Seminar

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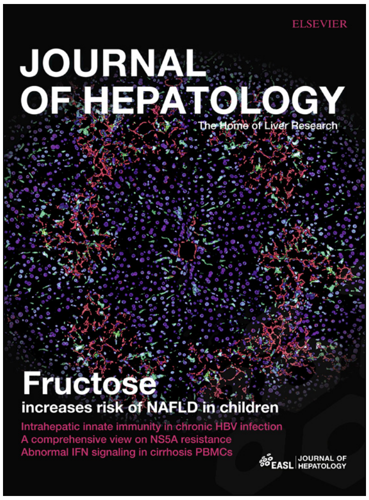

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Sepsis in Alcohol-related Liver Disease

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Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ALD, alcoholic liver disease; AH, alcoholic hepatitis; APC, antigen presenting cell; BAL, bronchoalveolar lavage; BT, bacterial translocation; CAID, cirrhosis-associated immune dysfunction; CMV, cytomegalovirus; DAMPs, danger-associated molecular patterns; ESBL, extended-spectrum β-lactamase; GM, galactomannan; GNB, Gram-negative bacillus; GPC, Gram-positive coccus; HCA, health care-associated; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IA, invasive aspergillosis; ICU, intensive care unit; IFI, invasive fungal infection; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; LPS, lipopolysaccharide; mDF, modified Maddrey discriminant function; MDRO, multidrug-resistant organism; MELD, model for end-stage liver disease; MERTK, MER receptor tyrosine kinase; MLN, mesenteric lymph node; MRSA, methicillin-resistant *Staphylococcus aureus;* NK, natural killer; PAMPs, pathogen-associated molecular patterns; PCP, pneumocystis pneumonia; PCR, polymerase chain reaction; PD1, programmed cell death 1; RCT, randomized controlled trial; sAH, severe alcoholic hepatitis; SB, spontaneous bacteremia; SBP, spontaneous bacterial peritonitis; TLR, Toll-like receptor; TIM3, T cell immunoglobulin and mucin domain-containing protein 3; TMP-SMX, trimethoprim-sulfamethoxazole; TNF, tumor necrosis factor; UTI, urinary tract infection; VSE, vancomycin-susceptible enterococcus; VRE, vancomycin-resistant enterococcus; XDR, extensively drug-resistant.

Keywords: infection, alcoholic cirrhosis, severe alcoholic hepatitis, corticosteroids, immune dysfunction, bacteria and fungus.

Key points:

1) Alcohol abuse is a risk factor for infectious complications.
2) Alcohol has pleiotropic effects on the innate and adaptive immune system resulting in an immunosuppressive state.
3) Alcohol modifies gut microbiome and increases gut permeability inducing translocation of bacteria and bacterial products.
4) Sepsis is a leading cause of death in advanced alcoholic liver disease, particularly in severe alcoholic hepatitis.
5) Opportunistic infections are increasingly described in severe alcoholic hepatitis, mainly in the context of corticosteroid treatment.
6) Specific preemptive and/or prophylactic strategies against infectious agents in patients with advanced alcoholic liver disease should be designed to reduce the incidence of infection and to improve outcomes for these patients.

Summary

Alcohol-related liver disease (ALD) remains the most important cause of death due to alcohol. Infections, particularly bacterial infections, are one of the most frequent and severe complications of advanced ALD, as alcoholic cirrhosis and severe alcoholic hepatitis (sAH). The specific mechanisms responsible of this altered host defence become to be deciphered. The aim of the present work is to review the current knowledge about infectious complications in ALD and the pathophysiological mechanisms, distinguishing the role of alcohol consumption and the contribution of different forms of ALD. To date, corticosteroids are the sole proven effective treatment in sAH but its impact on the occurrence of infections remains controversial. The combination of an altered host defence and corticosteroids treatment in sAH has been suggested as cause of the emergence of opportunistic fungal and viral infections. High level of suspicion with systematic screening and prompt, adequate treatment are warranted to improve outcome of those patients. Prophylactic or preemptive strategies in this high-risk population might be a preferable option due to the high short-term mortality rate despite adequate therapies but should be assessed in well-designed trials before clinical implementation.

Introduction

Excessive alcohol consumption is a major public health problem. In 2012, over three million deaths were attributed to alcohol consumption, corresponding to 5.9% of the total global deaths worldwide [1]. Alcohol is the most frequent cause of cirrhosis and accounts for approximately 40% of all liver transplants in Europe [2]. Although mortality from alcohol-related liver disease (ALD) has declined over the last few decades in most Western European countries, ALD remains the most important cause of death due to alcohol [3].

The spectrum of ALD includes steatosis, steatohepatitis, progressive liver fibrosis, and cirrhosis and its complications [4]. At any stage, patients can develop a severe form of ALD called alcoholic hepatitis (AH). Although most heavy drinkers develop steatosis, only a small subset of them will develop AH, and 10%-20% progress to cirrhosis [5]. Current management of ALD focuses on alcohol abstinence, nutritional support, and primary and secondary prevention of cirrhosis complications.

AH is a clinical entity (which typically presents abruptly) characterized by recent onset (< 3 months) of jaundice and typical histological lesions (macrovesicular steatosis with at least one of the following: ballooning hepatocytes, Mallory-Denk bodies and neutrophil infiltration, and intrasinusoidal fibrosis) in a patient with ongoing alcohol consumption (minimal threshold for women ≥ 40 g per day [3 drinks], for men ≥ 50-60 g per day [4 drinks]) [6]. The true prevalence of AH is currently unknown, due to the lack of systematic biopsy-driven diagnosis, but it has been reported to be as high as 20% in alcoholic hospitalized patients [7]. Its severe form (sAH; defined by a Maddrey discriminant function [mDF] ≥ 32) is associated with a high risk of mortality in the short-term (about 30% at 1 month). Although treatment for sAH remains a topic for debate, corticosteroids (prednisolone 40 mg per day) have been reported to result in a 14% reduction in 1-month mortality in patients with sAH in a meta-analysis of 5 randomized controlled trials (RCT) [8]. A recent large RCT (STOPAH study) confirmed that corticosteroids significantly improved survival at 28 days when compared to placebo and after adjustment for different severity factors, but at lower level than expected, and this survival benefit was not maintained at 90 days and 1 year [9]. The potential efficacy of pentoxifylline in sAH, suggested by one small RCT, was not confirmed, either alone or in combination with corticosteroids, by larger trials [9–11]. The addition of N-acetylcysteine (for 5 days and at doses equivalent to those used for acetaminophen overdose) to corticosteroids has been reported to further decrease (16%) mortality at 1 month compared to corticosteroids alone, but this benefit was lost at 6 months [12].

A newly defined syndrome, called acute-on-chronic liver failure (ACLF), which is characterized by (hepatic and/or extrahepatic) organ failures and a high risk of death in the short term, occurs frequently in the context of alcoholic cirrhosis (60% in Europe) [13]. sAH has been suggested to be a precipitating event for ACLF, mostly not biopsy-proven, because active alcohol consumption in the last three months is present in 20% of patients with ACLF [13].

Currently, infection, particularly bacterial infection, is one of the most frequent and severe complications of advanced liver disease [14–16]. In cirrhotic hospitalized patients with acute decompensation, bacterial infection was identified as the most common identifiable precipitating factor of ACLF [13]. The mechanisms underlying the increased risk of infection and infection-related death in advanced liver disease are complex and multifactorial, including impaired innate and adaptive immunity, bacterial overgrowth, dysbiosis, and translocation of gut-resident bacteria and bacterial products [16,17]. Very few well-designed prospective studies have specifically assessed the microbiological features of infection in ALD according to stage and clinical presentation. However, this information could help clinicians to better define preventive and empirical antimicrobial strategies, decrease risk of infection, and improve the prognosis of patients with severe forms of ALD.

