INFECTIOUS COMPLICATIONS IN PATIENTS WITH LIVER CIRRHOSIS

Sînziana Preda, Anca Trifan, Irina Girleanu, C. Stanciu, Camelia Cojocariu
University of Medicine and Pharmacy “Grigore T. Popa”- Iași
Faculty of Medicine
Discipline of Gastroenterology
Institute of Gastroenterology and Hepatology

INFECTIOUS COMPLICATIONS IN PATIENTS WITH LIVER CIRRHOSIS (Abstract): Liver cirrhosis is the end stage of any chronic liver disease. Complications occurring in patients with liver cirrhosis may be specific to this pathology and to gastroenterology (upper gastrointestinal bleeding, hepatic encephalopathy) or may interfere with other specialties (hepatorenal syndrome, spontaneous bacterial peritonitis, and other localized infectious complications). Over the past few decades, major efforts have been made to increase survival in patients with cirrhosis, but unfortunately, few therapeutic methods have been proven effective. Bacterial infections are frequent and serious complications of liver cirrhosis, resulting in high morbidity and mortality, especially in hospitalized patients, despite significant progress in health care for those with advanced liver disease. Keywords: LIVER CIRRHOSIS, INFECTIOUS COMPLICATIONS, BACTERIAL, MORTALITY.

EPIDEMIOLOGY

The estimated incidence of infectious complications in hospitalized patients without liver diseases is 5-7%, significantly lower than in cirrhotic patients (30-40%) (1).

Intrahospital mortality in cirrhotics with infectious complications is approximately 15%, significantly higher than in those without infectious pathology, while mortality from infectious complications is 20 times higher in patients with cirrhosis than in general population (2).

The most frequent infectious complications in cirrhotics are spontaneous bacterial peritonitis (25%), infections of the urinary tract (20%), pneumonia (15%), bacteremia (usually after therapeutic procedures - 12%), and cellulitis (1.2%) (1, 3).

Diagnosis and initiation of therapy are often delayed in infectious complications of cirrhosis due to negative bacteriology findings (culture and antibiogram). Blood cultures and cultures from ascitic fluid are positive in only 50-70% of cases (1).

Bacteria responsible for infectious complications are mostly Gram negative bacilli, especially Escherichia coli, accounting for almost 60% of infectious complications; Gram positive bacilli account for 30-35% of infectious complications, while bacterial association is confirmed in 5-10% of cases. Together with Escherichia coli, Staphylococcus aureus, Enterococcus faecali and Streptococcus pneumoniae are the bacterial agents that cause infectious complications in patients.
Infectious complications in patients with liver cirrhosis

Among infections occurring as complications during hospital stay, over 60% are caused by Gram positive cocci (4).

**PATHOGENESIS**

Patients with liver cirrhosis are exposed to infectious complications, but the mechanisms of an increased susceptibility to infection in these patients have not been fully established yet. Several mechanisms and favoring factors are suggested: qualitative dysfunctions of the reticuloendothelial system, increased intestinal permeability, presence of systemic shunts, systemic inflammatory response syndrome (5).

**Immunodeficiency**

Liver cirrhosis is characterized by a dysimmunitary status of multifactorial etiology, in which occur: decrease in the bactericidal activity of phagocytes, lower opsonic activity, low complement and protein C levels, alteration of the reticuloendothelial system, the main defensive system against hematogenously acquired infections (alteration of Kupffer liver cells activity and the existence of porto-systemic shunts result in deficient purge of systemic bacteria and endotoxins) (6).

**Bacterial translocation** is an important factor in the pathogenesis of infectious complications in cirrhotic patients; this mechanism is one of the key elements in the pathogenesis of spontaneous bacterial peritonitis and spontaneous bacteremia in liver cirrhosis. In conditions of sympathetic hyperactivity, in cirrhosis the reduction of intestinal motility favors stasis and bacterial overgrowth (7). In its turn, portal hypertension causes edema of submucosa and a change in intestinal permeability, thus favoring the translocation process (8).

