Bacterial Infections in Cirrhosis as a Cause or Consequence of Decompensation?

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KEYWORDS

• Sepsis • Cirrhosis • Decompensation • Ascites • Hepatic encephalopathy
• Variceal bleeding • Acute-on-chronic liver failure

KEY POINTS

- Patients with cirrhosis are at high risk of developing bacterial infections because of cirrhosis-associated immune dysfunction, increased intestinal permeability and gut dysbiosis.
- Bacterial infections induce systemic inflammation, oxidative stress and worsen portal hypertension and circulatory dysfunction, triggering decompensation and organ failures.
- In patients at high risk for developing infections, antibiotic prophylaxis reduces the incidence of infections and improve prognosis.
- Infections should be rapidly ruled out in all patients hospitalized with decompensated cirrhosis; antibiotic treatment should not be delayed.
- Patients with spontaneous bacterial peritonitis should receive volume expansion with human albumin to decrease the incidence of renal failure and improve survival.

INTRODUCTION

Liver cirrhosis is one of the leading causes of death worldwide. According to data from the Global Burden of Disease study 2017, cirrhosis is the 13th cause of death worldwide and was responsible for almost 200,000 deaths on 2017.[1] Most of death occurs after decompensation of the disease. In fact, liver cirrhosis is characterized by a compensated phase, in which the liver disease is asymptomatic or paucisymptomatic and the prognosis is quite good (median survival, 12 years).[2] However, the occurrence of complications of cirrhosis (ascites, variceal bleeding, hepatic encephalopathy, or jaundice) marks the transition to the decompensated phase, which is associated to a poor prognosis (median survival, 2 years).[2] Portal hypertension is the main driver of decompensation and has been a relevant target for

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preventing decompensation in patients with cirrhosis.[3,4] However, other factors can facilitate the occurrence of decompensation. Among them, bacterial infections (BIs) are increasingly recognized as the most common precipitating event of acute decompensation of cirrhosis.[5] Indeed, patients with cirrhosis have a high risk of developing BIs, which can trigger decompensation. In turns, after decompensation, the risk of developing BIs further increases, being associated with further episodes of decompensation. The net results of this vicious circle is a 4-fold increase in mortality rate in patients with cirrhosis and infections,[6] which has led some authors to consider BIs as a distinct stage of liver disease.[6,7] Beyond cirrhosis staging definitions, there is no doubt that strategies to prevent and/or early recognize and treat infections are key to improve prognosis of patients with cirrhosis.[8] Herein we review the role of BIs as a cause and consequence of decompensation in patients with cirrhosis.

CIRRHOSIS PREDISPOSES TO BACTERIAL INFECTIONS

Patients with cirrhosis have more than twice the risk of developing an infection than general population.[9] The most common infections in these patients are spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia, skin and soft tissues infections, and spontaneous bacteremia.[7,10–13] Several mechanisms are responsible for predisposing patients with cirrhosis to BIs, which involves changes in adaptive and acquired immunity, alteration of intestinal barrier with an increase in intestinal permeability and changes in quantity and quality of gut microbiome.[14]

Cirrhosis is associated with several abnormalities in the innate and adaptive components of the immune system's response to bacteria, leading to a state of immunodeficiency.[15] Circulating immune cells, such as neutrophils and lymphocytes, decrease in frequency and exhibit an alteration in bacterial phagocytosis and killing abilities. The defective production of complement and soluble pattern recognition receptors impairs the capability of bacterial recognition and opsonization. Finally, the disruption of liver architecture and portosystemic shunts compromise the immune surveillance function of the liver.[15]

The increase in intestinal permeability is caused by ultrastructural changes in the intestinal mucosa (tight junctions disruption, widening of intracellular spaces, vascular congestion, wall thickening, etc), oxidative stress, local inflammation, and hyperactivity of the autonomic nervous system.[16] More recently, bile acids showed to exerts a relevant role on promoting intestinal barrier integrity toward the activation of farnesoid X receptors (FXR), which are nuclear receptors expressed in the gut and the liver.[17] In cirrhosis, the decrease in gut bile acids availability is associated with an increased intestinal permeability and bacterial translocation, which can be reverted with the administration of FXR agonists.[17]

The gut microbiome in patients with cirrhosis is profoundly altered. The decrease in small bowel motility and the decrease in antimicrobial peptides such as α-defensins facilitates bacterial overgrowth. However, also the quality of bacteria is changed, with the depletion of the beneficial phyla *Lachnospiraceae* and enrichment of the phyla *Proteobacteria* (mainly *Enterobacteriaceae*) and *Enterococcaceae*.[18,19] *Enterobacteriaceae* and *Enterococcaceae* are more adapted to translocate from the gut to systemic circulation and are also the most common pathogens responsible for spontaneous infections in patients with cirrhosis.[10] More recently, metagenomics studies showed a decrease in gut microbial diversity in patients with cirrhosis, which was further reduced in decompensated cirrhosis and ACLF and associated with risk of being hospitalized.[20,21] Finally, experimental models of cirrhosis suggest that gut dysbiosis

impairs the intestinal immune response and leads to disrupted barrier function, promoting bacterial translocation.[22]

Putting all these data together, the balance of the host–pathogen interaction is altered in patients with cirrhosis with a reduction in barrier function, altered immune response and increase in pathogens abundance (**Box 1**).