The aim of the present work is to review the current knowledge about infectious complications in ALD and the pathophysiological mechanisms by which ALD increases the risk of infection, distinguishing the role of alcohol abuse and the contribution of different forms of ALD, such as alcoholic cirrhosis and sAH. We will discuss the potential influence of treatment of sAH on the occurrence of infections. Finally, we will propose diagnostic and therapeutic recommendations, and suggest preemptive or prophylactic strategies that can be applied to clinical practice.

Impact of alcohol and alcoholic liver disease on host defences

Effects of alcohol exposure on immune cells

Clinical observations and experimental data demonstrate that excessive alcohol use has broad and significant inhibitory effects on many key components of the immune system

(**Figure 1**) [18]. In addition to its “classical role” in host defence against pathogens, the immune system is integrally involved in processes such as sterile inflammation, recognition of modified and damaged host, and cancer surveillance [19]. To mount an effective immune response, coordination of the innate and adaptive immune systems is required between specific immune cell types and their regulatory pathways via direct cellular interactions or secreted molecules. The functions of most immune cells can be modulated by alcohol use that can undermine effective immune responses [18–20]. Cells of the innate immune system include neutrophils, monocytes, tissue-resident and recruited macrophages, dendritic cells, and natural killer (NK) cells. The adaptive immune system consists of different T lymphocyte subsets (CD4, CD8, Th1, Th2, Th17, Tregs), B lymphocytes, and NKT cells [21]. All immune cells produce various cytokines, chemokines, and inferferons (IFNs) that are key soluble mediators of immunity. The interactions between cells of the innate and adaptive immune systems are abundant and cannot be detailed in this review; thus, we focus on the effects of alcohol that are most fundamental in modulating immune responses.

Innate immunity provides rapid recognition of pathogen-derived (pathogen-associated molecular patterns; PAMPs) or sterile danger signals (danger-associated molecular patterns; DAMPs) via pathogen recognition receptors [22]. These receptors, including toll-like receptors (TLRs), NOD-like receptors, and RXR receptors, lead to common signalling pathways resulting in two major innate immune responses: NF-kB –mediated activation of pro-inflammatory cytokines involved in anti-bacterial activities and interferon regulatory factor (IRF)-mediated production of Type I IFNs that mediate anti-viral effects. These signalling pathways are affected by alcohol. Acute alcohol exposure was shown to inhibit lipopolysaccharide (LPS)-induced pro-inflammatory cytokine production by interfering with TLR4 signalling at multiple levels including TLR4 assembly in lipid rafts on the cell membrane, and activation of IRAK1/4 kinase and IKK kinases [23,24]. In contrast to acute alcohol exposure, chronic alcohol exposure results in increased pro-inflammatory cytokine production and TLR4 responsiveness due to alcohol-induced decreases in molecules that otherwise mediate TLR tolerance [25]. Alcohol-induced inflammation is also amplified by increased IL-1ß production as result of inflammasome activation [26,27]. Despite an increase in pro-inflammatory cytokine production at tissue sites, antimicrobial defences are insufficient after chronic alcohol use and the pro-inflammatory cytokine environment contributes to host tissue damage instead of effective elimination of pathogens [18,28,29]. Alcohol use also inhibits the anti-microbial function of innate immune cells. Microbial killing by neutrophils is impaired and macrophage phagocytosis is reduced [18–21,28].

Antigen presenting cells (APCs), including dendritic cells and monocytes, play a central role in connecting innate and adaptive immune responses through their antigen presentation function in which pathogen-derived specific antigens are presented to T lymphocytes to trigger T cell activation and proliferation [18–20]. Effective antigen presentation is dependent on expression of MHC class II molecules and co-stimulatory molecules CD80/86 on antigen presenting cells [18–20]. However, all of these components of antigen presentation function can be negatively affected by alcohol abuse. In vitro and in vivo studies suggest that even acute alcohol exposure inhibits the T cell stimulatory function of human monocytes [18–21,28]. Chronic alcohol exposure has also been shown to inhibit monocyte antigen presentation and antigen-specific T cell activation in vitro [18–21,28]. Dendritic cells are highly specialized immune cells of bone marrow origin that undergo maturation in the local tissue environment in response to pathogen and tissue-derived signals to assume full functional activity. Myeloid dendritic cells have been shown to be inhibited in reaching their full maturation by alcohol in vitro resulting in an immature phenotype with a predominantly inhibitory rather than an activating function on T cells [30]. The inhibitory effects of alcohol are linked to alcohol-induced increases in IL-10 and decreases in IL-12 production, cytokines regulating T cell activation and APC function. Plasmacytoid dendritic cells, while small in numbers, play a critical role in anti-viral immune responses due to their capacity to produce large amounts of IFN-α. Studies show that alcohol impairs IFN production pathways not only in plasmacytoid dendritic cells but even in other immune cell types in the peripheral blood mononuclear cell population in response to typical viral activation signals induced by TLR3, TLR7/8, or TLR9 stimulation [31].

Alcohol-related cirrhosis-associated immune dysfunction (CAID)

The course of cirrhosis, regardless of its etiology, is complicated by cirrhosis-associated immune dysfunction (CAID), which constitutes the pathophysiological hallmark of the increased susceptibility to bacterial infection distinctive of cirrhosis [32]. The term CAID includes two syndromic alterations that are present in cirrhosis: i) immunodeficiency, due to an impaired response to pathogens at different levels of the immune system, and ii) systemic inflammation, as a consequence of persistent and inadequate stimulation of immune system cells (**Figure 2**). Although the main characteristics of CAID are present in cirrhosis of any cause, specific etiologies, i.e. alcohol, can introduce distinctive features in the phenotypic expression of CAID.

Cirrhosis is associated with several abnormalities in the innate and adaptive components of the immune system response that compromise the surveillance role of the liver and the functions of circulating immune system cells, leading to a state of acquired immunodeficiency. The structural derangements of cirrhosis, including sinusoidal fibrosis and capillarization, septal fibrosis with portal-systemic shunts, and Kupffer cell loss or damage, which are especially prominent in alcoholic liver disease, diminish the clearance of endotoxins and bacteria from the blood, leading to bacteremia, and persistent immune system stimulation. A lack of Kupffer cells or of their complement receptors results in uncontrolled bacteremia and increased host death in experimental models [33]. In agreement with these findings, diminished reticulo-endothelial system function in cirrhosis has been associated with a greater risk of bacterial infection and lower survival [34]. Cirrhosis also impairs the synthesis of innate immunity proteins and of pattern recognition receptors, reducing the bactericidal capacity of phagocytic cells. Given the large functional reserve of the liver, lowered serum levels of these proteins are only evident in patients with advanced cirrhosis and ascites. Indeed, ascites due to cirrhosis increases susceptibility to bacterial infection, and this has been related to low opsonic activity as a result of reduced concentrations of C3, C4, and CH50 in serum and ascitic fluid [35].

