Infections in patients affected by liver cirrhosis: an update

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SUMMARY

Patients with liver cirrhosis present an increased incidence of infections.
The main cause has been founded in alterations of the enteric flora and of the intestinal barrier probably due to portal hypertension, in addition to a reticulo-endothelial system dysfunction. Furthermore, those living with cirrhosis can report a high predisposition to sepsis and septic shock, due to the excessive response of pro-inflammatory cytokines and a complessive hemodynamic derangement.
By the analysis in the experimental model of the cirrhotic rat, it was demonstrated that radio-labelled *Escherichia coli* given by the oral route resulted in the location of the bacteria in the gut, the ascitic fluid and mesenteric lymph nodes, a phenomenon known as bacterial translocation.
Bacteria encountered with the highest frequency are those colonizing the intestinal tract, such as *E. coli*, *Klebsiella pneumoniae* and *Enterobacteriaceae*, intracellular bacteria and parasites are reported with a lower frequency. Multi-drug resistant bacteria are cultured with the highest frequency in those with frequent hos-pitalisations and report both high septic shock and mortality rates.
Spontaneous bacterial peritonitis (SBP) is the commonest infection in cirrhotic, estimated to occur in 10-30% of the cases with ascites. A practical approach may include administration of a protected penicillin, III generation cephalosporin or quinolones in uncomplicated cases. Instead, in complicated cases and in nosocomial SBP, administration of cephalosporin or quinolones can be burned by the high resistance rate and drugs active against ESBL-producing bacteria and multidrug resistant Gram positive bacteria have to be considered as empiric therapy, until cultures are available. When cultures are not readily available and patients fail to improve a repeated diagnostic paracentesis should be performed. Current investigations suggest that norfloxacin 400 mg/day orally has been reported to successfully prevent SBP in patients with low-protein ascites and patients with prior SBP.

Keywords: cirrhosis, infection, spontaneous bacterial peritonitis, treatment, prophylaxis.

■ INTRODUCTION

Significant improvements in the management of cirrhotic patients in terms of antiviral therapy, portal hypertension management and liver transplantation have been reported during the last years, these improvements resulted in a reduction of the burden of the disease and of the mortality related. Patients with liver cirrhosis have an increased incidence of infections that are a major cause of morbidity and mortality. In addition to alterations in the enteric flora and the intestinal barrier due to portal hypertension, susceptibility to infection can be attributed to an impairment of the defence mechanisms against infections [1-3]. A number of dysfunctions of the reticulo-endothelial system, neutrophil granulocyte functions and humoral and cell-mediated immunity have been described in patients with cirrhosis [4]. These dysfunctions may result in an increase of the risk of infections sustained by bacteria and parasites. Indeed, some papers report infections by *Leishmania*, *Toxoplasma gondii*, *Listeria monocytogenes* and *Mycobacterium tuberculosis* suggesting an increased susceptibility to these pathogens [5-

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9]. Furthermore, those living with cirrhosis can report a high predisposition to sepsis and septic shock, due to the excessive response of pro-inflammatory cytokines and hemodynamic derangement [10].

■ CIRRHOSIS AND IMMUNITY

Systemic immune response is impaired in cirrhotic due to a number of reasons. It is clear that the large overflow of bacteria and bacterial products from the gut fail to be cleared by the liver, due to portosystemic shunting and the hepatocellular function failure. These abnormalities have been considered responsible of an ineffective phagocytic activity and of a correspondent reduction in serum albumin, complement and protein C activity that undermines efficacy of phagocytic activity of the liver where are located about 90% of the reticulo-endothelial cells in the body. Alcohol addiction and malnourishment can increase the cirrhosis associated immune dysfunction [11-13]. Permeability of gut to bacteria is altered in cirrhotic patients. By the analysis in the experimental model of the cirrhotic rat, it was demonstrated that radiolabelled *Escherichia coli* given by the oral route resulted in the location of the bacteria in the gut, the ascitic fluid and the mesenteric lymph nodes [14]. This phenomenon known as bacterial translocation is the migration of bacteria from the gut lumen through systemic circulation via the mesenteric lymph nodes and the portal vein to the bloodstream. Bacterial translocation can be enhanced by a number of factors including local innate and adaptive immunity, impaired intestinal motility and increased intestinal permeability, all these factors can be observed in cirrhotic patients [15].

