Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Review

Infections and liver cirrhosis: a dangerous liaison

[1]Andreea Pop, [1,2]Vasile Andreica
[1] Department of Gastroenterology, IIIrd Medical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] Department of Gastroenterology, "O Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania.

Abstract. Patients with liver cirrhosis have a multifactorial immunocompromised status predisposing to an increased risk of infection. Endothelial dysfunction is associated with a degree of liver dysfunction and is one of the key mechanisms favoring infections. On the other hand, endothelial dysfunction is associated with increased portal pressure and therefore with more episodes of decompensation of cirrhosis which may further increase the risk of infection.Infections are present at admission or develop during hospitalization, and their incidence is higher than in the general population. The most common infections are spontaneous bacterial peritonitis, urinary tract infections and pneumonia.A major problem in cirrhotic patients is the rising prevalence of multidrug resistant bacteria. They are commonly isolated in nosocomial and healthcare associated infections, which leads to increased failure rates of empirical antibiotic treatment.

Key Words: cirrhosis, bacterial infection, liver failure.

Corresponding Author: A. Pop, e-mail: kallos_andreea@yahoo.com.

Introduction

Liver cirrhosis is a progressive disease which evolves from a compensated stage, most often asymptomatic, to a decompensated one, when complications occur. The complications of cirrhosis (ascites, upper gastrointestinal bleeding, hepatic encephalopathy or hepato-renal syndrome) have a poor prognosis and high mortality rates. Not least, the risk of developing hepatocellular carcinoma (HCC) should also be considered, which increases with the progression of cirrhosis (D'Amico et al 2006).

The prognosis of cirrhosis can be estimated by using several clinical and biological parameters. The most widely used score in clinical practice is the Child-Pugh score that includes both subjective clinical parameters (ascites, hepatic encephalopathy) and objective serological parameters (serum albumin, bilirubin, prothrombin time) (Pascu et al 2011). More recently, MELD (Model for End-stage Liver Disease) score has gained ground. It uses INR, serum bilirubin and serum creatinine and currently represents the most used system for the prioritization of patients on waiting lists for liver transplantation (Kamath et al 2001).

Patients with cirrhosis usually have depressed (cellular and humoral) immune status due to changes in defense mechanisms, which predisposes them to an increased risk of infection. Bacterial infections are very common and represent one of the most important causes of liver failure progression, development of complications, and death in patients with cirrhosis (Jalan et al 2014). Both immune dysfunction and translocation of bacteria from the intestinal lumen, mainly favored by portal hypertension, are mechanisms that predispose cirrhotic patients to infections. Bacterial translocation in cirrhotic patients is high because they have low intestinal motility that may lead to bacterial overpopulation. Bacterial overgrowth along with a portosystemic shunt activate bacterial perpetuation and can cause bacteremia. In patients with liver cirrhosis the increase of endotoxin, proinflammatory cytokines and nitric oxide levels alters the structure and permeability of the intestinal mucosa in patients with liver cirrhosis. Along with local impairment of immune system function in cirrhosis, decreased intestinal motility and increased permeability facilitate the passage of intestinal bacteria to extraintestinal sites and predispose to the development of infections (Jalan et al 2014).

Recent studies confirm the fact that in patients with cirrhosis, infections increase mortality 4 times; 30% of patients die within the first month after infection and another 30% die within the first year (Arvaniti et al 2010). Also, bacterial infections were more common in advanced stages (Child B and C). Spontaneous bacterial peritonitis (SBP) is an important cause of morbidity and mortality in cirrhotic patients. SBP prevalence in hospitalized patients with cirrhosis and ascites is between 10% and 30% and almost half of these cases have SBP at presentation, while the rest develop it during hospitalization. The hospital mortality rate due to SBP is approximately 32%, and most of these infections are caused by Gram-negative bacteria (*E. coli, Klebsiella spp., Pseudomonas aeruginosa*) but, especially in hospital-acquired SBP, etiology can be represented by Gram-positive bacteria (*enterococci* and *streptococci*) (Bonnel et al 2011). The current recommendation is to perform diagnostic paracentesis in all patients with cirrhosis and ascites and also in patients with symptoms of peritoneal infection, systemic signs of infection, hepatic encephalopathy or renal failure during hospitalization (Ruyon 2013; Garcia et al 2009; EASL 2010).

