[40-45]. Previous exposure to flood or seawater, or prior consumption of uncooked seafood may be a clue for diagnosis[40-45]. Intravenous third-generation cephalosporins and/or fluoroquinolones are commonly used as an empirical therapy for community-acquired bacteremia without other risk for specific or resistant pathogens. The use of antipseudomonal and glycopeptide antibiotics should be considered for hospital-acquired infection depending on the local pattern of resistant bacteria.

Spontaneous bacterial empyema

Spontaneous bacterial empyema (SBEM) is the infection of a pre-existing hydrothorax in which pneumonia has been excluded. It has been reported to be present in 10%-20% of hospitalized patients with hepatic hydrothorax[46-48]. The pathogenesis of SBEM, SBP and spontaneous bacteremia are closely interconnected; thus, they share the same types of common pathogens. SBEM can occur either with SBP, through transdiaphragmatic spread, or without SBP, through hematogenous spread (53% associated with SBP, 30% had no clinical ascites and 17% had non-infected ascites)[49]. Therefore, thoracocentesis should be performed when an infection is suspected in cirrhotic patients with ascites and hydrothorax, particularly in those with non-infected ascites. Risk factors for developing SBEM are the presence of SBP, low pleural fluid protein and complement levels, and advanced liver disease[47,50].

The criteria for diagnosis are: (1) pleural fluid polymorphonuclear neutrophil (PMN) $\geqslant$ 250 cell/mm^3 with a positive culture or $\geqslant$ 500 cells/mm^3 with a negative culture; and (2) exclusion of parapneumonic infection[46,49]. Notably, culture of pleural fluid should be performed by inoculating 10 mL of pleural fluid into a blood culture bottle at bedside, which is the same as the standard recommendation for SBP[49,51]. Analysis of pleural fluid by reagent strip for leukocyte esterase might be a rapid and easy-to-use tool for the detection of SBEM[52]. Hospital mortality has been reported as 20%-40% in cirrhotic patients with SBEM[46-48]. Treatment with intravenous third-generation cephalosporin should be initiated immediately when pleural fluid PMN $\geqslant$ 250 cell/mm^3 while awaiting culture result. In cases with slow clinical recovery, a repeat thoracocentesis is suggested to document the treatment response. Chest tube drainage can be harmful in cirrhotic patients with hepatic hydrothorax and should not be used in the treatment of SBEM[49].

Skin and soft tissue infection

Several reasons can contribute to an increased risk of skin and soft tissue infection (SSTI) in cirrhotic patients, such as fragile, thin and edematous skin, poor hygiene