Besides spontaneous infections, bacterial translocation is responsible of other complications of cirrhosis involving the immune system. In fact, Endotoxin, other bacterial products and bacterial DNA translocate to extra-intestinal sites and promote host immunological and hemodynamic responses, causing the systemic pro-inflammatory and hyperdynamic circulatory state in cirrhosis [16]. Of note, translocation of viable bacteria is related to compromission of liver function and it is very high in those with end-stage liver disease, instead bacterial products translocate at a high rate

also during the early stage of cirrhosis, causing the susceptibility to infection reported in patients with compensated cirrhosis [17]. Overall, patients living with cirrhosis have a dysregulated cytokine response leading to a high degrade immunologic response causing tissue damage. In these patients, a pre-existing hyperdynamic state predispose to the complications due to the cytokine storm and oxide nitric overproduction sepsis-related which can cause hypotension, reduced tissue perfusion, multi-organ failure, and finally death [18,19].

■ EPIDEMIOLOGY

Bacterial infections impact on morbidity and mortality of cirrhotic [20]. It is estimated that over one-third of hospitalised patients with cirrhosis report an infection, a proportion significantly higher than hospitalised patients in general. Some factors, including gastrointestinal bleeding can increase this proportion. It is notable that mortality related to bacterial infection in cirrhosis can be very high [2].

On the basis of current investigations, spontaneous bacterial peritonitis, pneumonia, urinary tract infection, soft tissue infection, and bacteraemia are the most common infection reported in cirrhotic, but patients living with liver disease are estimated to report the highest risk of infection also during a number of surgical procedures [1, 21, 22]. Bacteria encountered with the highest frequency are those colonizing the intestinal tract, such as *E. coli*, *Klebsiella pneumoniae* and *Enterobacteriaceae*, intracellular bacteria and parasites are reported with a lower frequency, but relative diagnosis can be difficult in some cases due to low specificity of clinical pictures [23, 24]. Gram-positive bacteria are considered to be responsible in about 20% of cases, their frequency is related to recent or current hospitalisation, invasive procedures and quinolones administration.

Multi-drug resistant bacteria are cultured with the highest frequency in those with frequent hospitalisations and report both high septic shock and mortality rates [25].

As broad-spectrum antibiotics are administered to the majority of infected patients with cirrhosis, it is advisable that cultures had been obtained in all case to narrow as soon as possible the spectrum of the antibiotic treatment.

■ SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is commonly reported in cirrhotic. It has estimated to occur in 10-30% of the cases with ascites [26]. Bacterial translocation from the gut plays a pivotal role and the commonest bacteria colonizing the intestinal tract are those retrieved in patients with spontaneous bacterial peritonitis. It is estimated that bacteria reaching the ascitic fluid can grow due to the local decreased opsonic activity and systemic immune dysfunction [27].

SBP may be a silent process and up to one-third of the cases can present without the classic triad of fever, abdominal pain and worsening of ascites. It is advisable that patients with ascites undergo to a diagnostic paracentesis particularly when variceal bleeding is reported, when the signs of septic shock are present or when there is an unexplained worsening of liver or renal function. Prognosis of SBP can be poor in the cases with severe compromission of liver function or when encephalopathy is present. Patients acquiring SBP in hospital and those infected by multi-drug resistant bacteria report the highest mortality rate [28].