The assessment of the infection type and etiological spectrum in hospitalized cirrhotic patients is of utmost importance as it can improve their management and treatment, which is essential in the context of the increasing incidence of multiple antibiotic resistant bacterial infections. Also, the development of

Table 1. Type of infections (Fernández et al 2012; Wong et al 2005)

Clinical manifestations	Type of infection	Diagnostic methods
Abdominal pain, fever **Rarely: nausea, vomiting, diarrhea**	Spontaneous bacterial peritonitis	Abdominal ultrasound: ascites -> diagnostic paracentesis +/- evacuation paracentesis
Fever, chills, dyspnea	Spontaneous bacterial empyema	Lung X-ray or abdominal ultrasound: pleural collection-> diagnostic thoracentesis +/- evacuation thoracentesis
Dysuria, pollakiuria	Urinary tract infection	Urine examination: leukocyturia > 10 leu/field, + uroculture, or > 500 leu/field, negative uroculture
Cough+/- expectoration, fever, chills, odynophagia	Respiratory infection	Lung X-ray, sputum examination, pharyngeal secretion
Fever, skin rash, cutaneous wound	Cutaneous infection	Wound secretion
Fever, chills(Shivering)	Catheter infections	Positive hemocultures and catheter cultures
Fever, diarrhea, abdominal pain	Clostridium difficile infection	Toxin A and B for Cl. difficile
	Stool infection	Positive coproculture
Fever, chills, cardiac murmur	Infectious endocarditis	(Transthoracic or transesophageal) cardiac ultrasound(echocardiography)
Fever, chills	Spontaneous bacteremia	Positive hemocultures without detection of the cause(causative agent)
Fever or hypothermia, tachycardia, tachypnea	Sepsis	Positive hemocultures + demonstrated/suspected infection Increased procalcitonin levels
Fever, chills and other specific manifestations	Other infections (leptospirosis, TB, abscesses of various etiologies, etc.)	Anti-Leptospira antibodies, lung X-ray, ultrasound/CT-evacuation and drainage of abscesses

infections may result in more difficult control of portal hypertension-related complications more difficult (Ruyon 2013; Garcia et al 2009; EASL 2010).

Diagnosis of infections in liver cirrhosis

The diagnosis of infections in liver cirrhosis is an important step in the subsequent management of liver disease from the perspective of antibiotic therapy and treatment of complications.
Liver cirrhosis has a progressive evolution, from a compensated state to the decompensated cirrhosis stage. Compensated cirrhosis was defined by the absence of bleeding, ascites, jaundice or symptomatic encephalopathy and decompensated cirrhosis by any of these complications. Prognostic stages were defined, modifying The Baveno IV proposal as follows: stage 1: compensated cirrhosis without varices; stage 2: compensated cirrhosis with varices; stage 3: bleeding without other disease's complications; stage 4: first nonbleeding decompensating event; stage 5: any second decompensating event (D'Amico et al 2014).
The natural evolution of liver cirrhosis can be influenced by several factors including infections of any nature. This is why it is extremely important to know this factor of decompensation and perform the screening of infections in cirrhotic patients admitted to the hospital; once they are detected, a more careful monitoring will be required. Infectious screening is conducted starting with the first day of presentation to the hospital. All patients should be considered as having the infection until the contrary is proved (Kim et al 2014).

The table 1 shows the most important types of infections and diagnostic methods.

Types of infections in liver cirrhosis

Hospitalized patients with cirrhosis, especially those with upper gastrointestinal bleeding, have an increased risk of developing infections. Bacterial infections occur in 32%-34% of hospitalized cirrhosis cases, and 45% of them present digestive bleeding (Bonnel et al 2011).
The most common infections are spontaneous bacterial peritonitis (25% of infections), urinary tract infections (20%) and pneumonia (15%). Bacterial overgrowth and translocation from the intestinal tract are important mechanisms in the pathogenesis of SBP and bacteremia. These pathogenic processes lead to increased levels of endotoxins and cytokines, which is a trigger for an excessive inflammatory response, a cause of septic shock, organ dysfunction and death (Bonnel et al 2011).