**Systemic inflammatory response syndrome (SIRS)**

*Sepsis* is the systemic inflammatory response syndrome to infection. Other causes, such as acute pancreatitis, burns, and traumas, may also cause the same systemic inflammatory response syndrome (SIRS), but without infection as an etiological agent. The exact definitions of these syndromes cannot always be applied as such in liver cirrhosis, as patients may have leucopenia due to hypersplenism, increased basal heart rate (HR) due to hyperdynamic syndrome, hyperventilation caused by encephalopathy, or absence of fever syndrome.

Patients with liver cirrhosis present numerous factors that favor the occurrence of infectious complications, mostly with progression to septic shock, multiple organ failure (MOF) and, eventually, death (9). One of the pathogenic mechanisms of SIRS is the abnormal, exaggerated response of cytokines (TNF-α, IL-6, IL-1). Endotoxins stimulate the production and release of nitric oxide (NO), a vasodilator agent whose growth in a cirrhotic patient (by definition with vasodilator status) has disastrous effects. At the same time, nitric oxide metabolites increase cellular necrosis and platelet aggregability. Proinflammatory aggression factors are numerous, while the level of "protective" anti-inflammatory factors, such as protein C, is low in liver cirrhosis (3).

**Impact of infectious complications on the progression of cirrhosis**

The association of an infectious complication, sometimes common in other patients, may increase mortality 4 times in patients with liver cirrhosis in comparison with cirrhotic patients without bacterial/fungal infections (10, 11). A retrospective study of more than 11,000 patients
with cirrhosis suggests that there are some predictive factors for death in patients with infectious complications such as: severe liver failure, shock/multiple organ failure, digestive hemorrhage, hepatic encephalopathy, hepatocellular cancer, nosocomial infections (10). Acute renal insufficiency (hepatorenal syndrome, as a particular form of functional renal insufficiency) occurs in 27–34% of patients with decompensated liver cirrhosis, severe liver failure (12, 13); an infectious complication associated to hepatorenal syndrome (preexistent or precipitated by a septic status) increases the mortality rate to 40–50% in liver cirrhosis (10, 12).

Statistical data show an intrahospital mortality of 20–50% for cirrhotic patients with bacterial superinfections, twice higher than in cirrhotics without infections; infections are directly responsible for 30–50% of deaths in liver cirrhosis (14).

Bacterial infections in patients with cirrhosis can be asymptomatic or pauci-symptomatic, reason why they must be suspected in any cirrhotic patient with sudden unaccountable deterioration of liver function. Any suspicion of infectious complication requires close monitoring of vital functions: temperature, heart rate, respiratory rate, arterial pressure, physical exam of thorax and abdomen, presence of cutaneous lesions. Mandatory investigations in these cases include hemoleukogram, blood cultures, urine test and urine culture, thorax X-ray, sputum cultures, ascitic fluid/pleural fluid cultures, and abdominal ultrasound.

**Spontaneous bacterial peritonitis**

Spontaneous bacterial peritonitis (SBP) is the infection of ascitic fluid without organ perforation or abdominal inflammation such as abscesses, acute colecystitis, acute pancreatitis etc. SBP is a frequent and severe complication of cirrhosis, with an incidence of 7–25% in hospitalized cirrhotic patients.

**CLINICAL FEATURES**

Clinical symptoms are extremely variable in asymptomatic patients (in 30% of cases) progressing to severe deterioration of general status, with the occurrence of hepatorenal encephalopathy, hepatorenal syndrome or death from toxicoseptic shock without obvious cause (1).

The diagnosis of SBP is made by diagnostic paracentesis. This must be performed upon any clinical suspicion of ascitic fluid infection (refractory ascites, abdominal pain, fever etc.) in all admitted patients after the first episode of liver decompensation.