Main tools to diagnose SBP are the cell count on ascitic fluid and bacterial cultures. Role of reagent strips to assess leucocyte count has been proposed as a rapid and inexpensive method to obtain SBP diagnosis, but it reports low sensitivity. On the basis of recent investigations the test has the greatest role to exclude SBP diagnosis. On practical ground, a patient reporting a count above 250 PMN/mm^3 has to report the highest suspect of SBP, particularly when an explained worsening ascites, septic shock or encephalopathy are reported [28-30].
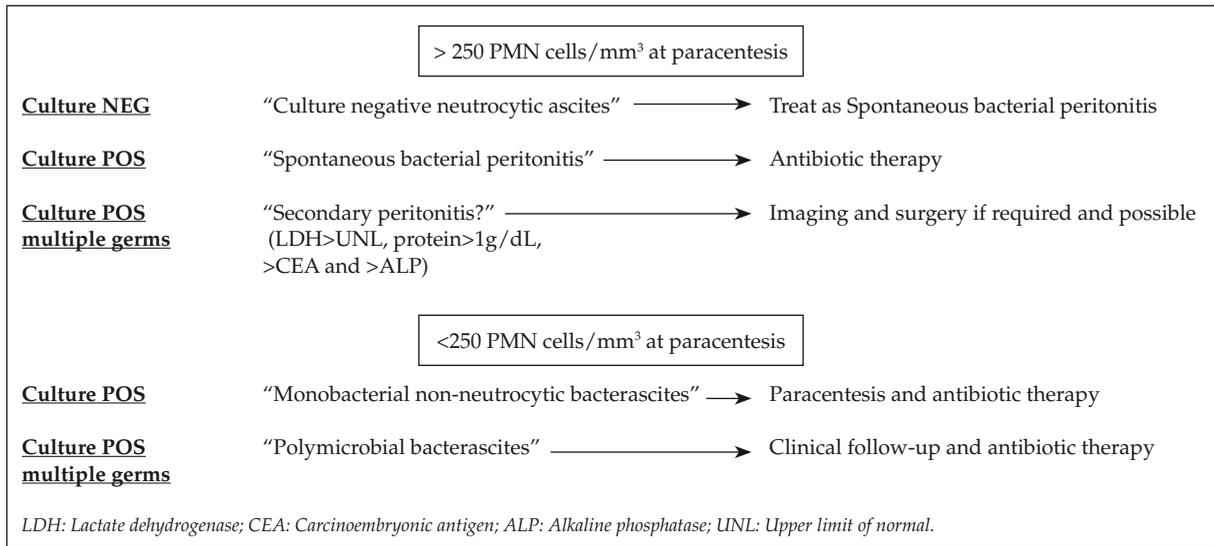
When SBP is diagnosed, an empiric therapy has to be administered, basing the choice on considerations regarding the possible origin of the infection, the presence of individual risk for multidrug resistant bacteria and the local microbiology. A practical approach may include administration of a protected penicillin, III generation cephalosporin or quinolones in uncomplicated cases. Instead, in complicated cases and in nosocomial SBP, administration of cephalosporin or quinolones can be burned by the high resistance rates and drugs active against ESBL-producing bacteria and multi-drug resistant Gram-positive bacteria have to be considered as empiric therapy, until cultures are available (Table 1). When cultures are not readily available and patients fail to improve a repeated diagnostic paracentesis should be performed (Figure). Patients not showing a reduction of 25% of PMN have to be considered unresponsive to treatment and should undergo a complete reassessment of the diagnostic and therapeutic approach [31, 32].

Besides antibiotic therapy, patients with SBP should receive support to renal function, due to renal failure results in an increase of mortality up

Table 1 - Type of infection and suggested empirical antibiotic therapy in patients with liver cirrhosis.