Spontaneous bacterial peritonitis

Ascites is the most common complication in patients with liver cirrhosis. Spontaneous bacterial peritonitis is defined as infected ascites in the absence of a surgically treatable abdominal source in patients with advanced cirrhosis. SBP occurs in 10-30% of hospitalized cirrhotic patients with ascites and is associated with increased mortality. Early diagnosis and eary paracentesis are very important for rapid initiation of antimicrobial therapy and

optimal therapeutic coverage in case of microorganism identification (Kim et al 2014).
The guidelines recommend that diagnostic paracentesis should be performed on admission in all patients with cirrhosis and ascites. (Ruyon 2013; Garcia et al 2009; EASL 2010).
Spontaneous bacterial peritonitis once diagnosed, albumin should be administrated at a dose of 1.5 g/kg body weight on day one and then 1 g/kg on day three for prevention of renal dysfunction (Bernardi et al 2014).
In a study of 239 patients with cirrhosis and ascites the effects of early (<12 hours) vs. delayed paracentesis (12-72 hours) after admission were compared. The group with delayed paracentesis had a higher hospital mortality rate, more days of intensive care, more days of hospitalization and a higher mortality at 3 months compared to the early paracentesis group. Every hour of delay in carrying out (performing) paracentesis was associated with a 3.3% increase of hospital mortality in cirrhotic patients (Kim et al 2014). SBP must also be differentiated from secondary peritonitis (Bonnel et al 2011).

Urinary tract infections (UTIs)
Urinary tract infections occur in 15%-20% of hospitalized patients with cirrhosis, two times more frequently than in control subjects. The female sex(women) has a 4 times higher bacteriuria rates than (men) the male sex. The most frequent pathogens are Gram-negative bacilli (*E. coli* and *Klebsiella spp.*). Bacteriuria is not associated with an increased risk of sepsis, SBP, or other infections commonly found in patients with cirrhosis (Bonnel et al 2011).

Respiratory infections
Pneumonia is the third leading type of infections in cirrhotic patients. Community-acquired pneumonia is most commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae. Staphylococcus aureus, M. pneumoniae, Klebsiella spp.* and *Legionella spp*. have also been implicated in community-acquired pneumonia. The risk of bacteremia in community-acquired pneumonia is increased in patients with cirrhosis (Bonnel et al 2011).

Skin and soft tissue infections
Chronic edema and increased bacterial translocation predispose cirrhotic patients to soft tissue infections, which account for about 11% of infections. Both Gram-positive bacteria (*S. aureus, group A streptococci*) and Gram-negative bacteria (*Klebsiella spp., Aeromonas spp., V. vulnificus*) are responsible for soft tissue infections (Bonnel et al 2011).
Cellulitis is the most common skin infection in patients with cirrhosis and has a 20% rate of recurrence. Necrotizing fasciitis, a rare but serious soft tissue infection, is generally caused by Gram-negative bacilli (Bonnel et al 2011).

Spontaneous bacteremia and sepsis
Systemic inflammatory response syndrome (SIRS) is not unusual in cirrhosis, and sepsis is defined as SIRS in the presence of confirmed bacterial infection (Wong et al 2005). SIRS and cirrhosis are interrelated determinants that influence survival. The severity of liver disease determines the development of SIRS, while SIRS leads to variceal bleeding, hepatic encephalopathy and adversely affects survival. Some aspects of cirrhosis may exacerbate SIRS and complicate its diagnosis. Patients with cirrhosis have high levels of endotoxins in circulation that inversely correlate with liver damage. Cirrhotic patients have increased levels of proinflammatory cytokines, in particular TNF-alpha and IL-6, compared to patients without cirrhosis. Nitric oxide, whose metabolite concentration is correlated with that of endotoxins, is increased in cirrhosis and is known to contribute to oxidative stress and worsen vasodilatation in sepsis. When organ function can no longer sustain homeostasis without intervention, patients develop multiple organ failure syndrome, which is a frequent outcome in cirrhosis and severe sepsis. Relative adrenal insufficiency is common in patients with septic shock and is associated with hemodynamic instability, renal failure and increased mortality (Bonnel et al 2011).
Other common infections found in patients with cirrhosis are represented by endocarditis, tuberculosis, Clostridium difficile infection and fungal infections (Bonnel et al 2011).

Consequences of bacterial infections and complications of cirrhosis

Hepatic encephalopathy
Hepatic encephalopathy is a severe complication with increased mortality in patients with liver cirrhosis (Bass et al 2010). A study that analyzed infections, one of the most frequent precipitating factors of hepatic encephalopathy, studied the most common type of infection and its etiology. The study included 137 patients with liver cirrhosis and hepatic encephalopathy (92 with cirrhotic hepatitis B (HBV cirrhosis) and 45 with alcoholic cirrhosis); 52 of these had infection as a precipitating factor. Respiratory infections were identified as the most common infectious precipitating factor, pneumococci and E. coli being the most frequent bacteria implicated in the etiology of respiratory and other infections. It was also shown that the number of leukocytes was low in patients with respiratory infections (Wang et al 2013).