BACTERIAL INFECTIONS AS A CAUSE OF DECOMPENSATION

Overall, almost 40% of patients hospitalized for an acute decompensation of cirrhosis experience a BI during the hospitalization.[11,23] About two-thirds of these infections are present at hospital admission, and 25% to 30% are nosocomial.[10,11] Several studies found an association between BIs and decompensating events such as hepatic encephalopathy,[24] gastrointestinal bleeding,[25,26] and ascites.[23] However, there is a paucity of studies clearly demonstrating whether BIs occurred before decompensation, thus triggering decompensation, or were a consequence of decompensation. In a large series of patients with compensated viral cirrhosis, Nahon and colleagues[27] showed that BIs occurred before decompensation in more than 80% of cases. Patients with BIs had a higher risk of developing decompensation (5-year incidence of decompensation of 45% vs 15% in patients with or without infections, respectively; $P<.001$).[27] In a post hoc analysis of the PREDESCI trial,[28] a trial investigating the ability of beta-blockers in preventing decompensation in patients with clinically significant portal hypertension, Villanueva and colleagues[29] showed that the occurrence of BIs significantly increases the risk of developing ascites and worsens survival.

When BIs occurs they frequently cause dysfunction and failure of organs other than the liver.[30] In fact BIs are recognized as the most common precipitating event of acute kidney injury (AKI)[23,31–33] and of ACLF, a syndrome characterized by acute decompensation of cirrhosis, organ failures, systemic inflammation, and high short-term mortality.[5] Furthermore, when ACLF is triggered by BIs, short-term mortality further increases.[34] After the first decompensation of cirrhosis, BIs facilitates further

Box 1
Summary of the host–pathogen changes occurring in patients with liver cirrhosis and predisposing to the development of infections

Host alterations
- Hypersplenism decreases circulating neutrophils and lymphocytes
- A decrease in complement and acute phase protein production with decreased opsonization of bacteria by immune cells
- Monocytes and neutrophils show an impaired bacterial phagocytosis and bacterial killing ability
- Portal hypertension induces ultrastructural changes in the intestinal mucosa (tight junctions disruption, widening of intracellular spaces, vascular congestion, wall thickening), increasing intestinal permeability
- A decreased availability of bile acids in the gut impairs the FXR signaling, disrupting the intestinal barrier function and increasing intestinal permeability
- Reticuloendothelial removal capacity is reduced because of alteration of liver structure and portosystemic shunts

Pathogen alterations
- Intestinal bacterial overgrowth
- Changes in microbiome composition with enrichment in pathogenic *Enterobacteriaceae* and *Enterococcaceae* and a decrease in beneficial *Lachnospiraceae*
- Decrease in gut microbial diversity

decompensation, such as variceal rebleeding,[35] recurrent hepatic encephalopathy,[36] and hepatorenal syndrome.[37] Finally, after BIs patients with cirrhosis have a high risk of early hospital readmissions.[38,39]

Pathophysiology of Decompensation Induced by Bacterial Infections

For several years, the hemodynamics consequences of portal hypertension have been considered the main drivers of decompensation of cirrhosis.[4] Portal hypertension is responsible for splanchnic arterial vasodilation, which causes a reduction of effective circulating volume and activation of endogenous vasoconstrictor systems (renin–angiotensin–aldosterone system, sympathetic nervous system, and nonosmotic release of vasopressin), which are responsible for sodium and water retention and thus the appearance of ascites and edema.[40] Portal hypertension induces the appearance of varices, which are responsible for bleeding. Finally, portal hypertension causes the appearance of portosystemic shunts, which are involved in the pathogenesis of hepatic encephalopathy.

More recently, systemic inflammation was shown to play a relevant role in promoting decompensation.[41] In fact, it has been shown that the levels of inflammatory cytokines increase in patients with ascites,[42] hepatic encephalopathy,[43] and organ failures.[44] Systemic inflammation in cirrhosis is caused by the interaction of immune system with pathogens-associated molecular pattern (PAMPs), which are molecule expressed by pathogens (eg, lipopolysaccharide for gram-negative bacteria) and danger-associated molecular patterns, which are molecules released by cell death. The recognition of PAMPs and danger-associated molecular patterns on pattern recognition receptors (such as Toll-like receptors) induces the production of inflammatory cytokines, nitric oxide (NO), the recruitment of leukocytes, and the release of reactive oxygen species.[41]

Sterile inflammation in cirrhosis is determined by translocation of PAMPs from the gut to the mesenteric lymph nodes and/or owing to the release of danger-associated molecular patterns after an acute hepatic inflammatory process. However, when overt BIs occur, the inflammatory response is quite higher.[44] The inflammatory response is crucial for providing defense against pathogens; however, it comes with relevant undesired drawbacks (**Fig. 1**). In cirrhotic rats, PAMPs aggravates portal hypertension by increasing the severity of intrahepatic microvascular dysfunction, exacerbating hepatic inflammation, increasing oxidative stress, and recruiting hepatic stellate cells.[45] Inflammation induces the production of NO in splanchnic circulation, further worsening arterial vasodilation.[41] Furthermore, experimental data suggests that inflammatory cytokines such as tumor necrosis factor-α cause an increase in the expression of inducible NO synthase and production of NO in the heart of cirrhotic rats, impairing cardiac contractility.[46,47] The consequent reduction in cardiac output causes a further drop in effective circulating volume. These hemodynamic changes favor the chain of events responsible for the development of ascites, dilutional hyponatremia and hepatorenal syndrome.