Defects in the immune system due to CAID are particularly evident in the function of circulating immune system cells. The circulating populations of most immune system cells are reduced in number, especially those of neutrophils and T lymphocytes, due to splenic pooling and also due to depressed bone marrow production caused by chronic alcohol consumption. In contrast, cirrhosis is associated with monocytosis, as the main increase in the pro-inflammatory non-classical CD14+CD16+ subset [36,37]. Besides reducing their circulating numbers, cirrhosis damages the function of APCs by compromising their bactericidal ability and their delivery to the infection sites. Neutrophils in cirrhosis show impaired phagocytosis of opsonized bacteria [38–41], including defective superoxide anion O_2^- production and myeloperoxidase activity and a lower response to peptidoglycan recognition protein [38,42,43], as well as impaired chemotaxis to the infection focus through decreased transendothelial migration [39,40]. Of note, and as is true for other circulating immune system cells, monocyte and neutrophil dysfunction has been linked to persistent in vivo stimulation, as shown by an increased resting respiratory burst, particularly observed in patients with higher serum levels of pro-inflammatory cytokines [40]. Circulating monocytes of patients with alcoholic cirrhosis produced higher amounts of pro-inflammatory cytokines and chemokines in response to LPS but have a defect in the induction of IFN-mediated program [44,45]. The defective APC function observed in cirrhosis is more evident in that caused by alcohol, since ethanol ingestion specifically damages the bactericidal and chemotaxis activity of neutrophils and the migration ability of APCs [46–48]. The T cell compartment is also depleted in cirrhosis, a fact that affects T-helper (Th) and T-cytotoxic (Tc) cells [49–52], and, regardless of disease etiology, is more pronounced in the naive than in the memory compartment [49,53,54]. Additionally, circulating T lymphocytes are activated in vivo and show diminished proliferation [55–57]. Circulating NK cells are also defective in cirrhosis and exhibit poor responses to cytokine stimulation [58]. Thus, characteristic features of cirrhosis, particularly that caused by alcohol, include reduced numbers and impaired bactericidal ability of circulating immune system cells, along with their activation and increased production of pro-inflammatory cytokines, as further discussed below.

A distinctive feature of CAID is the dynamic coexistence of acquired immunodeficiency and systemic inflammation. The latter results from the persistent stimulation of immune system cells and is defined by the increased production and enhanced serum levels of pro-inflammatory cytokines and the up-regulation of the expression of activation markers in immune cells. The activated circulating immune system cells eventually become the major contributors to increased serum concentrations of pro-inflammatory cytokines such as TNFα, TNFα soluble receptors I and II, IL-1β, IL-6 and IFNγ, IL-17, as well as ICAM-1 and VCAM-1 present in experimental and human cirrhosis [49,59,60]. The severity of this state of systemic inflammation parallels that of the cirrhosis itself, as assessed by Child-Pugh score [61–66], and it is particularly intense in cirrhosis with ascites.

A main part of these cirrhosis-associated immune alterations are dependent of humoral factors and can be improved by interventions. Circulating monocytes of patients with alcoholic cirrhosis, cultured in vitro without stimulation, lost their enhanced ability to produce pro-inflammatory cytokines, returning to levels of monocytes from healthy subjects [67]. In the same way, plasma from patients with cirrhosis induced neutrophil phagocytic dysfunction in cells from healthy subjects [40]. Different experiments suggested that the main factors responsible of CAID are circulating PAMPs coming from the intestine (see below). The suppression of enteric aerobic bacterial load by intestinal decontamination with antibiotics normalizes the expansion of circulating activated immune cells and attenuates the pro-inflammatory cytokine production [49].

Evidence of superimposed immune dysfunctions in severe alcoholic hepatitis (sAH)

There is a clear paradox in patients with sAH, whereby they can transition from evidence of marked systemic inflammatory response syndrome characterised by a pro-inflammatory cytokine milieu to immune failure, increased risk of infection, and mortality suggesting that the syndrome may well have distinct phenotypes from an immunological perspective (**Figure 2**) [68]. From a clinical and pathophysiological perspective, it is useful to consider sAH in terms of whether the patient has associated ACLF, because this can change the outlook for patients. Patients with ACLF due to sAH have a high risk of multiple organ failure and mortality [13]. Recent studies have started to describe the immunologic disturbances associated with sAH with and without ACLF and this is summarised below.

Cytokine milieu in patients with sAH

The best data describing cytokine profiles in sAH come from analysis of the CANONIC study [69]. This study showed that patients with sAH and ACLF have a very different cytokine profile to that of patients without ACLF. In patients with ACLF, both pro- (TNF-α, IL-6, and IL-8) and anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonist (Ra)) were markedly elevated compared to patients without ACLF. In those with ACLF, the pattern of changes in cytokines was different dependent upon whether they had sAH or not. Patients with sAH showed predominantly elevations in IL-8, clearly indicating that the cytokine milieu in sAH is specific [69]. In fully interpreting these data, one must take into account that these patients were not classified with liver biopsies.

The data suggest that although there is evidence of significant systemic inflammation, there is a simultaneous increase in the anti-inflammatory milieu making the risk of ‘immune failure’ and infection high. It is, therefore, not surprising that attempts to inhibit TNF-α using anti-cytokine strategies have failed by inducing infectious complications [70].

Cellular basis of immunologic dysfunction in sAH.

Almost all cell types have been shown to be deranged in patients with sAH affecting both adaptive and innate immunity. The main observations are summarised below (**Table 1**).

Adaptive Immunity

Lymphocytes: Studies on peripheral blood mononuclear cells from patients with sAH showed that T cells from these patients produced less IFN-γ in response to LPS and had greater numbers of IL-10–producing T cells compared to patients with alcoholic cirrhosis. This was shown to be associated with upregulation of programmed cell death 1 (PD1) and the T cell immunoglobulin and mucin domain– containing protein 3 (TIM3), which are inhibitory receptors that regulate the balance between protective immunity and immune-mediated damage by the host. Antibodies against PD1 and TIM-3 restored interferon production and decreased IL-10 producing T cell populations, providing potential therapeutic targets for the future [71].

Innate Immunity

Monocytes/Macrophages: The first comprehensive study of immune response in patients with ACLF was performed by Wasmuth et al., who studied a mixed group of patients, most of whom had alcoholic cirrhosis and possibly sAH. The study showed evidence of reduced TNF-α production from monocytes in response to LPS and reduced HLA-DR expression, which is known to be important for a fully functional innate immune response. The authors hypothesised the presence of an 'immune paralysis' in the patients that had associated ACLF [72]. Many subsequent studies have confirmed these initial observations pointing to the mixed inflammatory responses and have explored potential mechanisms. In a mixed population of patients, but particularly in the patients with sAH, O'Brien et al. also showed evidence of immune dysfunction affecting monocyte-derived macrophages and pointed to a potential inhibitor role of prostaglandin-E2 [73]. Bernsmeier et al. extended these earlier observations and their data suggested that the immune failure in ACLF patients may be related to increased expression of the MER tyrosine kinase (MERTK) on circulating monocytes. MERTK is a key negative regulator of innate immune responses and plays a central role in the resolution of inflammation through inhibition of pro-inflammatory responses and promoting the clearance of apoptotic cells [74]. These investigators also showed that, although the monocytes were able to phagocytose bacteria, they were not able to kill the microbes. This defect was associated with increased risk of infection and death. This reduced killing ability was suggested to be due to reduced NADPH oxidase [75].

Neutrophils: Neutrophils in patients with sAH have historically been shown to be primed, suggesting a potentially pro-inflammatory phenotype, while other studies have suggested they are dysfunctional and unable to phagocytose and kill bacteria. In a carefully performed study, including patients with biopsy-proven AH, Mookerjee et al. reported a wide range of neutrophil functions. In those that developed sepsis, organ failure, and had a risk of mortality, neutrophilic resting oxidative bursts were markedly increased and phagocytosis was markedly reduced [76]. Experimental data indicate that neutrophil dysfunction in sAH may be due to increased circulating LPS and that dysfunction may be potentially reversible with the removal of LPS or using TLR4 inhibitors, providing the basis for potentially novel therapies [77]. More recently, Boussif et al. confirmed the bactericidal defect in the neutrophils of patients with decompensated alcoholic cirrhosis, including about 40% who had sAH, and showed that this was related to a defect of myeloperoxidase release and AKT/P38-MAPK pathway [78]. They went on to show restoration of this pathway with agonists of the TLR7/8 pathway providing a potential therapeutic target. In another study, targeting PD1 and also TIM-3 was able to restore neutrophil function as was observed with lymphocytes [71].

