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Alcohol-related Liver Disease and sepsis

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Abstract. – OBJECTIVE: Sepsis is one of the most common complications and causes of death in patients with Alcohol-related Liver Disease. This narrative review will focus on several aspects of sepsis in the context of Alcohol-related Liver Disease. The pathophysiology of the increased susceptibility to infections consists mainly of impaired innate and adaptive immunity, changes in gut microbiota with consequent gut translocation of bacteria due to both alcohol abuse and the underlying liver disease. The diagnosis of sepsis in the context of Alcohol-related Liver Disease is challenging. Moreover, the use of classical acute-phase serum proteins (e.g., C-reactive protein and procalcitonin) has several limitations in this setting. The early administration of an adequate antibiotic treatment is pivotal. Finally, measures of infection control and prevention are needed because the prognosis of sepsis in patients affected by Alcohol-related Liver Disease is poor.

Key Words:
Alcohol-related Liver Disease, Sepsis, Alcoholic cirrhosis, Alcoholic hepatitis, Alcohol use disorders, Infection.

Abbreviations

AC: Alcoholic Cirrhosis; ALD: Alcohol-related Liver Disease; AH: Alcoholic Hepatitis; ACLF: Acute-on-chronic liver failure; CRP: C-reactive protein; LT: Liver Transplantation; PCT: Procalcitonin; SIRS: Systemic Inflammatory Response Syndrome.

Introduction

Alcohol-related Liver Disease (ALD) is the most common liver disease in Western countries[1]. ALD ranges from liver steatosis to steatohepatitis and cirrhosis with its complications[2]. At any stage of disease, patients with ALD can develop alcoholic hepatitis (AH), a severe clinical condition with a high risk of death, characterized by rapid onset of jaundice and worsening of liver function[3].

Sepsis represents one of the most common complications and causes of death in patients with ALD[4]. Moreover, infection represents one of the most common precipitating factors for Acute-on-Chronic Liver Failure (ACLF) also in patients with ALD[5]. Patients with ALD show an increased susceptibility to infection due to impaired innate and adaptive immunity, and changes in gut microbiota with consequent gut translocation of bacteria. Both mechanisms are secondary to the effects of alcohol abuse and chronic liver disease[6]. The exact prevalence of sepsis in ALD patients is unknown, both for the lack of well-designed studies assessing prevalence and related-mortality, and for the presence of other co-factors, such as gastrointestinal bleeding or acute kidney injury, that in turn may be precipitated by infection[6]. In addition, the diagnosis of sepsis in ALD patients is challenging because it may be difficult to differentiate it from the Systemic Inflammatory Response Syndrome (SIRS) typically showed by patients with AH and ACLF[6]. Finally, considering its high mortality, a prompt and appropriate treatment should be started in ALD patients developing sepsis, considering their adjunctive risks for poor outcome.

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Factors Predisposing to Sepsis in Alcohol-related Liver Disease

The effects of chronic alcohol abuse on immune system are well known and consist of an increased production of pro-inflammatory cytokines and, at the same time, of an inhibition of anti-microbial function of both innate and adaptive immune cells[4]. The microbial killing capacity of neutrophils and macrophages phagocytosis are also impaired. In addition, antigen presentation function is negatively affected in patients with chronic alcohol abuse, contributing to the reduction of host defences[4].

The course of cirrhosis, regardless of its etiology, is complicated by cirrhosis-associated immune dysfunction, a condition characterized by both immunodeficiency and systemic inflammation due to persistent stimulation of immune system cells[7]. In fact, liver cirrhosis impairs the synthesis of innate immunity proteins reducing the bactericidal capacity of phagocytic cells. Moreover, structural derangements of cirrhosis, porto-systemic shunts, and loss of Kupffer cells result in diminishing the clearance of endotoxins and bacteria from the portal blood, leading to bacteremia. All these factors lead to persistent stimulation of immune cells, increasing levels of pro-inflammatory cytokines[8]. The severity of this state of systemic inflammation in cirrhotic patients directly correlates with the disease severity and the degree of portal hypertension, and inversely, with survival[9].