As for the brain, in vitro studies showed that inflammatory cytokines (tumor necrosis factor-α, IL-1, IL-6 and IFN-γ) induce astrocyte swelling to a similar extent of ammonia. Furthermore, stimulation of astrocytes previously exposed to ammonia, further increased astrocyte swelling.[48] Finally, in vivo studies showed an increase in brain water content and protein nitration in bile duct ligated rats after stimulation with lipopolysaccharide.[49]

Severe inflammation is also responsible for the release of reactive oxygen species, which can cause mitochondrial dysfunction, decreasing the oxidative phosphorylation with a consequent shift of metabolism to glycolysis.[50] Glycolysis is more rapid, but

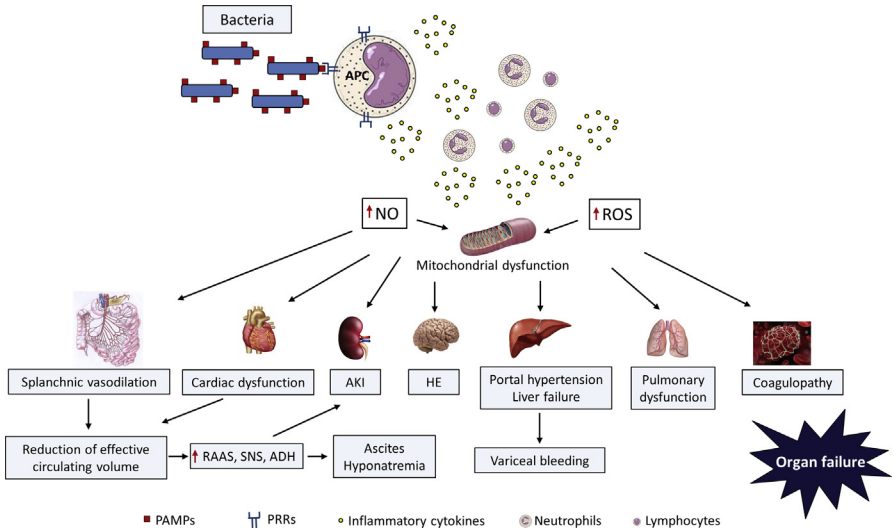

Fig. 1. The pathophysiology of decompensation induced by bacterial infections. Bacterial PAMPs are recognized by pattern recognition receptors on APCs, which promotes the production of inflammatory cytokines, and recruitment of inflammatory cells, which further enhances the inflammatory response. Inflammation induces the production of NO, which worsens splanchnic vasodilation and induces cardiac dysfunction. The result is a reduction in effective circulating volume which promotes the activation of vasoconstrictor systems and promotes water and sodium retention and renal hypoperfusion. Inflammation worsens intrahepatic microvascular dysfunction and oxidative stress increasing portal hypertension. Inflammation worsens brain edema and favors the occurrence of hepatic encephalopathy. NO and oxidative stress induces mitochondrial dysfunction which can cause organ failures. ADH, antidiuretic hormone; APC, antigen presenting cells; HE, hepatic encephalopathy; pattern recognition receptors, pattern recognition receptors; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system.

less efficient than oxidative phosphorylation and in case of severe inflammation, cells can be unable to meet their metabolic needs. Mitochondrial dysfunction is well known to occur in sepsis, but more recently, a metabolomic study in patients with decompensated cirrhosis and ACLF found features suggesting inhibition of mitochondrial energy production, which may contribute to the development of organ failures.[51]

BACTERIAL INFECTIONS AS A CONSEQUENCE OF DECOMPENSATION

After decompensation, patients with cirrhosis have a relevant risk for developing BIs. Variceal bleeding is a relevant risk factor for the development of infections in patients with cirrhosis. In fact, although about 20% of patients with variceal bleeding is already infected at the time of bleeding, infections can complicate the clinical course in almost 50% of patients.[52] When infections occur, they are associated with an increased rate of failure to control bleeding, rebleeding, and hospital mortality.[35,53] Patients with ascites are at risk of developing infections, in particular SBP.[52] Specific risk factors in this group are a low protein content in ascitic fluid and high levels of bilirubin.[54,55] Patients with hepatic encephalopathy are fragile and at risk of developing aspiration pneumonia. In patients with decompensated cirrhosis, BIs are associated with the risk of developing AKI, hepatorenal syndrome, organ failures and ACLF.[5,23,31] Remarkably, patients with ACLF have an increased risk of developing BIs, which increases mortality

rate.[34] Among organ dysfunction or failures, relative adrenal insufficiency has been associated with an increased risk of infections and sepsis.[56,57] In summary, a vicious circle links BIs and decompensation of cirrhosis, where decompensation can cause infections, which can cause further decompensation, further infections, organ failures and mortality (Fig. 2).