The main SBP diagnostic criteria are based on ascitic fluid microscopy findings (polymorphonuclear neutrophils (PMN) count – cut-off value: 250/ml) and microbial cultures. Ascitic fluid examination should reveal PMN>250/mm$^3$ and positive cultures (Gram negative bacilli in 60–80% of cases: *Echerichia coli, Klebsiella Pneumoniae*) (6).

There are two forms of ascitic fluid infection which do not meet all SBP diagnostic criteria, but must be treated similarly:

- neutrocytic ascites with negative culture
- monomicrobial non neutrocytic bacter ascites

*Neutrocytic ascites with negative culture* – the diagnostic criteria are similar to SBP, but cultures are negative. It is compulsory to rule out other causes outside cirrhosis: peritoneal tuberculosis, acute pancreatitis, and peritoneal carcinomatosis.
Infectious complications in patients with liver cirrhosis

Course and prognosis are similar to SBP and, consequently, treatment is identical.

Monomicrobial nonneutrocytic bacter ascites (without neutrophils) is characterized by positive cultures, but with less than 250 PMN/mm³ in fluid. It may signal the contamination of the ascitic fluid, but also an early form of SBP; clinical course depends on the presence or absence of signs of systemic infection; in patients with signs of infections, prognosis and treatment are similar to SBP.

SBP TREATMENT must be initiated early, immediately after fluid collection and empirically, without waiting for culture results. According to the present standard, 2g of Cefotaxim should be administered every 8h i.v. for 5 days, which is highly effective in approximately 85% of cases, and does not require dose adjustment depending on the degree of liver or renal insufficiency. Intravenous alternatives with similar efficacy are Ceftriaxone 2g every 24h, for 5 days, and Amoxicilin associated to Clavulanic acid 1.2g every 6-8 h, for 2 days (1). In patients who do not present other complications (SDH, encephalopathy, ileus, shock) fluoroquinolons may be administered p.o. for 8 days. The antibiotic must be changed according to the result of the antibiogram.

In cases marked by the occurrence of the hepatorenal syndrome, adjuvant treatment is recommended, some studies showing that associating albumin (1.5g/Kg in the first day, followed by 1g/Kg for another 72 h) with antibiotic is more efficient than the antibiotic administered alone (15).

Administration of early and efficient treatment has allowed us to reach a resolution rate of 90% in spontaneous bacterial peritonitis, with 70-90% intrahospital survival rate.

SBP PROPHYLAXIS

Prophylaxis is recommended in patients at increased risk for ascitic fluid infection: upper gastrointestinal bleeding, previous bacterial peritonitis or hypoproteic ascitis (<1g/dl) associated to severe circulatory dysfunction/insufficiency, when administration of Norfloxacin reduces SBP occurrence risk from 61% to 7% (16). In superior digestive hemorrhage, prophylaxis is of short duration and consists of either Norfloxacin p.o./naso-gastric tube for 7 days or a 3rd generation cephalosporine administered i.v. (Ceftriaxone/Cefotaxim). In this context, SBP prophylaxis reduces infectious complication rate, hemorrhage relapse rate, and consequently mortality rate (15% vs. 24%) (16).

In patients with no previous SBP episode the relapse risk is extremely high, reaching up to 70% in the first year, and requires permanent prophylaxis with Norfloxacin 400mg daily. Prophylaxis has considerable results: relapse reduction in the first year from 68% to 20%, with an even more spectacular improvement if only infections caused by Gram negative germs are present (from 60% to 3%) (14).

URINARY TRACT INFECTIONS

In terms of frequency, the infections of the urinary tract are the second most common location, after SBP, for infectious complications in patients with cirrhosis. Their incidence is higher in patients with urinary catheter and in females; also, severe liver insufficiency is often associated with this kind of infections (11).

In non-cirrhotic patients, the etiological spectrum is comparable with that of urinary
infections: Gram negative bacilli and coagulase negative staphylococci (3). The most commonly isolated microorganisms are *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus sporulatus*, but the prolonged use of antibiotic prophylaxis with fluoroquinolons during the last years has determined a significant increase in infections with Gram-positive bacteria, especially in nosocomial infections. Also, an increase in the prevalence of bacterial resistance has been recorded in the case of nosocomial infections (69%) as well as in community-acquired infections (22%) (3). Standard empirical treatment in cirrhotics with urinary infection includes 3rd generation cephalosporins or amoxicillin-clavulanic acid, avoiding fluoroquinolons.