The impact of alcohol and alcoholic liver disease on the intestine

Alcohol damages the intestinal barrier and increases permeability, which then facilitates the passage of bacteria and bacterial products to the internal milieu. Indeed, LPS and bacterial DNA increase in serum after binge and chronic alcohol consumption in healthy subjects and in experimental models [79,80]. Ethanol and/or its metabolites, such as acetaldehyde, have a direct effect on tight junction complex, by redistribution of occludin and dissociation from its actin cytoskeleton, and on adherens junction [81]. Ethanol also causes an absolute increase in aerobic and anaerobic bacteria load, especially in the proximal gut, as well as dysbiosis, which is characterized by a relative decrease of Firmicutes and an increase of Bacteroidetes and Proteobateria [82,83]. Such an effect of alcohol on luminal bacteria seems to be mediated by a reduction in the synthesis of antimicrobial peptides, such as lectinReg3, by epithelial and Paneth cells [83,84]. Intestinal inflammation with augemented synthesis of mediators that increase permeability could be the mechanism by which dysbiosis mediates barrier damage by ethanol. In this regard, intestinal permeability and recruitment of TNF-a activated monocytes in the lamina propria of mice fed with ethanol are reduced by administration of non-absorbable antibiotics or by using mutant mice for defective for TNF receptor type I or for myosin light-chain kinase, a downstream target of TNF-α [85]. The proposed model involves dysbiosis and bacterial overload due to reduced synthesis of antimicrobial peptides by ethanol, and increased permeability secondary to damage of the intestinal barrier by inflammatory mediators that allows the passage to the systemic circulation of bacteria and their products.

In cirrhosis, the deleterious effect of alcohol in the intestinal barrier is added to that caused by cirrhosis itself. Indeed, advanced cirrhosis is characterized by a profound damage of the interrelated levels of defense of the intestinal barrier, which results in an increased translocation rate of enteric bacteria and/or their products [87–89]. Specifically, cirrhosis leads to increased intestinal permeability due to compromised epithelial integrity, intestinal bacterial overgrowth and dysbiosis, caused by disruption of host microbiota homeostasis and intestinal and general immune defense impairment [89,90]. Concurrent damage to these three levels of defense explains the referred high rate of translocation of live bacteria and PAMPs from the gut that occurs in advanced human and experimental cirrhosis [49].

A specific dysbiosis has been observed in patients with sAH [91]. The transfer of human intestinal microbiobiota coming from patients with sAH induced increased gut permeability and BT in ethanol-exposed mice compared to intestinal microbiotia of patients without sAH. Moreover, more than 90% of patients with sAH have detectable circulating bacterial DNA, which is substantially higher than rates observed in other forms of decompensated cirrhosis [92]. Interestingly, pretreatment levels of circulating bacterial DNA predict the development of infection in patients with sAH treated with corticosteroids and high serum LPS levels predict the occurrence of in-hospital infection, suggesting that translocation plays a central role in the susceptibility to spontaneous infection [92,93].

Epidemiological, microbiological, and prognostic data on infections in patients with alcohol abuse and/or alcoholic liver disease

Alcohol abuse is a risk factor for infections

Individuals who chronically drink excessive amounts of alcohol are usually subclinically “immunocompromised” and this immune dysfunction becomes clinically significant only when a secondary insult occurs [18,28]. Clinical evidence indicates that chronic alcohol consumption increases the risk of viral and bacterial infections. For example, the combined immunosuppressive effects of alcohol and human immunodeficiency virus (HIV) infection are well described [94,95]. Excessive alcohol use is associated with increased risk of chronic hepatitis C infection and immunologic studies have found that alcohol and hepatitis C virus (HCV) are synergistic in inhibition of antigen-specific immune responses and activation of non-specific pro-inflammatory responses [96–99].

Certain bacterial infections are clearly more prevalent in individuals who abuse alcohol. Alcohol use has negative effects on pulmonary infections with *Legionella pneumophila* and *Mycobacterium tuberculosis* and predisposes patients to systemic dissemination of tuberculosis [29,100]. Pneumonia related to Gram-negative bacilli (GNB), such as *Klebsiella pneumoniae,* or Gram-positive cocci (GPC), such as *Streptococcus pneumoniae,* is more common in alcoholics compared to non-alcoholic individuals [101]. In patients with community-acquired pneumonia, a history of alcohol abuse is associated with infections caused by virulent GNB such as *Pseudomonas aeruginosa* and *Acinetobacter* species [102].

Infectious complications in the context of alcoholic cirrhosis

Bacterial infections constitute a major complication of alcoholic and non-alcoholic cirrhosis and are associated with high mortality rates [14–16,103]. Infections can occur in compensated and decompensated cirrhosis, frequently precipitate clinical decompensations (variceal hemorrhage, hepatic encephalopathy), and may further deteriorate decompensated patients (variceal rebleeding and hepatorenal syndrome [HRS]). Bacterial infections are also a major precipitating event of ACLF, a syndrome frequently observed in alcoholic patients [13,104]. It is, therefore, not surprising that bacterial infection is associated with increased in-hospital mortality (4-5 fold), and risk of death from sepsis (2-fold) [103].

Well-known clinical risk factors for the development of bacterial infections are poor liver function, upper gastrointestinal bleeding, low protein ascites, prior SBP, and hospitalization (especially if associated with invasive procedures and intensive care unit admission) [14,15]. Alcoholic cirrhosis, active alcohol consumption and poor nutritional status have also been suggested as predisposing factors to infection.

Risk of bacterial infection associated with alcoholic cirrhosis and active alcohol consumption

Several studies have reported a higher frequency of bacterial infections in patients with alcoholic cirrhosis when compared with non-alcoholic liver disease [105–107]. In the study by Rosa et al., 39% of alcoholic patients developed a bacterial infection at admission or during hospitalization in comparison to 28% of non-alcoholic patients. However, differences in the prevalence of infections were only statistically significant in patients with relatively preserved liver function (Child-Pugh A/B): 37% vs. 23% in alcoholic and non-alcoholic patients, respectively ($p=0.02$), but not in Child-Pugh C patients (49% each) [105]. Recently, Sargenti et al. evaluated the potential role of alcoholic etiology in the development, clinical type, and prognosis of bacterial infections in a population-based longitudinal cohort of 633 cirrhotic patients. During a median follow-up of 36 months, severe bacterial infections (those resulting in or occurring during hospitalization) developed more frequently in patients with alcoholic cirrhosis (45% vs. 28%, $p<0.05$). Frequency was especially high in those with active alcoholism (51% vs. 38%, $p=0.03$). However, after adjusting for confounders (MELD score and age), alcoholic cirrhosis and active alcoholism were not found to be independently associated with the development of bacterial infections [106]. An additional study has evaluated the impact of alcoholic etiology and active alcohol consumption on the risk of infection after variceal bleeding. Patients with alcoholic cirrhosis and Child-Pugh A/B had significantly more infections than those with cirrhosis of other etiologies (Child-Pugh A: 10% vs. 0%; Child-Pugh B: 24% vs. 3.5%, $p<0.05$) in spite of antibiotic prophylaxis. Among low-risk patients (Child-Pugh A), the risk of infection was significantly higher in patients with active alcohol consumption (21% vs. 0% in non-drinkers, $p=0.01$). Alcohol consumption was identified as an independent risk factor for infection [107]. The results of these three studies suggest that alcoholic etiology and alcohol consumption act as risk factors for bacterial infections mainly in cirrhotic patients without advanced liver dysfunction. In line with this hypothesis, other studies do not support the role of alcoholic cirrhosis or of active alcohol consumption as risk factors for the development of spontaneous or secondary bacterial infections in cirrhosis [13,108–116]. Poor nutritional status and low serum cholesterol levels, conditions frequently observed in alcoholic patients with and without cirrhosis, have also been associated with an increased risk of infection, multiple organ dysfunction and poor prognosis [117–119].