Pathophysiology of Bacterial Infections as a Consequence of Decompensation

After decompensation of cirrhosis, characteristics predisposing to BIs (immune dysfunction, gut dysbiosis, increased intestinal permeability) are further enhanced.[16] After variceal bleeding, the high amount of blood reaches the gut, altering intestinal flora and promoting bacterial translocation. Furthermore, hematemesis per se is a risk factor for aspiration pneumonia. In patients with ascites, the decrease in reticuloendothelial removal capacity is associated with the risk of developing infections.[58] Furthermore, the decrease in complement in ascites affects the ability of immune cells to opsonize of bacteria predisposing patients to the development of infections.[59] Hepatic encephalopathy is associated with portosystemic shunts, which lower the liver's ability to clear intestinal bacteria and are associated with the occurrence of SBP.[60] Furthermore, patients with severe hepatic encephalopathy are at risk for aspiration pneumonia.

As for patients with ACLF, it has been demonstrated that, despite a severe inflammatory response, ACLF is frequently associated with immune dysfunction, which impairs pathogen killing ability by macrophages and neutrophils.[61,62] This condition of immune paralysis is associated with the risk of developing infections.[34]

PREVENTION OF INFECTIONS AS A STRATEGY TO PREVENT DECOMPENSATION AND/OR FURTHER DECOMPENSATION IN CIRRHOSIS

Infections have such an important role in inducing decompensation and/or further decompensation that several strategies have been developed to prevent BIs in cirrhosis (Table 1).

Antibiotic Prophylaxis

Antibiotic prophylaxis has been used to prevent infections in patients with decompensated cirrhosis at high risk of developing BIs. In patients with gastrointestinal bleeding, antibiotic prophylaxis decrease the incidence of BIs, rebleeding and mortality.[63] Norfloxacin (400 mg 2 times per day) was shown to be effective for this purpose; however, it is less effective than ceftriaxone (1 g/d) in patients with advanced

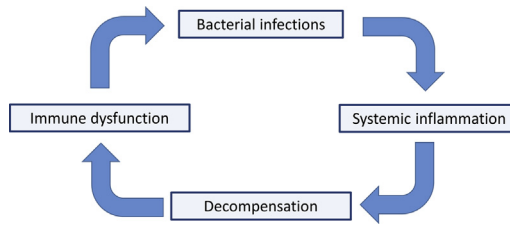

Fig. 2. Bacterial infections and decompensation: the ominous vicious circle. Bacterial infections can trigger hepatic decompensation by increasing systemic inflammation, oxidative stress and portal pressure. After decompensation, cirrhosis-associated immune dysfunction and dysbyosis worsens, favoring the appearance of infections, which triggers further decompensation.

Table 1
Evidence-based strategies to prevent bacterial infections and decompensation in cirrhosis

Treatment	Target Population	Effects
Norfloxacin 400 mg qd	Patients with previous episodes of SBP	Decreased incidence of SBP
Norfloxacin 400 mg qd	Patients with ascites, ascites protein of <15 g/L and advanced cirrhosis[a]	Decreased incidence of SBP, HRS and trends toward better survival
Ceftriaxone 2g[b] Norfloxacin 400 mg bid	Patients with variceal bleeding	Decreased incidence of infections, failure to control bleeding, rebleeding and mortality

Abbreviations: bid, 2 times per day; HRS, hepatorenal syndrome; qd, daily.
[a] Child-Turcotte-Pugh score of ≥9 points with a serum bilirubin of ≥3 mg/dL or a serum creatinine of ≥1.2 mg/dL/urea of ≥25 mg/dL, or serum sodium of ≤130 mmol/L.
[b] Ceftriaxone is more effective than norfloxacin in patients with advanced cirrhosis (≥2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin of >3 mg/dL).

cirrhosis (ie, ≥2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL).[64] However, norfloxacin is no more available in many countries (including the United States) and it should be avoided in countries with a high rate of quinolone resistant bacteria.[4]

In patients with ascites and a high risk of developing SBP (ie, ascitic fluid protein of <1.5 g/dL plus ≥1 among [i] a Child-Turcotte-Pugh score of ≥9 points with serum bilirubin ≥3 mg/dL; [ii] a serum creatinine of ≥1.2 mg/dL or a urea of ≥25 mg/dL; or [iii] a serum sodium of ≤130 mmol/L) norfloxacin prophylaxis (400 mg/d) decrease the incidence of SBP and hepatorenal syndrome, with a trend toward an improved survival.[65] More recently, a post hoc analysis of a randomized placebo-controlled trial showed improved survival in patients with cirrhosis, ascites, and Child-Turcotte-Pugh class C.[66] However, the survival benefit was observed only in patients with an ascitic fluid protein of less than 1.5 g/dL and quinolone prophylaxis should be reserved to these high-risk patients.

After the first episode of SBP, the recurrence of infection is almost 70% at 1 year. Prophylaxis with norfloxacin (400 mg/d) decreases the recurrence of SBP.[67]

Antibiotic prophylaxis can induce the development of multidrug-resistant bacteria,[68] which are a relevant emerging problem worldwide[10]; therefore, it should be reserved to high-risk patients.

Rifaximin, a nonabsorbable antibiotic, has been shown to prevent the recurrence of hepatic encephalopathy[69] and to decrease endotoxemia[70] in patients with cirrhosis. Whether rifaximin could replace quinolone in the prevention of SBP remain to be proven in well-designed randomized controlled trial. Anyway, it could represent an interesting strategy for preventing infections and decompensation.

Nonantibiotic Strategies to Prevent Infections

Antibiotics can lead to the development of multidrug-resistant bacteria and nonantibiotic strategies should be implemented to prevent infections in cirrhosis (**Table 2**). Among nonantibiotic strategies, the first relevant point is to avoid unnecessary and potentially hazardous drugs. Proton pump inhibitors use is frequently inappropriate in patients with cirrhosis and has been associated with the risk of SBP and non-SBP infections[71]; therefore, their use should be avoided unless clearly indicated.