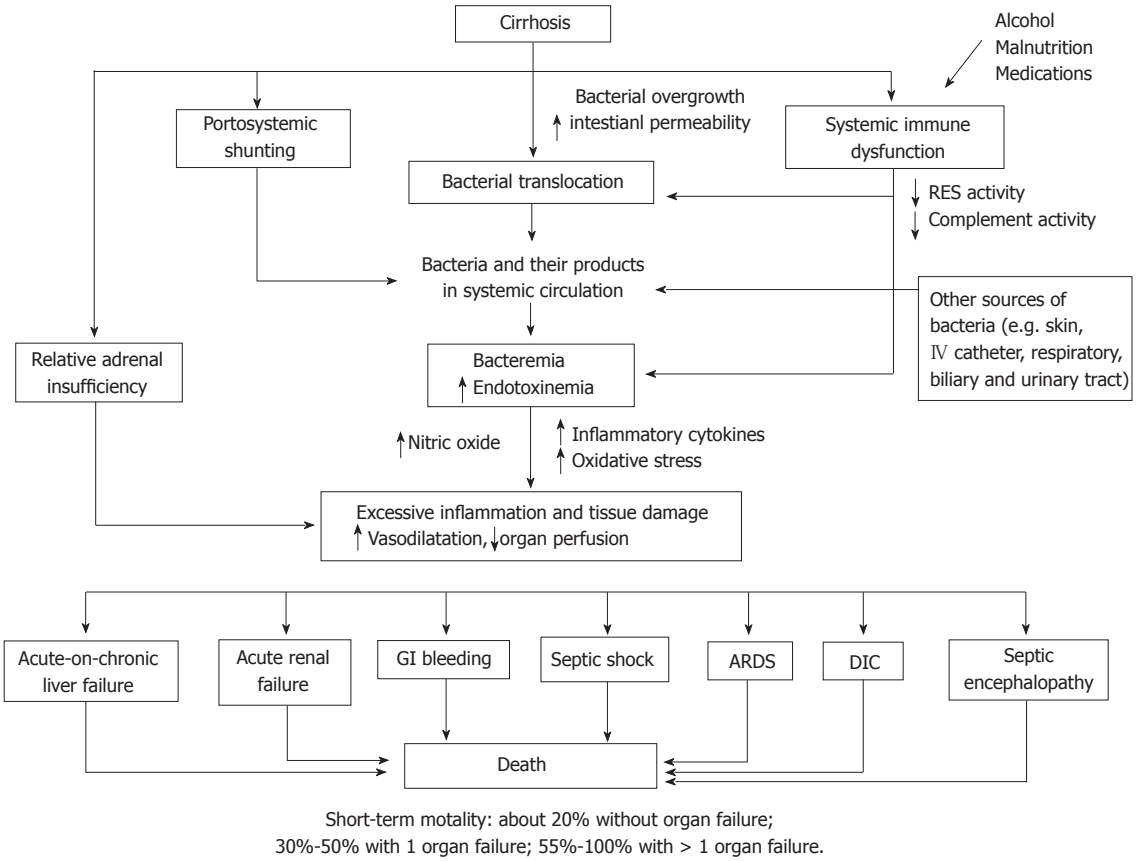

Figure 2 Proposed pathogenesis and consequences of bacterial infections in cirrhotic patients. GI: Gastroenterology; RES: Reticuloendothelial system; ARDS: Acute respiratory distress syndrome; DIC: Disseminated intravascular coagulation.

standards, malnutrition, frequent hospitalization and invasive procedures. Antibiotic therapy is generally effective for mild cellulitis; however, it is associated with a considerable recurrence rate of 21%[53]. Attention must be paid to severe cellulitis and necrotizing fasciitis that are increasingly reported and often carry a high mortality rate in cirrhotic patients, ranging from 6%-76% depending on the pathogens, extension of disease, presence of hemorrhagic bullae, severity of cirrhosis and management[54-56].

The common causative organisms are gram-positive cocci (*S. aureus,* beta-hemolytic streptococci) and gram-negative enteric bacteria (occasionally polymicrobial)[54]. Remarkably, the incidence of gram-negative pathogens, such as *E. coli, Klebsiella spp., P. aeruginosa, Aeromonas spp., Vibrio spp*., has evidently increased in cirrhotic patients[42-45,55-57]. Unlike the general population, necrotizing fasciitis in cirrhotic patients sometimes develops without an obvious portal of entry in the extremities, thereby suggesting a potential alternative pathway of bacterial translocation and bacteremia leading to SSTI[55,56]. In addition, approximately two thirds of cirrhotic patients with necrotizing fasciitis caused by gram-negative pathogens had concurrent bacteremia and/or initially presented with septic shock[55]. The presence of severe pain and/or SIRS out of proportion to the local wound appearance raises the possibility of necrotizing fasciitis. Careful evaluation with a high index of suspicion is mandatory since an early surgical intervention has been shown to reduce morbidity and mortality in necrotizing fasciitis[54-56,58].

There is no specific guideline for the empirical antibiotic therapy for severe SSTI in cirrhosis. Given a high morbidity/mortality and wide-range of possible pathogens in cirrhotic individuals, gram-stained smears from pus and/or infected tissue should be immediately obtained and broad-spectrum antibiotics should be prompt utilized, such as third or fourth generation cephalosporins, amoxicillin-clavulanate, piperacillin-tazobactam and carbapenams. Combination therapy with fluoroquinolones or cloxacillin may be considered if a gram-negative or gram-positive pathogen is highly suspicious, respectively. Empirical treatment is effective in approximately 80% of community-acquired SSTI. Importantly, it is effective in only half of cirrhotic patients with nosocomial SSTI, which is largely due to a higher incidence of MRSA and *P. aeruginosa*[32].

Endocarditis

Infectious endocarditis (IE) classically occurs in patients with underlying valvular heart disease and prosthetic valves. Interestingly, a recent review of 316 IE cases found that approximately 10% of patients had underlying liver cirrhosis[59]. IE in cirrhotic patients was often

observed in those patients who were hospitalized and/or had invasive procedures[7,59]. The common causative organisms are gram-positive such as Streptococci (*S. pyogenes, S. agalactiae, S. viridans), S. aureus, S epidemidis* and enterococci[59,60]. A minimum of 4-6 wk of antibiotic therapy is recommended. Caution should be taken since the majority of IE cases in cirrhosis are health-care associated and therefore the incidence of drug-resistant pathogens is considerably increased[59,60]. The mortality rate of cirrhotic patients with IE is high (27%-51%) despite treatment, especially in those patients with advanced cirrhosis and staphylococcal infection[59,60].