Type of bacterial infections and microbiology

Spontaneous bacterial peritonitis (SBP) and urinary tract infections (UTI) are the most frequent infections occurring in cirrhosis followed by pneumonia, cellulitis, and bacteremia. A higher risk of bacteremia and meningitis has been reported in patients with alcoholism [120–122]. A recent population-based study also suggests that alcoholic cirrhosis predisposes patients to the development of pneumonia (17% vs. 8% in non-alcoholic cirrhosis, $p=0.02$) [106]. A post-hoc analysis of a study involving 615 non-SBP infections in cirrhosis supports that pneumonia (16% vs. 11%, $p=0.05$) and cellulitis (19% vs. 12%, $p=0.02$) tend to occur more frequently in patients with alcoholic cirrhosis [123]. Finally, SBP episodes caused by *Listeria monocytogenes* have been sporadically reported in patients with cirrhosis, especially in those of alcoholic etiology [124].

Antimicrobial resistance has become a major global healthcare problem that is especially relevant in decompensated cirrhosis [125]. Alcoholism has been reported to be associated with infections caused by antibiotic-resistant organisms in non-cirrhotic individuals [126,127]. However, it is unclear whether this is also true for patients with alcoholic liver cirrhosis. Current/recent contact with the healthcare system, especially nosocomial infection, long-term quinolone prophylaxis, recent use of antibiotics (3 months), and infection by multidrug-resistant bacteria in the last 6 months are all well-known risk factors of infections caused by multidrug-resistant bacteria in cirrhosis [125,128,129]. A recent cohort study has also identified alcoholic etiology as a potential risk factor for bacterial infections caused by resistant strains. Resistance to piperacillin-tazobactam, third-generation cephalosporins, and carbapenems was more common in infections occurring in alcoholic than in non-alcoholic cirrhosis (13% vs. 5%, p=0.06 and 12 vs. 2%, p=0.009, respectively) in this series. However, alcoholic etiology was only identified as an independent predictor of infections caused by Gram-positive bacteria but not of infections caused by multidrug-resistant organisms (MDROs) [106]. No other study to date has reported alcoholic etiology as a risk factor for antimicrobial resistance in the cirrhotic population.

Impact of alcoholic etiology and active alcohol consumption on prognosis of bacterial infections

Published data on the clinical impact of alcoholic etiology and alcohol abuse on infection-related complications (acute kidney injury (AKI), severe sepsis, and ACLF) and short-term mortality in cirrhosis are controversial. Initial studies reported a similar prevalence of alcoholic cirrhosis in patients with and without infection-related AKI and with and without systemic inflammatory response syndrome [130,131]. In contrast, a recent study has shown a higher propensity of infected patients with alcoholic cirrhosis to develop infection-related AKI (57% vs. 40%, p=0.002), sepsis (78% vs. 66%, p=0.01), and severe sepsis (44% vs. 25%, p=0.001) [106].

Infection-related and infection-unrelated ACLF occurs more frequently in patients with alcoholic cirrhosis than in those with non-alcoholic cirrhosis, especially in those with active alcohol consumption [13,132]. Sargenti et al, recently published a population-based investigation assessing the impact of bacterial infections on the course of compensated and decompensated cirrhosis as well as the occurrence and predictors of infection-related ACLF. The study was performed between 2001-2010 in patients residing in an area of Sweden of 600,000 inhabitants. Bacterial infections (n=398) developed in 241 patients (106 with compensated cirrhosis and 135 with decompensated cirrhosis). ACLF occurred in 95 patients and was associated with a high mortality rate (49%). MELD score, active alcohol consumption, and healthcare-associated infection were identified as independent predictors of infection-related ACLF [132].

The impact of alcoholic etiology and active alcoholism on infection-related short-term mortality in cirrhosis is unclear with some studies reporting a worse outcome in infected patients with alcoholic cirrhosis [121,133] and others showing no difference between groups [108,109,120,131,134]. The negative impact of alcohol on prognosis of infected patients with cirrhosis is probably linked to the increased risk of infection-related ACLF.

Clinical characteristics of infections in severe alcoholic hepatitis (sAH)

Infection is one of the main complications of sAH, as well as one of the major causes of mortality in this setting. In a study by Louvet et al., up to 25% of patients with sAH were found to have an active infection at admission before corticosteroid treatment following systematic screening [135]. Moreover, incidence of infection has been evaluated in therapeutic trials as part of secondary outcome or adverse event analyses of the studied intervention. A meta-analysis of 12 randomized trials found a cumulative incidence of infection of 20% in patients with sAH during 28-day corticosteroid treatment period [136]. Others have reported incidences as high as 50% to 67% during a 3-month follow-up (**Table 2**) [93,137].

Infections accounted for 24% of all deaths in the largest trial to date on sAH [9]. Infected patients with sAH suffer from a further increase in mortality of 30% at 2 months. If responders to corticosteroids get an infection, they have survival similar to that of non-responders [135]. Reported mortality attributable to infection is probably underestimated because even other causes of mortality in sAH, such as liver-related events/ failure and gastrointestinal bleeding may be precipitated by or occur concomitant to an unidentified infection.

Contribution of treatment to infections in sAH

One of the major controversies of the past few years has been whether corticosteroids, used for the treatment of sAH, induce infection or whether severe liver injury *per se* accounts for the development of sepsis. Unfortunately, clear evidence is lacking, making it impossible to firmly respond to this question. Infection is not an independent predictor of outcome and is closely related to non-response to corticosteroids [135]. This suggests that severe liver dysfunction caused by the lack of efficacy of medical treatment is the main driver of mortality and infection, rather than corticosteroids alone. Nevertheless, it is tempting to suggest that corticosteroids might enhance infection because they are known to induce infectious events in other fields, mainly by inducing a defect in lymphocyte signaling. Data from randomized controlled trials (RCTs) help answer this question. The RCT STOPAH reported a higher incidence of infection in patients treated with prednisolone (13% vs. 7%) than in patients without prednisolone, whereas prednisolone use was associated with lower mortality [9]. Recently, a meta-analysis from 12 RCTs has shown that patients treated with corticosteroids had no increased risk of infection or higher mortality from infection than those treated with placebo [136]. However, in this meta-analysis, opportunistic infections, especially fungal, seemed to be more frequent, despite a low occurrence of cases. Opportunistic infections, in particular invasive aspergillosis, have also been reported by other teams but the link with steroid use has not been investigated in these studies [138,139].

Few data are available on the other treatment options for severe alcoholic hepatitis. It is important to remember that no pharmacological strategy except prednisolone has been shown to be effective in improving short-term survival in patients with severe alcoholic hepatitis. Several trials have shown that pentoxifylline use, either alone or in combination with corticosteroids, did not seem to affect the incidence of infection [9,11,140]. Pentoxifylline use was associated with a lower incidence of infection in patients with decompensated cirrhosis, including 40% with severe alcoholic hepatitis [141]. However, pentoxifylline does not improve survival in severe alcoholic hepatitis and the rationale for its use is very limited. Similar results (i.e. lower incidence of infection without significant improvement in survival) have been observed in patients treated with N-acetylcysteine and prednisolone compared to corticosteroids alone [12]. TNF-α inhibitors have been shown to promote the risk of mortality and infection, either alone or associated with corticosteroids and must no longer be used [70,142]. In a single-center RCT, addition of granulocyte colony-stimulating factor (G-CSF) to pentoxifylline improved survival of patients with sAH compared to pentoxifylline alone [143]. In another RCT, the G-CSF-induced survival benefit of patients with ACLF (57% had sAH) seems to be related to the prevention of sepsis [144].