Vitamin D deficiency, that is present in up to 92% of patients with liver disease[10,11], could also play a role in the higher susceptibility to infection among ALD patients. The role of vitamin D deficiency has been investigated in sepsis[12] and in other infectious disease, such as SARS-CoV-2 infection[13]. In fact, besides regulating bone metabolism, vitamin D has also antimicrobic activities and immuno-modulatory properties. With this regard, vitamin D is a co-factor for the maintenance of tight junctions', gap junctions' and adherences junctions' integrity. Moreover, it enhances cellular innate immunity through the induction of antimicrobial peptides, including cathelicidin and defensins, which show direct antimicrobial activities against pathogens. Finally, vitamin D is able to prevent and reduce the cytokine storm induced by the innate immune system hyperactivation[12,14].

About 20% of patients with compensated cirrhosis and more than 50% of patients with decompensated liver disease are malnourished[15,16]. By impairing both innate and adaptive immunity as a consequence of reduced complement components, compromised phagocyte function, impaired activation of T cells, and deficit of cytokine production[17], malnutrition is associated with a high rate of infections and sepsis in patients with LD[17].

Several drugs are also implicated in the high rate of infection in patients with ALD. Proton pump inhibitors are extensively prescribed in cirrhotic patients although their use resulted inappropriate in nearly a half of them[18]. Moreover, their use increases the susceptibility to *Clostridium difficile* infection and spontaneous bacterial peritonitis[19,20].

Corticosteroids are used for the treatment of patients with severe AH, being able to reduce the 28-day mortality[21,22]. However, their use is associated to an increased risk of infectious events among treated patients due to defective lymphocyte signalling[23]. It has been shown that high levels of circulating bacterial DNA before corticosteroid treatment can predict the risk of infection within 7 days from prednisolone treatment[23]. This might help to better identify which of the corticosteroid-treated patients will benefit from preventive antibiotic therapy[24].

Evidence suggests a critical role of gut-liver axis alterations (e.g., changes of gut microbiota, increased intestinal permeability and endotoxemia) in patients with ALD[25-27]. While in a condition of "eubiosis" the gut microbiota appears to enhance the immune response to both enteric and systemic pathogens[28], "dysbiosis" of patients with ALD could contribute to increase the risk of infection and sepsis[29]. In fact, some studies[30-32] demonstrate that the gut microbiota can direct the systemic immune response in a regulatory or proinflammatory direction and enhance the innate and adaptive immune response against bacteria, viruses, and fungi. Moreover, the increased intestinal permeability secondary to the damage of intestinal barrier could allow bacteria to enter the systemic circulation increasing the risk of sepsis[4]. Considering these findings, the development of microbiota-targeted therapies may be crucial to restore a state of eubiosis in patients with ALD in order to prevent infection and sepsis.

Microbiological Data and Patients' Clinical Characteristics

Bacteria are the most frequent cause of infective complications in patients affected by ALD[4]. Among them, *Enterobacteriaceae* (Gram-negative bacteria of intestinal origin), such as *Esch-*

erichia coli and *Klebsiella pneumoniae* are the most frequent[33]. Among Gram-positive bacteria, the most common causes of infection are *Staphylococcus aureus* and *Enterococci*[33]. Multidrug-resistant bacteria represent a common cause of infection in patients receiving care either in hospital or in other health care facilities, long-term quinolone prophylaxis or antibiotics in the last three months[34]. Spontaneous bacterial peritonitis and urinary tract infections are the most frequent infections occurring in patients with ALD, followed by pneumonia, cutaneous infections, and bacteraemia[4]. Recent studies[35,36] have shown a higher propensity of patients with alcoholic cirrhosis (AC) and infection to develop acute kidney injury[35] and ACLF[36].