Upper gastrointestinal bleeding
Bacterial infections are strongly associated with gastrointestinal bleeding in patients with cirrhosis and appear to be related to the inability to control bleeding (early rebleeding - within 5 days). A study was performed to evaluate the influence of infections on early rebleeding and mortality in patients with cirrhosis who did not receive prophylactic antibiotics. The study included 92 patients with hemorrhage; infection screening was performed at time 0 and when clinical signs suggested infection. A variceal etiology of bleeding was found in 72 (79%) of the patients. Early rebleeding occurred in 24 patients (26%), and 10 patients (11%) died. Compared to the group without infection, early rebleeding (65% vs.15%) and mortality (40% vs. 3%) were more frequent(prevalent) in patients with infections. Multivariate analysis showed that bacterial infections and the presence of shock were independently associated with early rebleeding. It was also demonstrated that bacterial infections, hepatic encephalopathy and shock were predictive factors for death (Vivas et al 2001).
There are data supporting that bacterial infections are involved in inducing bleeding, especially variceal bleeding in patients

Table 2 Definition of refractory ascites (Salerno et al 2010)

Refractory ascites: ascites that cannot be mobilized or the early recurrence of which (i.e. after therapeutic paracentesis) cannot be satisfactorily prevented by medical therapy.
It can be divided into:
1. Diuretic-resistant ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic treatment.
2. Diuretic-intractable ascites: ascites that cannot be mobilized or the early recurrence of which cannot be prevented because of the development of diuretic-induced complications that preclude the use of an effective diuretic dosage.

with cirrhosis. There is a hypothesis according to which bacterial infections are an important triggering factor for the production (occurrence) of variceal bleeding, particularly through the release of endotoxins. In patients who already have large varices with increased pressure in the wall, endotoxins cause a further increase in portal pressure, especially through the synthesis of nitric oxide and endothelin (Goulis 2001).

Hepatorenal syndrome

Hepatorenal syndrome is a distinct clinical syndrome that occurs in cirrhotic patients. A study on 70 cirrhotic patients was performed, which evaluated kidney function and survival in patients with hepatorenal syndrome associated with infection (Barreto et al 2014). The main results were: irreversibility of type I hepatorenal syndrome throughout therapy for infection, and 3 month survival. Of the 70 patients, 67% had irreversible type I hepatorenal syndrome during treatment of infections. The main predictor of the irreversibility of hepatorenal syndrome was the lack of resolution of infection (96% vs. 48% irreversibility in patients without and with infection resolution). The independent predictive factors of the irreversibility of hepatorenal syndrome were older age, serum bilirubin at admission, nosocomial infection and a decrease of serum creatinine by < 0.3 mg/dL on day 3 of antibiotic treatment. Following this study, two recommendations were made. The first recommendation is that patients with cirrhosis and kidney failure suggestive of type I hepatorenal syndrome should be treated as soon as an infection is suspected with empirical antibiotics. The second recommendation is that patients with at least one of the following risk factors: age > 60 years, bilirubin > 8 mg/dL or nosocomial infection should be treated with vasoconstrictors (terlipressin) and albumin immediately after the diagnosis of hepatorenal syndrome type I. In patients without risk factors, specific hepatorenal syndrome treatment should be delayed until day 3 of antibiotic treatment. If serum creatinine levels do not decrease > 0.3 mg/dL, treatment with terlipressin and albumin should be started. In patients with a decrease of creatinine levels > 0.3 mg/dL, the treatment administration decision should be made based on the evolution of renal function (Barreto et al 2014).

Refractory ascites

Between 5-10% per year of patients with ascites are refractory to standard medical treatment. According to the International Ascites Club, refractory ascites is defined as ascites that cannot be mobilized or recovers quickly after paracentesis, ascites that cannot be prevented by medical treatment. The term refractory ascites includes two different subtypes: diuretic-resistant ascites and diuretic-intractable ascites (Table 2).