Table 2
Promising strategies to prevent bacterial infections and decompensation in cirrhosis

Treatment	Mechanism	Preliminary and Established Evidence
Rifaximin	Nonabsorbable antibiotic	Decrease the recurrence of hepatic encephalopathy Decreases endotoxemia
Nonselective beta-blockers	Inhibition of β1 and β2 adrenergic receptors, Decrease in portal pressure	Decreased incidence of SBP Decreased incidence of decompensation Decrease intestinal permeability, bacterial translocation and ameliorates immune dysfunction
Long-term use of albumin	Scavenging of PAMPs Counteracting reduction of effective circulating volume	Decreased incidence of infections, HRS, and refractory ascites Improved survival[b] Attenuates immune dysfunction, systemic inflammation and circulatory dysfunction
Statins	Pleiotropic effects with anti-inflammatory and antifibrotic effects Decrease in the portal pressure	Improved survival[a] Preclinical evidence of reduced inflammation and liver damage after the administration of PAMPs
FXR agonists	Activation of FXR signaling	Preclinical evidence of improved intestinal barrier integrity and decrease in bacterial translocation
Fecal microbiome transplantation	Counteracts dysbiosis	Decreased recurrence of *Clostridium difficile* infection Preliminary data suggesting decreased the hospitalization rate

Abbreviations: HRS, hepatorenal syndrome; PAMPs, pathogens associated molecular patterns.
[a] In patients with ascites and requiring ≥200 mg of antialdosteronic drugs and 25 mg of furosemide.
[b] In patients with variceal bleeding.

Among drugs to be used, it is remarkable that beta-blockers were associated with a reduced risk of SBP in patients with cirrhosis.[72] Beta-blockers were shown to decrease intestinal permeability, bacterial translocation, and levels of inflammatory cytokines.[73] These findings, which were partially independent of hemodynamic changes, could involve the effects of beta-adrenergic blockade on immune function. In fact, the administration of beta-blockers in cirrhotic rats ameliorates systemic and splenic immune dysfunction.[74]

Albumin administration is widely used to prevent or treat the complications of cirrhosis such as postparacentesis circulatory dysfunction and hepatorenal syndrome.[52] More recently, the long-term use of albumin (40 g twice a week for 2 weeks followed by 40 g per week) has been shown to improve survival in patients with cirrhosis and ascites requiring at least 200 mg of an antialdosteronic drug and 25 mg of furosemide.[75,76] Interestingly, in addition to improving the control of ascites, albumin also decreased the incidence of SBP and non-SBP infections, hepatorenal

syndrome, and hepatic encephalopathy.[75,76] These effects could be related to the nononcotic properties of albumin, which attenuated the immune dysfunction in experimental models of cirrhosis,[77] and decreased systemic inflammation and cardiocirculatory dysfunction in patients with decompensated cirrhosis.[78] However, the beneficial effects of the long-term use of albumin were not confirmed in a randomized placebo-controlled trial (with a different design, a smaller sample size, and a lower dose of albumin).[79]

Other interesting strategies to be explored in future studies involves the use of statins, FXR agonists, and fecal microbiota transplantation. Statins had anti-inflammatory and antifibrotic effects, and were shown to decrease the portal pressure in patients with cirrhosis, as well as improving survival in those with variceal bleeding.[80] In experimental models of cirrhosis simvastatin decreased lipopolysaccharide-induced inflammation and liver damage. Therefore, statins represent an interesting drug. However, owing to the potential hepatotoxicity and muscular toxicity of simvastatin,[81] further studies are needed before its implementation in clinical practice. In experimental cirrhosis, FXR agonists showed to promote intestinal barrier integrity and to reduce bacterial translocation[82] and may represent a promising nonantibiotic strategy to prevent SBP. Finally, fecal microbial transplantation showed to be effective in preventing recurrence of *Clostridium difficile* infection and it is currently under investigation to prevent complications of cirrhosis.[83]

TREATMENT OF INFECTIONS AS A STRATEGY TO PREVENT DECOMPENSATION AND/OR FURTHER DECOMPENSATION IN CIRRHOSIS

The early identification and management of BIs is crucial to prevent and treat decompensation of cirrhosis (**Table 3**). In fact, without an effective treatment of infections, the occurrence of AKI, hepatorenal syndrome, and ACLF dramatically increases.[10] Infections should be rapidly ruled out in all patients hospitalized for an acute decompensation of cirrhosis (chest radiographs; blood, urine, and ascites cultures; and diagnostic paracentesis).