Among patients treated with corticosteroids because of AH, respiratory tract infections are predominant[37]. According to the STOPAH trial, respiratory tract infections represent about the 50% of all infections during follow-up, probably due to corticosteroid treatment, previous hospitalization or admission to Intensive Care Unit[21]. Patients with AH are also more susceptible to *Clostridium difficile* infection than other hospitalized patients[38]. Invasive candidiasis or aspergillosis, *Pneumocystis carinii* and viral infections are rare, but they typically affect immunocompromised patients with AH and concomitant corticosteroid treatment[4].

Liver transplant candidates show a higher risk to develop severe infectious complications, because of their advanced liver disease. Bacterial infections have a major impact on liver disease progression and significantly increase mortality rates before Liver Transplantation (LT)[39]. In addition, the need for immunosuppression after LT makes transplant recipients at high risk to develop infection and sepsis. That being said, patients with alcoholic etiology undergoing LT should expect the highest risk for infection than others. However, a recent retrospective study did not show differences in term of prevalence of infectious complications after LT between patients with alcoholic and those with viral cirrhosis[40,41]. This observation is in line with data from European Liver Transplant Registry not showing any higher risk of infective complication after LT among alcoholic recipients[42].

Diagnosis

Differentiating systemic inflammation from sepsis could be challenging both in patients with AH and acute decompensation of AC. In fact, most of patients with these two conditions fulfil criteria for SIRS although they have no evidence of infection[43]. In addition, the use of beta-blockers for the prevention of variceal bleeding and hypersplenism could respectively mask tachycardia and leukocytosis with a possible underestimation of diagnosis of infection[43]. Finally, in the setting of advanced liver disease, sepsis could manifest even the rise of bilirubin level, newly onset hepatic encephalopathy, deterioration of liver and/or renal function. All these aspects add complexity to the diagnosis of sepsis in patients with ALD.

Acute phase proteins, such as C-reactive protein (CRP) and procalcitonin (PCT) are commonly used as early markers of infection in general population[44]. Patients with AC may show reduced CRP and PCT levels in response to infection, because CRP is mainly produced by the hepatocytes[43] and liver is considered the most relevant site of PCT production[44]. By contrast, patients with AH with no signs of infection could show high levels of CRP and PCT[45]. In fact, liver disease as well as other chronic states (e.g., chronic kidney, heart diseases, metabolic disorders) represents a condition in which PCT level could be spontaneously elevated[44].

Beta-D-glucan and galactomannan are two components of the fungal cell wall currently used as biomarkers for fungal infection. Differently from general population, none of them has been validated in patients with AH[45].

The assessment of serum lactate level represents the cornerstone for the diagnosis of septic shock[46]. A serum lactate level greater than 2 mmol/L after adequate fluid resuscitation together with hypotension requiring vasopressor therapy to maintain mean blood pressure 65 mm Hg or greater identify patients with septic shock. However, liver dysfunction is significantly associated with an impaired lactate clearance during the early resuscitation of sepsis because lactates are mainly metabolized by the liver[47].

Other biomarkers, such as serum lipopolysaccharide and 16s ribosomal DNA have been studied to predict infection, but their application needs further validation before being available for routine clinical practice[23,48].

A report[49] from the North American Consortium for the Study of End-Stage Liver Disease has detailed criteria for infection in patients with chronic liver disease. However, the use of these criteria in patients with ALD has some limitations due to a lack of growth of pathogenic organisms in standard laboratory media, false positive

culture for contamination, the delay of isolation of microorganisms using standard microbiological techniques[23].

As a practical approach, when sepsis is suspected in patients with ALD, chest X-ray, urine and blood culture should be promptly obtained. Culture of ascitic fluid and sputum should be also obtained when respectively ascites or low respiratory tract infection are suspected[45].