SBP, spontaneous bacteremia, SBE
Enterobacteriaceae, Streptococcus pneumoniae, Streptococcus viridans 1st line: Cefotaxime or ceftriaxone or BL-BI* iv Options: Ciprofloxacin per os for uncomplicated SBP; carbapenems iv for nosocomial infection in areas with a high prevalence of ESBL *BL-BI could be preferred in those with suspicious for enterococcal infection
Pneumonia
Streptococcus pneumoniae, Enterococcus spp, Haemophilus infuenzae, Mycoplasma pneumoniae, Enterobacteriaceae, S. aureus Community-acquired: ceftriaxone or BL-BI iv + macrolide or levofloxacin IV/PO Nosocomial and health care-associated infections: Meropenem or cetazidime iv + ciprofloxacin iv (iv vancomycin or linezolid should be added in patients with risk factors for MRSA)
Urinary tract infection
Enterobacteriaceae, E. faecalis, E. faecium 1st line: Ceftriaxone or BL-BI iv in patients with sepsis. Ciprofloxacin or cotrimoxazole PO in uncomplicated infections Options: In areas with a high prevalence of ESBL, iv carbapenems for nosocomial infections and sepsis (+ iv glycopeptides for severe sepsis); and nitrofurantoin PO for uncomplicated cases

BL-BI: Beta-lactam/beta-lactamase inhibitors (e.g., amoxicillin/clavulanic acid, ampicillin/sulbactam, and piperacillin/tazobactam)

	> 250 PMN cells/mm³ at paracentesis	
Culture NEG	"Culture negative neutrocytic ascites" ⟶	Treat as Spontaneous bacterial peritonitis
Culture POS	"Spontaneous bacterial peritonitis" ⟶	Antibiotic therapy
Culture POS multiple germs	"Secondary peritonitis?" ⟶ (LDH>UNL, protein>1g/dL, >CEA and >ALP)	Imaging and surgery if required and possible
	<250 PMN cells/mm³ at paracentesis	
Culture POS	"Monobacterial non-neutrocytic bacterascites" ⟶	Paracentesis and antibiotic therapy
Culture POS multiple germs	"Polymicrobial bacterascites" ⟶	Clinical follow-up and antibiotic therapy

LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; ALP: Alkaline phosphatase; UNL: Upper limit of normal.

Figure 1 - Algorithm for the management of cirrhotic patients with suspicious for ascitic fluid infection.

to 40%. Albumin administration should be considered, as its administration at a dosage of 1.5 g/kg within 6 hours from diagnosis followed by administration of 1 g/kg on day 3, coupled with antibiotic treatment, is associated with a considerable reduction of renal failure and mortality on the basis of a randomised study evaluating 126 patients with SPB. Following a protocol based on administration of both Cefotaxime and Albumin, the authors obtained a reduction in term of mortality approaching to 20%. In the patients analysed in the study, renal impairment was a strong predictor of mortality [33]. Plasma expanders have been proposed to replace Albumin in patients with SBP, on the basis of a study comparing albumin to hydroxyethyl starch. Only treatment with albumin was associated with a significant increase in arterial pressure and a suppression of plasma renin activity, indicating an improvement in circulatory function. A significant expansion of central blood volume (increase in cardiopulmonary pressures and atrial natriuretic factor) and an increase in systolic volume and systemic vascular resistance was associated with the highest rate of therapeutic response. In contrast, no significant changes were observed in these parameters in patients treated with hydroxyethyl starch [34]. On the basis of accurate investigations, Albumin should be administered to patients with serum creatinine>1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL, but it is

not necessary in patients who do not meet these criteria [35].

Patients living with liver cirrhosis experience a high rate of recurrence of SBP. On the basis of currently available data, administration of prophylaxis can reduce the incidence of SBP in the at risk settings. Current investigations suggest that norfloxacin 400 mg/day orally can prevent SBP in patients with low-protein ascites and in patients with prior SBP. Norfloxacin 400 mg orally twice per day for 7 days helps prevent infection in pa-

Table 2 - Prophylaxis regimens in SBP.