**RESPIRATORY INFECTIONS**

Microorganisms involved in *community-acquired pneumonia* in patients with cirrhosis are generally the same as in general population, except that in cirrhotics there has been noticed an increased rate of bacteremia, multilobar affectation, renal insufficiency, and septic shock; the course is fatal in almost 15% of cases, mortality being significantly higher than in general population.

The most common causative agent of pneumonia is *Streptococcus pneumoniae*, but other bacteria, normally present in the oral cavity, especially anaerobes, such as *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae* or *Legionella* are often involved. In these patients, empirical antibiotic therapy consists in the administration of macrolides (erythromycin) combined with one of the following: cefotaxim, ceftriaxone, amoxicillin-clavulanic acid or quinolons active on pneumococci (17).

*Nosocomial pneumonia* is caused mainly by Gram-negative bacilli and staphylococci. Patients at increased risk for aspiration pneumonia are mostly those in the ICU, with upper gastrointestinal bleeding (especially those with mechanical tamponade with Blackmore catheter), hepatic encephalopathy or orotracheal tube, situations which favor tracheobronchial aspiration, as well as orotracheal intubation, esophageal tamponade and hepatic encephalopathy. Empirical antibiotic therapy must include 3rd generation cephalosporins (cefotaxim i.v.), carba-penems or piperacillin-tazobactam plus ciprofloxacin or levofloxacin and vancomycin or linezolide (3).

Cirrhotic patients with hydrothorax may develop *spontaneous bacterial empyema* (by analogy with SBP), which occurs in the absence of a pneumonic infection or other obvious cause for empyema) (18,19). Spontaneous pleural empyema occurs in 10-20% of cirrhotic patients with hydrothorax, the main risk factor being SBP (17). The initiation of antibiotic therapy (3rd generation cephalosporins) is indicated even in the absence of bacteriological confirmation, if the pleural fluid contains over 250 PMN/mm³ (3).

**SKIN AND SOFT TISSUE INFECTIONS**

Cellulitis and lymphangitis are other infections frequently occurring in patients with cirrhosis as compared to those without cirrhosis. Incriminated risk factors are thin fragile skin, edemas, poor hygiene, malnutrition, frequent hospitalizations, and invasive maneuvers. The involved germs are often *Staphylococcus aureus*, *Streptococcus pyogenes* and Gram-negative enteric
bacteria, while the incidence of Gram-negative bacilli, such as *E. coli, Klebsiella spp.* or *Pseudomonas aeruginosa,* has increased (3).

Although skin infections may seem common at a first glance, they may progress to severe cellulitis and necrotizing fasciitis, complications associated with an extremely high mortality, up to 76% (20, 21).

Antibiotic therapy is efficient in most cases with mild forms of cellulites, still with a high degree of recurrence. Antibiotic therapy must be initiated on suspicion of skin infection, as further delay will definitely result in severe forms, where therapeutic intervention is limited, and mortality high.

Standard empirical treatment includes amoxicillin plus clavulanic acid or cephalosporin and ofloxacin, with 83% efficiency in community-acquired infections, but only 50% efficiency in the nosocomial ones (20). Surgical debridement of necrotized tissue is mandatory in necrotizing fasciitis.

**MENINGITIS**

As with other infectious complications, meningitis has a higher incidences and severity in cirrhotic patients; mortality may reach 50-65% and even exceeds these values in elderly patients or in those with alcoholic cirrhosis (3).

While community-acquired meningitis is mostly caused by pneumococcus and meningococcus, in cirrhotics an increase in the number of meningites caused by *E. coli* and *Listeria* has been observed (3). Another characteristic of meningitis in cirrhosis is the increased risk of recurrence.