There is still a number of several other conditions that do not lead to a diuretic response or lead to an insufficient response and cannot be properly defined as refractory ascites. In the first place, inappropriate diuretic treatment should be ruled out, for example: treatment with loop diuretics alone, or diuretic treatment that induces an exaggerated response by producing excessive diuresis with rapid weight loss and consequent prerenal azotemia. Transient refractory ascites may occur when renal function is impaired by other iatrogenic causes such as administration of NSAIDs through inhibition of vasodilator prostaglandins, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists that can damage renal blood perfusion and reduce glomerular filtration in patients with cirrhosis and ascites, or administration of nephrotoxic drugs such as aminoglycosides (Salerno et al 2010).

Complications that precipitate kidney failure include loss of fluids through vomiting, diarrhea or bleeding, or bacterial infections such as spontaneous bacterial peritonitis that can enhance vasodilation and consequently, the disturbance of the balance between intravascular volume and vascular capacity. In such cases, withdrawal of incriminated drugs or resolution of complications along with an adequate increase in plasma volume can restore responsiveness to standard treatment of low sodium intake and diuretics (Salerno et al 2010).

Infectious episodes are more frequent in patients with decompensated cirrhosis, who have an increased risk of developing sepsis, multiple organ failure and death. Factors associated with the development of infections are liver failure, low levels of protein in ascites and previous episodes of spontaneous bacterial peritonitis (Pleguezuelo et al 2013).

Liver failure

Acute decompensation, defined as the acute development of a major complication of liver disease (ascites, hepatic encephalopathy, gastrointestinal bleeding, and bacterial infection) is the leading cause of hospitalization in patients with cirrhosis (Moreau et al 2013). Regarding liver transplantation, the identification and eradication of bacterial, viral, fungal or parasitic infections is important. The frequency of post-transplant bacterial infections is between 20 % - 80%, three-fourths occurring within first month. These infections are mostly endogenous and are caused by aerobic gram-negative bacteria, but fluoroquinolones administrated from the time of transplantation did not confirm the protective effect, according to a recent study from Spain(Fagiuoli et al 2014). Acute decompensation in most of the cirrhotic patients develops in the absence of other significant changes, while in other cases it is associated with organ failure (liver function impairment and/or renal failure and/or other organ failure). Patients with acute decompensation and organ

failure have an increased risk of death in a short time. These patients are considered to have acute chronic liver failure. To diagnose organ failure, the SOFA (sequential organ failure assessment) score is used in intensive care units. However, this score does not take into account all specific characteristics of cirrhotic patients, which is why the CLIF-SOFA score is used (Moreau et al 2013).

The CANONIC study provides a definition of acute chronic liver failure (ACLF), which was divided into 3 degrees, with the increase of the short-term risk of death from grade 1 (22%) to grade 3 (77%) (Jalan at al 2014).Bacterial infection was the most common precipitating factor of ACLF (33%). Among patients with bacterial infection, ACLF was more frequent in patients with spontaneous bacterial peritonitis or pneumonia than in those with infections at other sites; sepsis and septic shock were also more common in patients with ACLF compared to those without ACLF. The mechanisms by which infections induce ACLF are incompletely understood (Jalan at al 2014; Moreau et al 2013; Arroyo et al 2015).

Consequences of antibiotic therapy in cirrhotic patients

Clostridium difficile infection

Clostridium difficile (CD) is the cause of pseudomembranous colitis. As the infection spreads through a fecal-oral mechanism, gastric acid can provide protection, and treatment with proton pump inhibitors (PPIs) may increase the likelihood of infection with CD. Patients with cirrhosis may be at particular risk for developing *Clostridium* infection for three reasons. Firstly, the use of antibiotics in cirrhotic patients is common; prophylactic use of antibiotics (quinolones, betalactams) is standard to prevent infections and reduce mortality in cirrhotic patients with low protein in ascites, a history of spontaneous bacterial peritonitis, and gastrointestinal bleeding. Secondly, cirrhotic patients frequently receive PPIs for gastroesophageal reflux, a history of gastric ulcer, as well as for unproven indications such as esophageal ulcers after performing endoscopic ligatures. Thirdly, the frequent need for hospitalization to treat the complications of cirrhosis, places the patient in an environment where the likelihood of exposure to *Clostridium* is high (Bajaj et al 2010). The prophylactic use of antibiotics for the prevention of spontaneous bacterial peritonitis and the use of PPIs are also associated with a high risk of developing CD infection (Bajaj et al 2010). *Clostridium* infection occurs less frequently in patients with upper gastrointestinal bleeding or hepatic encephalopathy, who routinely receive antibiotic treatment (a major risk factor for *Clostridium* infection). This particularity can be explained by the fact that lactulose, constantly administered to cirrhotic patients with these types of complications, reduces the production of short-chain fatty acids and suppresses the proliferation of CD (Preda et al 2014).