Antibiotic Management of Bacterial Infections

Antibiotic treatment should be started as soon as possible in patients with cirrhosis and BIs, because the early initiation of an effective empirical antibiotic treatment is the most important measure to improve survival these patients.[10,11] Ideally, the antibiotic treatment should cover all bacteria potentially responsible for infections, which depends on the site of infection, local epidemiology and contact with health care.[14,52] The spread of multidrug resistant bacteria made more challenging the management of infections in patients with cirrhosis.[10,11] On clinical ground, the selection of antibiotic is based on the following principles: (a) site of infection, (b) risk factors for multidrug resistant bacteria (nosocomial infections, previous use of antibiotics, recent hospitalization), (c) the severity of the infection, and (d) the local epidemiology.[8] In patients with SBP, third-generation cephalosporins are the first choice for community acquired SBP, although they are poorly effective in nosocomial infections and a broader spectrum treatment should be considered.[68] In centers with a high rate of multidrug resistant species, meropenem plus daptomycin was more effective than a third-generation cephalosporins in treating nosocomial SBP.[84] Similarly, in centers with a high rate of multidrug resistant in health care–associated infections (eg, those occurring in patients hospitalized in the previous 3 months, resident in nursing home facilities, etc), a broader spectrum antibiotic treatment is associated with higher efficacy and improved survival.[85] In patients with sepsis, septic shock, and ACLF clinicians should

Table 3
Strategies for the management of bacterial infections in cirrhosis

Strategy	Intervention	Clinical Significance
Early diagnosis of infections in patients with acute decompensation of cirrhosis	Rule out infections (chest radiographs, diagnostic paracentesis, urinalysis, cultures of blood, ascites and urine)	Delay in diagnosis and treatment of infections is associated with worse outcomes
Early initiation of empirical antibiotic treatment	Administer antibiotic treatment as soon as possible in patients with infections	Delay in administering antibiotic treatment is associated with worse outcomes
Optimal selection of antibiotic treatment	Antibiotic treatment should be selected according to the following: a. Type of infections b. Severity of infection c. Contact with health care system d. Recent use of antibiotics e. Local epidemiology	Patients with nosocomial infections/previous contact with health care system, or recent use of antibiotics are at risk of multidrug resistant bacteria. Broader spectrum antibiotics should be considered in these cases. Local epidemiology is heterogeneous
De-escalation of antibiotic	In case of positive cultures narrow the antibiotic treatment whenever possible	Broad spectrum antibiotics can select multidrug resistant bacteria. De-escalation is safe
Prevention of AKI	Albumin administration[a] is recommended in patients with cirrhosis and SBP	Albumin is associated with reduced incidence of AKI and improved survival
Avoid nephrotoxic drugs	Aminoglycosides and NSAIDs should be avoided in patients with cirrhosis and bacterial infections	Aminoglycosides and NSAIDs are associated with a high risk of AKI

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Give 1.5 g/kg of body weight at diagnosis followed by 1 g/kg of body weight on day 3.

consider to start early a broad spectrum antibiotic treatment, because any delay in starting an effective therapy increases the mortality rate.[52] In any case, biological samples for cultures should be collected and antibiotic treatment should be de-escalated whenever possible.

Nonantibiotic Management of Bacterial Infections

Nonantibiotic management of infections involve both the general management (treatment of organ dysfunction and failures) and strategies to prevent AKI. Nephrotoxic drugs such as aminoglycosides and nonsteroidal anti-inflammatory agents should be avoided. In patients with SBP, the use of albumin solution (1.5 g/kg of body weight on day 1 followed by 1 g/kg of body weight on day 3) decreased the incidence of AKI and improve survival.[86] As for other infections, results were controversial. Guevara

and colleagues[87] found an improvement in renal function in patients treated with albumin, which was found an independent predictive factor of survival. Thévenot and colleagues[88] showed a delay in the incidence of renal failure in patients treated with albumin, however, no benefit in survival was found with the use of albumin. More recently, in the INFECIR-2 trial, in-hospital mortality was similar between those who received albumin versus controls. However, patients receiving albumin were sicker at baseline and, during the follow-up period, had a higher rate of ACLF resolution and a lower rate second infections.[89]

SUMMARY

Patients with cirrhosis have a high risk of developing BIs, which are a relevant trigger of decompensation, organ failure, and ACLF. After decompensation the risk of developing infections further increases in an ominous vicious circle. Antibiotic prophylaxis is indicated in patients with variceal bleeding, previous episodes of SBP and in patients with ascites and high risk of developing SBP. Nonantibiotic strategies targeting microbiome, intestinal permeability and immune response are needed to prevent both infections and decompensation. BIs should be diagnosed and treated as soon as possible in all patients with decompensated cirrhosis and antibiotic treatment should not be delayed.

CLINICS CARE POINTS

- Bacterial infections can be sublte in cirrhosis. All in patients with cirrhosis should be investigated for infections at admission and in case of clinical deterioration.
- Broad spectrum antibiotic treatment (high doses, short time) should not be delayed in patients with cirrhosis and sepsis.
- Broad spectrum antibiotic treatment improve survival in patients with cirrhosis and BIs at high risk of MDR bacteria.
- De-escalation of antibiotics (whenever possible) is a good clinical practice and may help to reduce the spread of MDR bacteria.
- Albumin administration prevents AKI and improve survival in SBP.
- Antibiotic prophylaxis should be limited to evidence based indications.
- Non antibiotic strategies are urgently needed to prevent infections in cirrhosis and limit the further spread of MDR bacteria.

DISCLOSURE

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REFERENCES

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736–88.

2. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–31.
3. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–8.
4. de Franchis R. Expanding consensus in portal hypertension. J Hepatol 2015;63(3):743–52.
5. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37.e9.
6. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139:1246–56.e5.
7. Dionigi E, Garcovich M, Borzio M, et al. Bacterial infections change natural history of cirrhosis irrespective of liver disease severity. Am J Gastroenterol 2017;112:588–96.
8. Piano S, Brocca A, Mareso S, et al. Infections complicating cirrhosis. Liver Int 2018;38:126–33.
9. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the national hospital discharge survey. Chest 2003;124:1016–20.
10. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. Gastroenterology 2019;156:1368–80.e10.
11. Fernández J, Prado V, Trebicka J, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol 2019;70:398–411.
12. Borzio M, Salerno F, Piantoni L, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis 2001;33:41–8.
13. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the north American Consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology 2012;56:2328–35.
14. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:1310–24.
15. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol 2014;61:1385–96.
16. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol 2014;60:197–209.
17. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol 2020;72(3):558–77. https://doi.org/10.1016/j.jhep.2019.10.003.
18. Bajaj JS, Heuman DM, Hylemon PB, et al. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol 2014;60:940–7.
19. Qin N, Yang F, Li A, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature 2014;513:59–64.

20. Bajaj JS, Idilman R, Mabudian L, et al. Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort. Hepatology 2018;68:234–47.
21. Sole C, Llopis M, Solà E, et al. Gut microbiome is profoundly altered in acute-on-chronic liver failure as evaluated by quantitative metagenomics. Relationship with liver cirrhosis severity. J Hepatol 2018;68:S11–2.
22. Muñoz L, Borrero M-J, Úbeda M, et al. Intestinal immune dysregulation driven by dysbiosis promotes barrier disruption and bacterial translocation in rats with cirrhosis. Hepatology 2019;70:925–38.
23. Fasolato S, Angeli P, Dallagnese L, et al. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 2007;45: 223–9.
24. Merli M, Lucidi C, Pentassuglio I, et al. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. J Hepatol 2013;59:243–50.
25. Bleichner G, Boulanger R, Squara P, et al. Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage. Br J Surg 1986;73: 724–6.
26. Soriano G, Guarner C, Tomas A, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 1992;103:1267–72.
27. Nahon P, Lescat M, Layese R, et al. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). Gut 2017;66:330–41.
28. Villanueva C, Albillos A, Genescà J, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2019; 393:1597–608.
29. Villanueva C, Albillos A, Genescà J, et al. Bacterial infections in patients with compensated cirrhosis and clinically significant portal hypertension: implications on the risk of developing decompensation and on survival. Hepatology 2019; 70(Suppl):36–37A.
30. Piano S, Bartoletti M, Tonon M, et al. Assessment of sepsis-3 criteria and quick SOFA in patients with cirrhosis and bacterial infections. Gut 2018;67:1892–9.
31. Terra C, Guevara M, Torre A, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. Gastroenterology 2005;129:1944–53.
32. Huelin P, Piano S, Solà E, et al. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute on chronic liver failure. Clin Gastroenterol Hepatol 2017;15:438–45.
33. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64:531–7.
34. Fernández J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–80.
35. Bernard B, Cadranel JF, Valla D, et al. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology 1995; 108:1828–34.
36. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60:715–35.

37. Angeli P, Tonon M, Pilutti C, et al. Sepsis-induced acute kidney injury in patients with cirrhosis. Hepatol Int 2016;10:115–23.
38. Bajaj JS, Reddy KR, Tandon P, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. Hepatology 2016;64:200–8.
39. Piano S, Morando F, Carretta G, et al. Predictors of early readmission in patients with cirrhosis after the resolution of bacterial infections. Am J Gastroenterol 2017; 112:1575–83.
40. Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology 1988;8:1151–7.
41. Bernardi M, Moreau R, Angeli P, et al. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015;63:1272–84.
42. Turco L, Garcia-Tsao G, Magnani I, et al. Cardiopulmonary hemodynamics and C-reactive protein as prognostic indicators in compensated and decompensated cirrhosis. J Hepatol 2018;68:949–58.
43. Romero-Gómez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol 2015;62:437–47.
44. Clària J, Stauber RE, Coenraad MJ, et al. Systemic inflammation in decompensated cirrhosis: characterization and role in acute-on-chronic liver failure. Hepatology 2016;64:1249–64.
45. Tripathi DM, Vilaseca M, Lafoz E, et al. Simvastatin prevents progression of acute on chronic liver failure in rats with cirrhosis and portal hypertension. Gastroenterology 2018;155:1564–77.
46. Yang Y-Y, Liu H, Nam SW, et al. Mechanisms of TNFα-induced cardiac dysfunction in cholestatic bile duct-ligated mice: interaction between TNFα and endocannabinoids. J Hepatol 2010;53:298–306.
47. Bortoluzzi A, Ceolotto G, Gola E, et al. Positive cardiac inotropic effect of albumin infusion in rodents with cirrhosis and ascites: molecular mechanisms. Hepatology 2013;57(1):266–76.
48. Rama Rao KV, Jayakumar AR, Tong X, et al. Marked potentiation of cell swelling by cytokines in ammonia-sensitized cultured astrocytes. J Neuroinflammation 2010;7:66.
49. Wright G, Davies NA, Shawcross DL, et al. Endotoxemia produces coma and brain swelling in bile duct ligated rats. Hepatology 2007;45:1517–26.
50. Wang A, Luan HH, Medzhitov R. An evolutionary perspective on immunometabolism. Science 2019;363:eaar3932.
51. Moreau R, Clària J, Aguilar F, et al. Blood metabolomics uncovers inflammation-associated mitochondrial dysfunction as a potential mechanism underlying ACLF. J Hepatol 2020;72:688–701.
52. Angeli P, Bernardi M, Villanueva C, et al. EASL clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69: 406–60.
53. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998;27:1207–12.
54. Llach J, Rimola A, Navasa M, et al. Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. Hepatology 1992;16:724–7.