Bacterial infections in sAH

Bacterial infections represent the vast majority (nearly 80%) of infectious episodes in the context of sAH but invasive fungal infections are increasingly reported (up to 20% in some reports) [138].

Urinary tract infections (UTI) and respiratory infections seem to occur more commonly during sAH, compared to cirrhosis, where SBP is predominant [93,128,145]. Based on a study by Louvet et al., the sites of infection vary between admission and follow-up [135]. Indeed, at baseline, SBP or spontaneous bacteremia (SB) occurred more frequently, followed by UTI, respiratory and cutaneous infection episodes. After or during corticosteroid treatment, a shift towards respiratory infections was noted (40% of all episodes), but SBP or SB and UTI decreased, while cutaneous infections remained stable. Concerning in-hospital infections only, Altamirano et al. reported pneumonia as being the most frequent (26%), followed by UTI and skin and soft tissue infection, while SBP was present only in 6% of infected patients [146]. Interestingly, the STOPAH trial also found a high prevalence of respiratory infections, representing 50% of all infections during follow-up [9]. A possible interpretation for this shift from spontaneous infections, frequently seen as a hallmark of cirrhosis, towards respiratory infections, may be corticosteroid treatment, nosocomial origin, and/or intensive care unit admission.

Data regarding pathogens are scarce in sAH studies. Nearly, half of infectious episodes are nosocomial [135,137]. In a small study on patients with AH, GNB, mainly *Escherichia coli*, represented 75% of all isolated bacteria, as in cirrhotic patients without AH [147]. In another report, isolated bacteria were 67% GNB and 29% GPC, *E. coli* being the most frequently isolated organism, followed by *Staphylococcus aureus* [137]. These observations are confirmed by the STOPAH trial where GNB, in particular *E. coli*, was the most isolated microorganism [92]. Another small study, focusing on bloodstream infections, found a high prevalence of GPC (44%), while GNB were present in only 22% [148]. MDROs were isolated in 24% of patients with sAH [137]. Moreover, according to a large United States database, *Clostridium difficile* infection, among patients with AH followed-up during hospitalization, had a prevalence of 1.6%, which was 1.5-fold higher than that of hospitalized patients without AH [149].

Invasive fungal infections (IFI) in sAH

IFI are common complications in deeply immunocompromised patients. In patients with sAH mostly treated by corticosteroids, the prevalence of IFI is reported to be as high as 14% to 26% [138,150]. The diagnosis of IFI and distinguishing infection from colonization in these patients is challenging. Therefore, the prevalence of IFI is directly dependent on the intensity of diagnostic screening.

Invasive aspergillosis (IA)

One study of a prospective cohort of 94 patients with biopsy-proven sAH who underwent systemic screening (frequent galactomannan [GM] testing, chest and cerebral CT, bronchoalveolar lavage [BAL]) for IA reported an IA incidence of 16% after a follow-up of three months [138]. In this study, risk factors for acquisition of IA were ICU admission and baseline MELD score ≥ 24. The diagnosis was made after 6 to 80 days of corticosteroid initiation (median of 25 days). The sites of IA were the lungs, in most cases, and brain. Diagnosis of IA in sAH remains challenging. Indeed, radiological imaging of pulmonary IA shows mainly non-specific lung infiltrates by chest CT and, more rarely (in only 36% of the cases), multiple excavated nodules or ‘classical’ condensations with a halo sign. Serum GM may be a good screening test for IA in sAH (cut-off ≥ 0.5, sensitivity of 89%, and specificity of 84%). The accuracy of this test must be validated externally because others have reported lower sensitivity and specificity in other contexts [151]. GM in BAL samples seems to have higher diagnostic accuracy. sAH complicated by IA is associated with a dramatically poor outcome despite adequate antifungal treatment.

Pneumocystis pneumonia (PCP)

Sporadic cases of PCP have been described in patients with sAH and concomitant corticosteroid treatment, with a 100% mortality rate [152–154]. In a prospective cohort, PCP was suspected in 8% of patients [138]. The diagnosis was based on the positivity of polymerase chain reaction (PCR) for *Pneumocystis jirovecii* in BAL samples, direct examination (Giemsa staining) being negative. The distinction between colonization and invasive infection was challenging due to poor general condition of the patients and non-specific CT scan lung lesions.

Invasive candidiasis and others

The rate of diagnosis of invasive candidiasis, mainly candidemia, in sAH varies between 2% and 8% [138,150]. The accuracy of the 1,3-β-D-glucan assay in the diagnosis of invasive candidiasis is currently unknown in patients with liver disease making its utility in clinical practice uncertain. The prognosis of candidemia and other invasive candidiasis in sAH is extremely poor with exceptional case of survival [138,155]. Some isolated cases of mucormycosis, cryptococcosis, and fusariosis have been reported in sAH [150].

Viral infections

Seven cases of cytomegalovirus (CMV) pneumonia have been reported in patients with sAH, five of them concomitantly with PCP, with fatal outcomes [152–154]. Herpes simplex virus (HSV) pneumonia has also been reported in 3 cases [156,157]. Data remain indicative, but considering diagnostic challenges of CMV or HSV pneumonia, occurrence may be largely underestimated, highlighting the need for systematic and invasive screening.

Treatment

Antibiotic strategies

Early diagnosis and adequate empirical antibiotic treatment of bacterial infections is the cornerstone in the management of patients with alcoholic cirrhosis or severe alcoholic hepatitis given their high risk of developing severe sepsis, ACLF, and death [13,15,16,132]. Several studies have demonstrated that delays in the administration of proper antibiotics has a prohibitive price in terms of mortality in cirrhotic patients with severe infections (increase in the risk of death of 8%-10% per hour of delay) [158,159]. The emergence and spread of antibiotic resistance, a problem that is especially relevant in patients with cirrhosis, requires the delineation of new first-line antibiotic strategies in this population [125,160]. In the current epidemiological scenario, initial antibiotic schedules should be tailored according to different factors including the severity of infection, recent or current antibiotic exposure, presence or absence of risk factors of MDROs (previous colonization; antibiotic treatment ≥ 5 days in the last 3 months; hospitalization ≥ 5 days in the last 3 months, nursing-home; long-term antibiotic prophylaxis), and the local epidemiological pattern of antibiotic resistance. Third-generation cephalosporins and quinolones are frequently ineffective in nosocomial and healthcare-associated infections due to the increasing rate of MDROs. Empirical treatment in the population at high risk of infection by MDROs requires the use of broad-spectrum antibiotics (i.e. carbapenems or tigecycline) or of drugs active against specific resistant bacteria.

Currently recommended empirical antibiotic strategies

Third-generation cephalosporins and amoxicillin-clavulanic acid, the gold-standard empirical antibiotic treatment for many of the infections occurring in cirrhosis in the past, now may have limited efficacy. Current guidelines only recommend the use of these β-lactams in infections and areas with low risk of antibiotic resistance [16]. In this setting, third-generation cephalosporins are recommended in community-acquired infections and piperacillin-tazobactam in nosocomial episodes. Empirical antibiotic therapy of healthcare-associated (HCA) infections should be decided according to the severity of infection: patients with risk factors for MDROs or with severe sepsis or shock should receive the schedules proposed for nosocomial infections (**Table 3**) [16,161].