Diagnosis of meningitis in cirrhotics is often more difficult, especially in those with hepatic encephalopathy, where neuropsychic symptoms, apparently justified, may confuse and delay diagnosis. Physical examination of the cirrhotic patients with fever syndrome, cephalalgia and neuropsychic disorders must not exclude meningitis. Early diagnosis (it is estimated that in cirrhotic patients this is delayed by 4 times compared to other patients) and empirical antibiotic therapy (with antibiotics that cross the blood-brain-barrier – vancomycin combined with 3rd generation cephalosporins and ampicillin) can help reduce mortality (11).

**INFECTION WITH CLOSTRIDIUM DIFFICILE**

The incidence of *Clostridium difficile* (CD) infection has increased in the past years, while patients admitted to gastrohepatoenterology units, especially those with liver cirrhosis, show favoring conditions for this complication (3).

What seems intriguing is that this infection occurs less frequently in patients with superior digestive hemorrhage or hepatic encephalopathy, who usually receive antibiotic treatment (an important risk factor in CD infection); this peculiarity may be accounted for by the fact that lactulose (constantly administered in cirrhotic patients with such complications) causes reduction in the production of short chain fatty acids and suppresses CD proliferation (22).

**TUBERCULOSIS IN LIVER CIRRHOSIS**

Bacillus infection occurs frequently in immunocompromised patients, in chronic alcoholics; by definition, cirrhosis is an important risk for the occurrence of pulmonary or extrapulmonary tuberculosis (23).

Bacillus peritonitis may often be mistaken for SBP (refractory ascites, abdominal
pain etc.), but it usually occurs in patients without significant liver insufficiency. Peritoneal biopsy is often necessary for differential diagnosis, showing multiple disseminated white-yellow nodules, inflammation predominantly with lymphocytes and granulomas.

Cirrhotics with tuberculosis usually have a satisfactory response to tuberculous treatment, but with more severe hepatotoxic adverse effects and significantly decompensated liver functions (10).

**CONCLUSIONS**

Bacterial infections represent an important cause of morbidity and mortality in patients with cirrhosis as a consequence of their immunocompromised status. All patients with liver cirrhosis must be monitored for early diagnosis of infectious complications. Over the past few years, prompt diagnosis and correct antibiotic therapy have determined a significant reduction in mortality due to bacterial infections in patients with liver cirrhosis.

**REFERENCES**

Infectious complications in patients with liver cirrhosis


MEASLES VACCINATION IN THE PRESENCE OR ABSENCE OF MATERNAL MEASLES ANTIBODY: IMPACT ON CHILD SURVIVAL

Measles vaccine (MV) has a greater effect on child survival when administered in early infancy, when maternal antibody may still be present. Abay et colab. reanalyzed data from 2 previously published randomized trials of a 2-dose schedule with MV given at 4–6 months and at 9 months of age. In both trials antibody levels had been measured before early measles vaccination. In trial I (1993–1995), the mortality rate was 0.0 per 1000 person-years among children vaccinated with MV in the presence of maternal antibody and 32.3 per 1000 person-years without maternal antibody. In trial II (2003–2007), the mortality rate was 4.2 per 1000 person-years among children vaccinated in presence of maternal measles antibody and 14.5 per 1000 person-years without measles antibody. Possible confounding factors did not explain the difference. In a combined analysis, children who had measles antibody detected when they received their first dose of MV at 4–6 months of age had lower mortality than children with no maternal antibody, the MRR being 0.22 (95% CI, .07–.64) between 4–6 months and 5 years. In conclusion, child mortality in low-income countries may be reduced by vaccinating against measles in the presence of maternal antibody, using a 2-dose schedule with the first dose at 4–6 months (earlier than currently recommended) and a booster dose at 9–12 months of age. (Abay P, Martins CL, Garly ML et al, Measles vaccination in the presence or absence of maternal measles antibody: impact on child survival Clin Infect Dis. (2014) 59 (4):484-492.

Ecaterina Enache