Meningitis

The incidence of community-acquired bacterial meningitis in the general population is estimated around 5/100 000 adults per year; the majority of these caused by *S. pneumoniae* and *N. meningitides*[61]. Several reports suggested that the incidence and the virulence of bacterial meningitis are substantially increased (up to 10-fold) in cirrhotic patients; thus, mortality rate in these patients is approximately 50%-63% and even higher in older patients and those with alcohol-related cirrhosis[62-65]. Cirrhotic patients, compared to non-cirrhotic patients, had a longer duration of symptoms before the time of diagnosis (> 4 d: 32% *vs* 16%, respectively), less obvious physical signs (nuchal rigidity: 75% *vs* 92%, respectively); greater incidence of relapse (18% *vs* 1%, respectively), and increasing incidence of *E. coli* and *L. monocytogenes*[62,64].

In the clinical setting of fever with headache and/or alteration of conscious in cirrhotic patients, the possibility of a central nervous system infection should not be overlooked. Neurological examinations are sometimes limited and ambiguous, particularly in the presence of concurrent hepatic encephalopathy. Prompt empirical central nervous system-dosed antibiotics and an appropriate diagnostic approach are key to decrease morbidity and mortality in patients with bacterial meningitis[66]. A combination of vancomycin, third generation cephalosporins and ampicillin is recommended for empirical therapy in cirrhotic patients with bacterial meningitis[66].

PATHOGENS AND THEIR CLINICAL FEATURES

Vibrio spp.

V. vulnificus is a gram-negative, motile, marine bacterium that is endemic in warm coastal water[42]. Exposure to this organism usually occurs through the ingestion of seafood (e.g. shellfish, raw oyster) or inoculation *via* traumatic injury in marine environments. *V. vulnificus* infection generally occurs in patients who are elderly or those who are compromised with comorbidities, especially cirrhosis[42,57]. It typically manifests as three clinical features: (1) SSTI: direct inoculation of organism causing wound infection or cellulitis, which generally occurs within 24-48 h after exposure. The lesions are typically painful and associated with rapid evolution to the hemorrhagic bullae and then to necrotic ulcers, necrotizing fasciitis and secondary bacteremia; (2) primary sepsis; and (3) gastrointestinal illnesses characterized by abdominal pain, diarrhea, and vomiting[42,67]. The virulence of *V. vulnificus* is linked to the availability of iron and its secreting toxin.

Infections from other marine *Vibrios* also increasingly occur and are associated with poor outcomes in cirrhotic patients[10,58,67-69]. *V. cholera* non-o1 infection occurs in endemic areas, such as the United States, Mexico, East and Southeast Asia[10,58,67-69]. The route of acquisition and clinical features can mimic *V. vulnificus* infection. *V. parahemolyticus* generally causes watery diarrhea, abdominal pain and vomiting.

An early recognition, aggressive treatment of shock and surgical management of SSTI is crucial. Most isolated marine *Vibrios* are susceptible to third generation cephalosporins, tetracyclines and fluoroquinolones. The combination of cefotaxime and minocycline or fluoroquinolones has been shown to have a synergistic effect against marine Vibrios[10,67,69].

Aeromonas spp.

Aeromonas spp. is a gram-negative, facultative anaerobic bacteria that is ubiquitous in fresh and brackish water. Infections are more frequently encountered in immunocompromised patients, particularly cirrhosis and malignancy[44,45,67,70-72]. *A. hydrophila* and *A. veronii* biovar *sobria* are the most often isolated species from symptomatic patients. Aeromonas bacteremia in cirrhotic patients tends to be monomicrobial, whereas polymicrobial bacteremia (frequently combined with *E. coli* or *Klebsiella spp.*) is commonly seen in patients with malignancy[44,72]. Drug of choice for empirical treatment is either intravenous carbapenams or a combination of intravenous third generation cephalosporins and aminoglycosides or fluoroquinolones.

Mycobacterial tuberculosis

The incidence and virulence of tuberculosis (TB) are increased in cirrhotic patients. Extrapulmonary involvement is more frequently observed (11%-31%)[73,74]. TB peritonitis possibly mimics SBP. TB peritonitis occurs in less advanced cirrhosis and its ascites has a lower white blood cell count, higher proportion of mononuclear cells, higher levels of protein and adenosine deaminase (ADA)[75]. More than 50% of TB peritonitis cases in the United States had underlying cirrhosis, especially alcohol-related[76]. Though ADA level is generally helpful in the detection of TB peritonitis, the presence of cirrhosis may reduce its sensitivity to 30%[76-78]. Laparoscopic biopsy sometimes is required for definitive diagnosis by revealing multiple whitish nodules scattered over the peritoneum, lymphocytic inflammation with granulomas and/or acid-fast organisms on the histopathological examination[77,79]. Patients with TB and cirrhosis often respond well to anti-TB treatment but are associated with more treatment-related hepatotoxicity incidence[73,77].