Infection with CD has an increased prevalence of 12% as a second infection in cirrhotic patients; these patients have a significantly higher mortality (40%) compared to patients without cirrhosis with CD and to cirrhotic patients without CD (Bajaj et al 2012). Clostridium difficile infection is associated with an increased mortality risk, a longer hospitalization period and higher hospitalization costs (Bajaj et al 2010).

Selection of resistant strains

Prolonged prophylactic antibiotic therapy has led to the emergence of quinolone-resistant bacteria. A percentage of 26% from spontaneous bacterial peritonitis episodes were caused by Gram-negative bacilli resistant to quinolones for a period of two years, in relation to long-term treatment with norfloxacin; 50% of positive SBP cultures in patients who received prophylaxis were due to the same microorganisms versus 16% in patients who did not receive prophylactic antibiotic therapy. Prolonged treatment with norfloxacin was also associated with an increased rate (44%) of positive SBP cultures caused by Gram-negative bacteria resistant to trimethoprim/sulfamethoxazole, suggesting that this antibiotic is not an alternative to norfloxacin. Fortunately, quinolone-resistant *E. coli* is still sensitive to third generation cephalosporins. In addition, there is a high probability of Gram-positive bacterial infections in patients receiving prophylactic treatment for SBP (Wong et al 2005).

A major problem in cirrhotic patients is the rising prevalence of multiple antibiotic resistant bacteria, frequently isolated in nosocomial and healthcare associated infections. The definition of multiple antibiotic resistant bacteria includes methicillin-resistant *Staphylococcus aureus, Acinetobacter baumannii,* Gram-negative extended-spectrum beta-lactamase (ESBL) producing strains and any isolated bacterium resistant to at least three classes of antimicrobials. Over the past year, the incidence of multiple antibiotic resistant bacteria has increased, especially in nosocomial and HCA (healthcare associated infections) infections (33% in community infections, 50% in nosocomial infections, and 80% in HCA infections) (Merli et al 2012).

Fungal infections

Cirrhosis increases susceptibility to infection with *Cryptococcus neoformans*. Cirrhosis underlies a third of Cryptococcus infections and is a strong predictor of 30-day mortality in patients who acquire human immunodeficiency virus. Spontaneous cryptococcal peritonitis is rare (Bonnel et al 2011).

Candidal peritonitis is usually found in critical surgical patients. Its isolation from ascites in cirrhotic patients is an unusual event whose clinical significance is unknown. According to the literature, primary fungal peritonitis is underdiagnosed (Krashin et al 2015).

It is suggested that in patients at high risk for fungal peritonitis (prolonged antibiotic therapy, recent hospitalization, unsuccessful antibiotic therapy), fungal cultures of ascites should be sent to a microbiology laboratory, regardless of the number of neutrophils. Antifungal therapy should be considered in critically ill patients. Candida peritonitis is associated with poor prognosis in cirrhotic patients (Krashin et al 2012).

Prognosis of liver cirrhosis associated with infections

In patients with cirrhosis, infections increase mortality four times; 30% of patients die a month after infection and another 30% die a year after it. The average mortality rate in all studies is 38%. Mortality at 1 month, 3 months and 12 months is 30.3%, 44% and 63%, respectively. Thus, almost half of the patients who survive the first month after infection die within one year. Meta-analysis studies show that mortality is significantly

higher in infected cirrhotic patients compared to patients without infections (Arvaniti et al 2010).

Conclusions

The natural evolution of liver cirrhosis can be influenced by infections. This is why it is extremely important to know this factor of decompensation and perform the screening of infections in cirrhotic patients starting with the first day of admission. All patients should be considered as having the infection until the contrary is proved. Early diagnosis of infections in liver cirrhosis is an important step in the subsequent management of liver disease from the viewpoint of antibiotic therapy and treatment of complications. In patients with cirrhosis, infections increase mortality four times.

Acknowledgments

This paper was published under the frame of European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776.

References

Arroyo V, Moreau R2, Jalan R3, Ginès P4; EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. J Hepatol 2015;62(1 Suppl):S131-43.

Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139(4):1246-56.