Secondary Prophylaxis in SBP
Norfloxacin 400 mg PO daily (preferred), Trimethoprim-sulfamethoxazole one tablet daily, Ciprofloxacin 500 mg PO daily, Levofloxacin 250 mg PO daily; *(duration indefinite as long as ascites is present)*
Primary Prophylaxis in SBP for patients with advanced liver diseases
Norfloxacin 400 mg PO daily (preferred), Trimethoprim-sulfamethoxazole one tablet daily, Ciprofloxacin 500 mg PO daily, Levofloxacin 250 mg PO daily; *(duration indefinite as long as ascites is present)*
Acute gastrointestinal hemorrhage
Ceftriaxone1 mg IV daily (preferred), Norfloxacin 400 mg PO BID, Ciprofloxacin 500 mg PO BID. *(duration 7 days)*

tients with variceal hemorrhage. Moreover, an intravenous antibiotic administration can be effective in preventing SBP during an active bleeding (Tab 2). Due to wide use of antibiotics can lead to infections sustained by resistant bacteria as well as *Clostridium difficile*-associated diarrhea, antibiotic prophylaxis has to be administered for selected patients with severe liver function impairment and ascitic fluid protein below 1.5 g/dl [reviewed in 29].

◼ OTHER BACTERIAL INFECTIONS IN CIRRHOSIS

Outcome of cirrhotic experiencing infections is poor. An accurate analysis reviewing the papers on the argument investigated the outcome of cirrhotic after an infective episode considering the characteristics of 11,987 patients with cirrhosis and infection included in 225 Cohorts reporting mortality data. After an observation period of 1, 3 and 12 months, mortality rate after a major infective episode was 30%, 44%, and 63% respectively. Considering 1135 patients with infection and 2317 without infection: 459 (40.4%) and 451 (19.5%), respectively, died during the follow-up period ($P = .00001$). On the basis of the studies selected, antibiotic prophylaxis did not ameliorate mortality rate [36].

Bacterial infection can trigger liver decompensation in patients living with liver cirrhosis and an acute liver failure can be reported in up to 30% of cases. SBP is the most investigated infection in cirrhotic patients, but non-SBP infections represent the majority of the cases reported.

Only few studies report the findings of the not-SBP infections in cirrhotic patients and data about clinical findings and mortality are not conclusive due to the low amount of the cases considered. A recent study evaluating 615 infections (not-SBP) diagnosed to 441 cirrhotic patients highlighted that the most frequent infection was UTI (26%), followed by cellulitis (15%), pneumonia (14%), and spontaneous bacteremia (10%). About 60% of the cases were healthcare associated or nosocomial of origin. Mortality was 11% and was extremely high in those with endocarditis. It is notable that infections commonly reporting a low mortality rate such as arthritis or vertebral osteomyelitis reported a mortality rate exceeding 10% in cirrhot-

ics. Moreover, in this population, the highest risk for 30-day mortality was associated to age, hepatic encephalopathy, serum sodium, and albumin levels. Infections sustained by MDR bacteria were associated with the in-hospital mortality [37, 38]. Non-SBP infections, therefore, constitute a heterogeneous population that includes patients with high and low risk of death depending on the severity of liver and renal dysfunction and on the type of infection. It is important to underline that some infections can have a poorer prognosis in cirrhotic patients as in those with endocarditis or bacterial meningitis. In these patients microbiologic aspects can be different than reported in the whole adult population and bacterial translocation and the impairment of immunity can justify the high frequency of *E. coli* and *Listeria* as causative agents of meningitis reported. It is relevant that findings of important life-threatening infections such as meningitis can be different and signs of meningeal irritation can be absent, making the diagnosis difficult due to the overlap of meningitis symptoms and those due to hepatic encephalopathy [39-42].

In summary, infections represent a heterogeneous group whose high mortality rate is related to liver function and renal impairment [43-45]. In the next future, infections in cirrhosis are projected to decrease due to the effect of the antiviral therapy on liver function [46]. SBP is the most investigated infection, probably due to its close association with an impaired liver function and variceal bleeding. Patients experiencing SBP have to be evaluated for long-term antibiotic prophylaxis that can be effective in reducing mortality. Every infective episode needs to be carefully evaluated in patients living with cirrhosis, particularly when liver function is considered to be low. In these cases, mortality can be higher than the whole adult population, clinical manifestations can be aspecific or overlap those of liver cirrhosis, and the bacteria encountered can be different than observed in patients without cirrhosis.

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