Table 2 Individual pathogens and their clinical manifestations in cirrhotic patients

Pathogens	Common clinical features	Key points
E.coli, Klebsiella spp. Enterobacter spp. and other gram-negative enteric bacteria[6,7,9,12,13]	SBP, bacteremia, UTI, biliary tract infection, meningitis	↑ Incidence of resistant organisms in hospital-acquired infection and in patients taking prophylactic quinolones
Plesiomonas shigelloides [10,81,99]	Septicemia, diarrhea, SBP, meningitis, SSTI	↑ Incidence in hemochromatosis Risk factors: contaminated food and water
Vibrio spp. (*V. vulnificus, non-o1 V. cholera, V. parahemolyticus*)[10,42,43,57,81]	SSTI, bacteremia, gastroenteritis	↑ Incidence in cirrhosis, particularly hemochromatosis ↑ Virulence; mortality 50%-60% in bacteremic form and about 24% for SSTI Risk factors: contaminated food and seawater
Aeromonas spp. (*A. hydrophilla, A. sobria*)[44,45,67,70-72]	Bacteremia, biliary tract infection, gastroenteritis, SBP, SSTI	↑ Incidence ↑ Virulence; mortality 20%-60% Risk factors: contaminated food and water
Yersinia spp. (*Y. enterocolitica, Y. pseodotuberculosis*)[10,81]	Bacteremia, SBP, hepatosplenic abscesses	↑ Incidence in hemochromatosis ↑ Virulence; mortality about 50% in bacteremic form
Campylobacter spp. (*C. jejuni, C. fetus*)[10,100]	Bacteremia, SBP	↑ Incidence Mortality about 10% in bacteremic form
Pateurella multocida[13, 101,102]	SSTI, bacteremia, arthritis, meningitis	↑ Incidence Mortality about 10% in bacteremic form Risk factors: cat and dog bites or scratches
Staphylocccus aureus[7,11,13]	Bacteremia, SSTI, endocarditis	↑ Incidence, particularly in those who are hospitalized and/or had invasive procedure ↑ Incidence of MRSA carriage and infection
Streptococcus pneumonia[94,95]	Bacteremia, pneumonia, SBP, SSTI, meningitis	↑ Incidence of invasive pneumococcal disease ↑ Virulence Vaccination is recommended
Streptococcus group B[103,104]	Bacteremia, SBP, SSTI, pneumonia	↑ Incidence Mortality 10%-25%
Clostridium difficile[80]	Antibiotic-associated diarrhea and colitis	↑ Incidence ↑ Virulence; mortality 14% Risk factors: hospitalization, antibiotics, proton pump inhibitors
Clostridium spp. (*C. perfringens, C. bifermentans, C. septicum*)[13,105]	Bacteremia, SSTI, peritonitis	↑ Incidence ↑ Virulence; mortality 54%-65%
Enterococcus spp (*E. faecium, E. faecalis, E. galinarum*)[7,11,59,106-109]	SBP, bacteremia, UTI, endocarditis, biliary tract infection	↑ Incidence, particularly in hospital-acquired infection and in patients taking prophylactic quinolones ↑ Virulence; mortality rate up to one third in bacteremic form and up to 60% in enterococcal peritonitis Pre-transplant VRE colonization (13%-15% from surveillance) is associated with increased morbidity and mortality following liver transplant
Listeria monocytogenes[10,64,81]	Bacteremia, meningitis, SBP	↑ Incidence in cirrhosis, particularly hemochromatosis
Mycobacterium tuberculosis (TB)[73,74,77]	Pulmonary TB, extra-pulmonary TB (e.g. peritonitis, disseminated TB)	↑ Incidence ↑ Virulence; mortality 22%-48% ↑ Extra-pulmonary forms ↑ Risk for multi-drug resistance TB ↑ Risk for anti-TB hepatotoxicity

SBP: Spontaneous bacterial peritonitis; UTI: Urinary tract infection; SSTI: Skin and soft tissue infection; TB: Tuberculosis.

Clostridium difficile

C. difficile infection has recently been recognized as a significant problem in hospitalized cirrhotic patients. US database of over 80 000 patients analysis suggested that *C. difficile*-associated diarrhea (CDAD) is an independent risk of death in hospitalized cirrhotic patients (OR 1.55, 95% CI: 1.29-1.85)[80]. It is also associated with an increase in the length of hospital stay and hospital cost in these patients. There was no correlation between severity of cirrhosis and the development of CDAD[80] (Table 2).