Antibiotic strategies in areas with high rates of MDROs are far more complex. As mentioned before, classical β-lactams (third-generation cephalosporins and amoxicillin-clavulanic acid) are only recommended in non-severe infections acquired in the community. In severe HCA or community-acquired infections, especially if the patient has additional risk factors for antibiotic resistance, and in nosocomial infections empirical strategies must include drugs active against MDROs (**Table 3**). In these infections, antibiotics should be selected according to two major parameters: the local epidemiological pattern of antibiotic resistance and the type of antibiotics to which the patient has recently been exposed. In areas with a high prevalence of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL), carbapenems should be started empirically (**Table 3**). The addition of antibiotics active against Gram-positive MDROS is recommended in areas with a relevant rate of infections caused by vancomycin-susceptible enterococci (VSE), vancomycin-resistant enterococci (VRE), or methicillin-resistant *Staphylococcus aureus* (MRSA). In patients with clinical improvement within 48-72 hours and a known pathogen, immediate tailoring of empirical antibiotics is recommended in order to prevent further antibiotic resistance [15,125,160,161].

Antibiotic strategies for extensively drug-resistant bacteria

Extensively drug-resistant (XDR) bacteria are especially difficult to treat since currently available therapeutic options are very limited, with very few new agents in development. Carbapenemase-producing *Enterobacteriaceae* can be susceptible to tigecycline, a drug also active against MRSA, VSE, VRE, and ESBL-producing *Enterobacteriaceae*. Some experts recommend combining tigecycline at high doses with carbapenem in a continuous infusion to treat this XDR strain [125,161]. A new cephalosporin-β-lactamase inhibitor combination, ceftazidime-avibactam, is active against different types of carbapenemase-producing *Enterobacteriaceae* [125]. Avibactam inactivates class A (KPC) and D (OXA-48) carbapenemases, but lacks activity against *Enterobacteriaceae* producing metallo-β-lactamases (Verona integrin-encoded [VIM] and New Delhi metallo-β-lactamases [NDM]). In these latter XDR strains, combined treatments including aztreonam should be evaluated [162].

Severe infections caused by MDR *Pseudomonas aeruginosa (*resistant to carbapenems, ceftazidime, and quinolones) usually required in the past the combination of IV amikacin/tobramycin or colistin plus a carbapenem/ceftazidime (needed as synergistic antibiotics in spite of antibiotic resistance). Ceftolozane-tazobactam is a new antibiotic combination active against this XDR bacteria. VRE should be treated with linezolid, daptomycin, or tigecycline [161].

Antifungal treatments

Invasive aspergillosis (IA)

The recognized first-line treatment for IA is voriconazole [163]. Experts suggest a combination of voriconazole and an echinocandin, i.e. caspofungin, for severe microbiologically documented IA in immunocompromised patients [164]. Liposomal amphotericin B is an alternative treatment when voriconazole is not tolerated or contraindicated. Liposomal amphotericin B is nephrotoxic and renal function is crucial in the prognosis of sAH [165,166]. Voriconazole induces frequently transient self-limited hepatotoxicity but several cases of acute liver failure attributed to voriconazole have been reported [167]. Currently, it is not known if alcoholic liver diseases or advanced liver failure increase the risk of hepatotoxicity but good outcomes are sometimes described in patients with liver insufficiency and IA treated with voriconazole [168]. In the setting of sAH, a transplant-free mortality rate of 100% was observed despite different adequate antifungal regimens [138]. Success with a combination of liposomal amphotericin B and caspofungin was reported in a patient with sAH and probable IA [169].

Pneumocystis pneumonia (PCP)

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice for PCP [170]. There are limited data on the efficacy of adjunctive corticosteroids for the treatment of PCP in HIV-uninfected patients [171,172]. One report of seven patients with sAH and PCP described a 100% mortality rate despite adequate treatment with TMP-SMX [153].

Invasive Candidiasis

A diagnosis of invasive candidiasis in patients with sAH requires a prompt initiation of an echinocandin (anidulafungin, caspofungin, or micafungin) [173]. Due to the emergence of resistant organisms, such as *Candida glabrata* and *C. krusei*, fluconazole becomes a second choice, in particular in severely ill patients. In contrast to caspofungin, the pharmacokinetics of anidulafungin are unaffected in Child-Pugh B or C cirrhosis and classical doses (200 mg day 1 and then 100 mg per day intravenously) are appropriate [174].

Prevention

As infection is frequently due to translocation of intestinal Gram-negative bacteria, prevention is usually based on selective intestinal decontamination with a fluoroquinolone (e.g., norfloxacin, ciprofloxacin) administered in patients with a high risk of developing bacterial infection. This includes patients with acute variceal hemorrhage, patients who recover from an SBP episode, and patients with ascitic fluid protein concentration below 10-15 g/L.

Established indications for antibiotic prophylaxis

Acute variceal hemorrhage

In this context, antibiotic prophylaxis reduces the incidence of severe infection (SBP and/or septicemia) and decreases mortality [175]. Oral norfloxacin (800 mg/day for 7 days) is commonly used [176]. The alternative could be intravenous ceftriaxone (1 g/day for 7 days) in patients with advanced cirrhosis (at least two of the following: ascites, severe malnutrition, encephalopathy, or jaundice) [177].

Recovery of an SBP episode

After an episode of SBP, secondary prophylaxis using oral norfloxacin (400 mg/day) decreases the recurrence of SBP from ~70% to 20% [178]. The impact of secondary prophylaxis on survival is unknown.

Primary antibiotic prophylaxis

There are 4 double-blind, randomized placebo-controlled trials of prolonged fluoroquinolone therapy in the context of primary prophylaxis in cirrhosis with a majority of alcohol etiology (**Table 4**) [179–182]. The 4 trials enrolled patients with ascitic fluid protein concentration below 15 g/L (i.e., patients at risk of SBP). However, the primary end point of these trials differed across studies. The primary end point was primary prophylaxis of SBP in 2 studies [179,182], primary prophylaxis of Gram-negative bacteria-related infection in another [180] and mortality in the final study [181] (**Table 4**). These findings show that the objectives of primary antibioprophylaxis have not yet been clearly established, even if there was a consensus to enroll patients at risk of developing SBP. Moreover, only 2 studies out 4 found that quinolone administration decreased the risk of SBP [179,181] and only 2 studies out 4 found a decrease in mortality with the antibiotic [181,182]. Finally, in each trial, the total number of enrolled patients was small, ranging from 60 to 107. A small sample size combined with low adherence and retention (a hallmark of studies enrolling patients with advanced cirrhosis) may make “positive” or “negative” results questionable. Therefore, it is difficult to draw firm conclusions from these 4 trials, in particular about patients who would benefit from primary antibioprophylaxis. A large double-blind, randomized, placebo-controlled trial of norfloxacin in patients with Child-Pugh class C cirrhosis has been recently completed (NORFLOCIR ClinicalTrials.gov number, NCT01037959). Results of this trial will help to clarify the indications for primary antibiotic prophylaxis in patients with advanced cirrhosis.

Issues with long-term antibiotic therapy

There is no consensus on the duration of long-term oral antibiotic therapy in the prevention of the first episode of SBP or its recurrence. However, antibiotic therapy is associated with the emergence of resistant organisms [128]. Thus, alternative approaches are needed. Results of a large double-blind RCT showed that oral pentoxifylline administration (1,200 mg/day) significantly decreased the risk of bacterial infection in patients with advanced cirrhosis [141]. Short-term administration of subcutaneous granulocyte colony-stimulating factor (5 µg/Kg every 12-24h alone or in combination with darbopoietin (a synthetic analog of erythropoietin) has shown to improve liver function, reduce the incidence of severe sepsis and increase survival in comparison to placebo in patients decompensated cirrhosis and with ACLF, many of them alcoholics, and in sAH [143,144,183]. Induction of hepatic regeneration and restoration the immune imbalance are proposed as potential mechanisms.