Bajaj JS, Ananthakrishnan AN, Hafeezullah M, Zadvornova Y, Dye A, McGinley EL, et al. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. Am J Gastroenterol 2010;105(1):106-113.

Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. NACSELD 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(6):2328-35

Barreto R, Fagundes C, Guevara M, Solà E, Pereira G, Rodríguez E, et al. Type-1 hepatorenal syndrome associated with infections in cirrhosis: natural history, outcome of kidney function, and survival. Hepatology 2014;59(4):1505-13.

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy C, et al. Rifaximin Treatment in Hepatic Encephalopathy. N Engl J Med 2010;362:1071-1080.

Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol. 2014;4(4):302-11.

Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis .Clin Gastroenterol Hepatol 2011;9(9):727-738.

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: 217-231.

D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39(10):3.

EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397– 417.

Fagiuoli S, Colli A, Bruno R, Craxì A, Gaeta GB, Grossi P, et al. 2011 AISF Single Topic Group. Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. J Hepatol 2014;60(5):1075-89.

Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012;55(5):1551-61.

Garcia-Tsao G, Lim J. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Af airs Hepatitis C Resource Center Program and the National Hepatitis C Program. Am J Gastroenterol 2009;104:1802 – 29 .

Goulis J. Bacterial infection in the pathogenesis of variceal bleeding. Is there any role for antibiotic prophylaxis in the cirrhotic patient? Annals of gastroenterology 2001;14(3):205-211.

Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol 2014;60:5-32.

Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL. A model to predict survival in patients with end-stage liver disease. Hepatology 2001:33(2):464-70.

Kim JJ, Tsukamoto MM, Mathur AK, Ghomri YM, Hou LA, Sheibani S, Runyon BA.Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis.Am J Gastroenterol 2014;109(9):1436-1442

Krashin E, Lishner M, Chowers M, Reisfeld S. Candida albicans in peritoneal fluid in a patient with hepatic encephalopathy. Isr Med Assoc J 2015;17(3):193-4.

Merli M, Lucidi C.Bacterial resistance in cirrhotic patients: an emerging reality. J Hepatol 2012;56(4):756-7

Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144(7):1426-37.

Pascu O. Cirozele hepatice. In: Pascu O, Acalovschi M, Andreica V, Grigorescu V, editors. Gastroenterologie hepatologie-Bazele practicii clinice. Editia a IV-a. Cluj-Napoca: Editura Medicala Universitara Iuliu Hatieganu; 2011.

Pleguezuelo M, Benitez JM, Jurado J, Montero JL, De la Mata M. Diagnosis and management of bacterial infections in decompensated cirrhosis. World J Hepatol 2013;5(1):16-25.

Preda S, Trifan A, Gîrleanu I, Stanciu C, Cojocariu C. Infectious complications in patients with liver cirrhosis. Rev Med Chir Soc Med Nat Iasi 2014;118(3):590-7.

Runyon B. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012 . Hepatology 2013;57:1651–3.

Salerno F, Guevara M, Bernardi M, Moreau R, Wong F, Angeli P, et al. Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis. Liver Int 2010;30(7):937-47.

Vivas S, Rodriguez M, Palacio MA, Linares A, Alonso JL, Rodrigo L. Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding. Dig Dis Sci 2001;46(12):2752-7.

Wang QM, Ji Q, Duan ZJ, Zhang M, Chang QY. A study on the position and etiology of infection in cirrhotic patients: A potential precipitating factor contributing to hepatic encephalopathy. Exp Ther Med 2013;6(2):584-590.

Wong F, Bernardi M, Balk R, Christman B, Moreau R, Garcia-Tsao G, Pet al; International Ascites Club. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 2005;54(5):718-25.

Authors

•Andreea Pop, Department of Gastroenterology, IIIrd Medical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, 8 Victor Babes Street, 400012, Cluj-Napoca, Cluj, Romania, EU, e-mail: kallos_andreea@yahoo.com

•Vasile Andreica, Department of Gastroenterology , "O Fodor" Regional Institute of Gastroenterology and Hepatology, 5 Constanta Street, 400158, Cluj-Napoca, Cluj, Romania, EU.

Citation	Pop A, Andreica V. Infections and liver cirrhosis: a dangerous liaison. HVM Bioflux 2015;7(4):264-270.
Editor	Ştefan C. Vesa
Received	30 August 2015
Accepted	4 September 2015
Published Online	4 September 2015
Funding	European Social Fund, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/138776
Conflicts/ Competing Interests	None reported