LIVER DISEASE-SPECIFIC ISSUES

Hemochromatosis

The association of hemochromatosis and certain pathogens has been well described. Several mechanisms have been proposed to explain this association. Iron excess induces oxidative stress which results in organ damage and impairment of immune function[81]. Hepcidin, a central iron-regulatory hormone, has recently been recognized for an immunomodulatory and broad antimicrobial property[82,83]. Inadequate expression and functional impairment of hepcidin in patients with hemochromatosis may connect to the increased susceptibility for infections[82,83]. Hemochromatosis is associated with a decrease in proliferation, migration, phagocytic activity and cytokines secreting ability of the immune cells, thereby, principally impairing cell-mediated immune response[81].

Aside from impaired host defense, the growth and virulence of various organisms are enhanced by a high

iron environment[81]. Interestingly, chelation therapy with desferoxamine in patients with hemochromatosis secondary to long-term transfusion may further stimulate the growth of particular bacteria, such as *V. vulnificus*, *Y. enterocolitica*, *K. pneumonia* and *S. aureus*, which can use it for efficient iron uptake *via* specific receptors[84,85]. On the other hand, newer iron chelators (deferasirox and deferiprone) do not act as siderophores and therefore may depress the growth of iron-dependent organisms[84,85].

A number of pathogens have been reported to be of increased susceptibility in patients with hemochromatosis, such as *E. coli*, *Vibrio spp.* (*V. vulnificus*, *V. cholerae*), *L. monocytogenes*, *Yersenia spp.* (*Y. pseudotuberculosis, Y. enterocolitica*), *Plesiomonas shigelloides*, *Mycobacterium tuberculosis*, cytomegalovirus and fungi (*A. fumigatus*, *Mucor spp.*)[81,86].

Primary sclerosing cholangitis

Patients with primary sclerosing cholangitis (PSC) are susceptible to repeated episodes of bacterial cholangitis, especially after biliary tract manipulation[87,88]. The incidence of cholangitis following endoscopic retrograde cholangiopancreatography (ERCP) is higher in PSC patients (4%-16%) compared to non-PSC patients, particularly in those who had therapeutic ERCP procedures[89]. If cholangitis occurs without biliary intervention, the presence of stones, dominant strictures or cholangiocarcinoma should be considered. Most common causative organisms are gram-negative enteric bacteria and enterococci[90]. Recurrent bacterial cholangitis may benefit from long term antibiotic prophylaxis[87].

PREVENTIVE MEASUREMENTS

All cirrhotic patients should be aware of the risk of infections and contact their physicians instantly when they are febrile or ill. Raw/uncooked foods, close contact to at-risk animals or sick people and wound exposure to flood or seawater should be avoided, particularly in those with advanced liver disease.

Prophylactic antibiotics should be utilized in cirrhotic patients at high risk of developing infection, including gastrointestinal bleeding and those undergoing invasive endoscopic or surgical procedures[28,39]. Long-term prophylaxis for patients with a history of SBP and those who have low ascitic fluid protein (< 1.5 gm/dL) is recommended[51]. On the other hand, overuse of antibiotic prophylaxis can lead to the development of resistant organisms and CDAD[7,80]. The rate of culture-positive infection caused by quinolone-resistant gram-negative bacilli was very high (65%) in patients on long-term norfloxacin prophylaxis[7]. Notably, prophylactic antibiotics are not recommended for routine endoscopy, elective variceal band ligation and abdominal paracentesis[39,51,91].

Immunization against hepatitis A and B viruses, influenza and pneumococcus are recommended in patients with cirrhosis[92,93]. Both cellular and humoral immune responses are suppressed in cirrhotic patients which may be associated with suboptimal early post-vaccination response and loss of long-term immunogenicity[92]. Therefore, a booster dose early during the follow-up is suggested in order to improve the immune response[92]. Cirrhotic patients are able to receive both inactivated and live vaccines according to the current guidelines[92,93]. *S. pneumoniae* infections are common, more severe and frequently associated with poor outcome in cirrhotic patients[94,95]. Anti-pneumococcal vaccination is recommended with booster injections every 5 years[92]. Incidence of seasonal flu is not evidently increased in cirrhotic patients; however, influenza infection may precipitate hepatic decompensation[92,96]. Influenza vaccine is well-tolerated and clinically effective in cirrhotic patients despite a slightly reduced immunogenicity[97,98].

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