Management and Prevention

Since gut with bacterial translocation is the main source of infection in ALD, intestinal decontamination by orally administering poorly absorbed antibiotics (e.g., rifaximin) could play an important role in infection prevention for these patients[50]. In a recent retrospective study, the long-term use of rifaximin in patients with liver cirrhosis and hepatic encephalopathy was significantly associated with prolonged overall survival and reduced risk of spontaneous bacterial peritonitis, without significantly increasing the risk of developing resistant microorganisms[51]. Other prevention strategies could be gut microbiota modulation using probiotics or fecal microbiota transplantation[50]. However, these strategies need to be investigated in well-designed studies.

Vitamin D supplementation has a pathophysiological rationale in the infection prevention of these patients, although this hypothesis has not been yet tested in well-designed clinical studies. In cirrhotic patients with vitamin D levels less than 20 ng/ml, the administration of vitamin D to reach serum levels above 30 ng/ml has a rationale[15].

Alcohol abstinence reverses most of the immunological abnormalities related to immune dysfunction in patients with ALD[52]. The most effective treatment for promoting abstinence is a combination between psychosocial interventions and anti-craving medication. Among anti-craving drugs, baclofen is the only medication with a safety profile formally tested in patients with ALD[53-55].

Albumin is used in cirrhotic patients to regulate blood volume and to prevent renal failure[56]. Given its antioxidative and immunoregulatory properties, its role in infection prevention has been also investigated in cirrhotic patients[8]. Albumin administration has been shown to reduce plasma levels of TNF-α and IL-6, and ascitic fluid levels of endotoxin, TNF-α and IL-6 in cirrhotic patients with spontaneous bacterial peritonitis[57]. A recent study[58] has also shown that infusion of human albumin is able to reverse plasma-mediated immune dysfunction by binding and inactivating PGE2. However, these promising results need to be confirmed in other studies[8].

Relative adrenal insufficiency is a condition of inadequate cortisol response to stress described in cirrhotic patients with sepsis or septic shock[56]. Concerning the treatment with hydrocortisone in this setting, the authors of a randomized clinical trial enrolling cirrhotic patients with septic shock concluded that despite initial favorable effects on hemodynamic parameters, hydrocortisone did not reduce mortality and was associated with an increase in adverse effects[59]. For these reasons, hydrocortisone treatment cannot be routinely recommended in cirrhotic patients with sepsis or septic shock as an infection prevention strategy[56].

Other measures of infection prevention in ALD patients also include avoiding invasive catheterization (e.g., urinary or vascular catheters) or hospitalization whenever possible[45].

The early diagnosis of sepsis requires a prompt and adequate antibiotic treatment. The choice of empirical antibiotics should be based on suspected source, severity of infection and local epidemiological data on antibiotic resistance[43]. Patients should be also stratified for risk of multidrug resistant infection, considering both the recent exposure to antibiotics and healthcare environments. In any case, the development of sepsis after 48 hours from hospital admission must be classified as nosocomial infection.

In patients with AH receiving corticosteroids, antibiotic therapy for prior infection should be continued alongside corticosteroid treatment[43]. About the role of antibiotic prophylaxis in this setting the ongoing clinical trial, Antibiocor Study (NCT02281929), is assessing its impact on survival in these patients[60].

Conclusions

Patients with ALD are at high risk to develop sepsis. Several pathogenetic mechanism ranging from alcohol abuse, cirrhosis-related immune dysfunction, malnutrition, changes in gut microbiota and bacterial translocation are involved in this complex syndrome. New laboratory markers with higher specificity and sensibility are needed to improve the diagnosis of sepsis in this setting. A higher level of suspicion and systematic screening of hospitalized ALD patients are warranted to improve the prognosis of these patients.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contribution
GA Vassallo, T. Dionisi and C. Tarli interpreted literature data. GA Vassallo, A. Mirijello and G. Addolorato thought the scientific rationale, wrote and revised the paper. G. Addolorato, G. Augello, S. De Cosmo and A. Gasbarrini revised the final version of the paper. Each one of the authors has contributed to the writing and reviewing of the paper and approved the final version.

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