55. Andreu M, Sola R, Sitges-Serra A, et al. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology 1993;104:1133–8.
56. Acevedo J, Fernández J, Prado V, et al. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. Hepatology 2013;58(5):1757–65.
57. Piano S, Favaretto E, Tonon M, et al. Including relative adrenal insufficiency in definition and classification of acute-on-chronic liver failure. Clin Gastroenterol Hepatol 2020;18:1188–96.e3.
58. Bolognesi M, Merkel C, Bianco S, et al. Clinical significance of the evaluation of hepatic reticuloendothelial removal capacity in patients with cirrhosis. Hepatology 1994;19:628–34.
59. Runyon BA, Morrissey RL, Hoefs JC, et al. Opsonic activity of human ascitic fluid: a potentially important protective mechanism against spontaneous bacterial peritonitis. Hepatology 1985;5:634–7.
60. Simón-Talero M, Roccarina D, Martínez J, et al. Association between portosystemic shunts and increased complications and mortality in patients with cirrhosis. Gastroenterology 2018;154:1694–705.e4.
61. Bernsmeier C, Pop OT, Singanayagam A, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology 2015;148(3):603–15.e14.
62. Bernsmeier C, Triantafyllou E, Brenig R, et al. CD14(+) CD15(-) HLA-DR(-) myeloid-derived suppressor cells impair antimicrobial responses in patients with acute-on-chronic liver failure. Gut 2018;67:1155–67.
63. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding – an updated Cochrane review. Aliment Pharmacol Ther 2011;34:509–18.
64. Fernández J, del Arbol LR, Gómez C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006;131:1049–56.
65. Fernández J, Navasa M, Planas R, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 2007;133:818–24.
66. Moreau R, Elkrief L, Bureau C, et al. Effects of long-term norfloxacin therapy in patients with advanced cirrhosis. Gastroenterology 2018;155:1816–27.e9.
67. Ginès P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology 1990;12:716–24.
68. Fernández J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55:1551–61.
69. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–81.
70. Kimer N, Pedersen JS, Busk TM, et al. Rifaximin has no effect on hemodynamics in decompensated cirrhosis: a randomized, double-blind, placebo-controlled trial. Hepatology 2017;65:592–603.
71. Wang J, Wu Y, Bi Q, et al. Adverse outcomes of proton pump inhibitors in chronic liver disease: a systematic review and meta-analysis. Hepatol Int 2020;14:385–98.
72. Senzolo M, Cholongitas E, Burra P, et al. β-Blockers protect against spontaneous bacterial peritonitis in cirrhotic patients: a meta-analysis. Liver Int 2009;29:1189–93.

73. Reiberger T, Ferlitsch A, Payer BA, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. J Hepatol 2013;58:911–21.
74. Tsai H-C, Hsu C-F, Huang C-C, et al. Propranolol suppresses the T-Helper cell depletion-related immune dysfunction in cirrhotic mice. Cells 2020;9(3):604.
75. Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391:2417–29.
76. Di Pascoli M, Fasolato S, Piano S, et al. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. Liver Int 2019;39:98–105.
77. O'Brien AJ, Fullerton JN, Massey KA, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med 2014;20:518–23.
78. Fernández J, Clària J, Amorós A, et al. Effects of albumin treatment on systemic and portal hemodynamics and systemic inflammation in patients with decompensated cirrhosis. Gastroenterology 2019;157:149–62.
79. Solà E, Solé C, Simón-Talero M, et al. Midodrine and albumin for prevention of complications in patients with cirrhosis awaiting liver transplantation. A randomized placebo-controlled trial. J Hepatol 2018;69:1250–9.
80. Abraldes JG, Villanueva C, Aracil C, et al. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. Gastroenterology 2016;150:1160–70.e3.
81. Pose E, Napoleone L, Amin A, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVERHOPE-SAFETY): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol 2020;5:31–41.
82. Sorribas M, Jakob MO, Yilmaz B, et al. FXR modulates the gut-vascular barrier by regulating the entry sites for bacterial translocation in experimental cirrhosis. J Hepatol 2019;71:1126–40.
83. Bajaj JS, Khoruts A. Microbiota changes and intestinal microbiota transplantation in liver diseases and cirrhosis. J Hepatol 2020;72:1003–27.
84. Piano S, Fasolato S, Salinas F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: results of a randomized, controlled clinical trial. Hepatology 2016;63:1299–309.
85. Merli M, Lucidi C, Di Gregorio V, et al. An empirical broad spectrum antibiotic therapy in health-care–associated infections improves survival in patients with cirrhosis: a randomized trial. Hepatology 2016;63(5):1632–9.
86. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–9.
87. Guevara M, Terra C, Nazar A, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol 2012;57:759–65.
88. Thévenot T, Bureau C, Oberti F, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol 2015;62:822–30.
89. Fernández J, Angeli P, Trebicka J, et al. Efficacy of albumin treatment for patients with cirrhosis and infections unrelated to spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2020;18:963–73.e14.