Potential prophylaxis in corticosteroid-treated sAH

Due to the high incidence of bacterial infection associated with corticosteroid treatment, antibioprophylaxis could be an attractive option for improving outcomes for patients with sAH. This strategy is currently being assessed in a multicenter RCT (ANTIBIOCOR ClinicalTrials.gov number, NCT02281929). In view of the poor prognosis for IFI despite adequate antifungal therapies, a prophylactic or preemptive treatment might be more efficient. Prospective studies should be conducted to identify the true incidence, and risk factors for invasive candidiasis, IA or PCP in corticosteroid-treated patients with sAH, and to evaluate prophylactic strategies. Then, we proposed an strategic algorithm in patients with sAH to reduce infectious complications (**Figure 3**).

Perspectives and area of research

Systemic inflammation is the hallmark of ALD. Numerous animal experiments, not reproducing all spectrum of human ALD, support the contribution of activation of innate immune response in its progression. Logically, current therapeutic targets were based on this paradigm. On the other side, coming mainly from human translational studies, an immunoparalysis is described particularly in severe forms of ALD, as sAH. This can explain the failure of therapeutic options targeting pro-inflammatory cytokines as TNFα by inducing infection complications [70,142]. Corticosteroids remain the sole proven effective treatment in sAH and their impact on the immune system is complex. The beneficial survival effect of corticosteroids might be lessened by their impat on the infectious risk. Glucocorticoids exert both negative and positive effects with a dynamic and bi-directional spectrum of activities on various limbs and components of the immune response [184]. They modulate genes involved in the priming of the innate immune response, while their actions on the adaptive immune response are to suppress cellular immunity and promote humoral immunity. Deciphering the effects of corticosteroids on the immune system of patients with sAH to reveal more specific therapeutic options is an urgent medical need. Such strategies have been already tested [185] but must be developed using state-of-the-art high-throughput immunological technologies. Therapeutic targets to improve immune dysfunction in patients with sAH are suggested in table 1.

We must invest also in non-antibiotic strategies to prevent infections in patients with severe ALD to avoid the emergence of MDROs. The modulation of gut microbiome and the correction of increased intestinal permeability are attractive options. In exemple, the administration of enoxaparin to prevent portal vein thrombosis in Child-Pugh B-C cirrhosis reduced the occurrence of SBP and bacteremia in a RCT [186]. The mechanisms of this prevention are incompletely understood but some experimental data suggest a reduction of bacterial translocation under enoxaparin treatment.

Conclusions

In conclusion, alcohol abuse, alcoholic cirrhosis and sAH are recognized as risk factors for infections. The immune defect seems to increase gradually with the severity of ALD. The leaky gut and intestinal dysbiosis, particularly described in ALD, contribute to this immune defect and infectious complications. Infection in patients with sAH is a major driver of mortality. Systematic screening of infection should be performed at admission, before the initiation of corticosteroids. The controversy about the contribution of corticosteroids in the susceptibility of infections remains. Although one study observed an increased risk of infection in patients treated with corticosteroids, this was not confirmed in a recent meta-analysis and the higher risk in the STOPAH trial was conversely associated with a lower risk of death in patients treated with prednisolone. Opportunistic infections become an emergent problem, particularly in patients with sAH treated by corticosteroids. High level of suspicion with systematic screening and prompt, adequate treatment are warranted to improve outcome of those patients. Prophylactic or preemptive strategies in this high-risk population might be a preferable option due to the high short-term mortality rate despite adequate therapies but should be assessed in well-designed trials before clinical implementation.

Figure legend

Figure 1.

Summary of the different effects of alcohol at multiple levels of the immune system. IFN, interferon; IL, interleukin; ROS, reactive oxygen species.

Figure 2.

Diagram about the link between immune dysfunction associated with alcohol-related liver diseases (ALD) and the susceptibility to infections and opportunistic pathogens. The exacerbation of systemic inflammation following the progression of ALD is associated with relative paralysis of immune cells to respond to further stimuli resulting in a immunosuppressive state. DCs, dendritic cells; IL, interleukin; NK, natural killers; DCs, dendritic cells; TNF, tumor necrosis factor.

Figure 3.

Proposed algorithm to diagnose, to manage and to prevent infection in patients with severe alcoholic hepatitis (sAH). * Infections is considered as controlled using the following criteria: (1) for spontaneous bacterial peritonitis or bacteremia, a decrease in neutrophil count of >50% in ascitic fluid within the first 48 hours and a neutrophil count of <250/mm^3 at the end of therapy; (2) for urinary tract infection, negative culture under therapy; (3) for bacteremia, negative blood culture and absence of fever; (4) for respiratory infection, combined criteria that included a decrease in C-reactive protein, absence of fever, improvement in physical examination, and no need for oxygen supply; (5) for cutaneous infection, a decrease in C-reactive protein, absence of fever, and improvement in skin lesions [135]. # In bronchoalveolar lavage (BAL), the following exams should be performed: direct microscopic examination, Giemsa coloration or immunofluorescence for *Pneumocystis jirovecii*, bacterial and fungal cultures, galactomannan (GM), PCR for *Pneumocystis jirovecii*, CMV and HSV. Mycobacterial cultures should also be considered according to epidemiological setting. & We propose to stop corticosteroids when a diagnosis of infection is made except for non-complicated urinary tract infection. mDF, modified Maddrey discriminant function; NAC, N-acetylcystein

Tables

Table 1. Cellular basis of immune dysfunction in sAH, associated mechanisms and possible therapeutic targets.

Cell Type	**Main functional derangement**	**Mechanism**	**Therapeutic target**
T Lymphocytes [71]	Reduced T cell IFN production in response to LPS Increased T cell production of IL-10	Increased expression of PD1 and TIM-3	• Antibodies to PDI and TIM-3 restored function
Monocytes and Macrophages [72–75]	Reduced LPS-induced TNFα production	Reduced HLA-DR expression	• Reduce bacterial translocation
	Reduced pro-inflammatory cytokine secretion and bacterial killing	Increased Prostaglandin E2	• PGE2 receptor antagonists • COX-2 inhibitors • Albumin infusion
	Reduced pro-inflammatory cytokine secretion in response to LPS	Increased expression of MERTK	• Inhibition of MERTK, UNC569
	Reduced monocyte oxidative burst and bacterial killing	Reduced gp91^{phox} subunit of NADPH oxidase	• NADPH modulators
Neutrophils [76–78]	Increased resting burst but reduced *E. coli*-induced oxidative burst and reduced phagocytosis	Involvement of humoral factor possibly LPS and TLR4	• Reduce bacterial translocation • Removal of LPS using plasma exchange or specific filters • TLR4 antagonists
	Reduced bactericidal activity	Defect of myeloperoxidase release and the AKT/p38 MAP kinase pathway	• TLR7/8 agonists

Table 2. Prevalence and incidence of infections in sAH

	N pts	Prevalence at baseline %	Incidence during follow-Up %	Incidence in the control group	Incidence in the corticosteroid-treated group	Follow-up duration for infection
Vergis, 2017 [92]	1092	12*	31	33	29	3 months
Moreno, 2016 [187]	133	ND *	61	NA	61	6 months
Michelena, 2015 [93]	162	20	44	36	52 #	During hospitalization
Karakike, 2015 [137]	79	30	51	NA	NA	3 months
Park, 2014 [140]	121	6 *	8	5	12	6 months
Gustot, 2014 [138]	94	ND	67	NA	NA	3 months
Mathurin, 2013 [11]	270	ND *	33	NA	33	6 months
Nguyen-Khac, 2011 [12]	174	ND *	30	NA	30	6 months
Moreno, 2010 [188]	47	ND *	36	36	NA	1 month
Louvet, 2009 [135]	246	26	23	NA	23	2 months

*Exclusion of uncontrolled infections before randomization. # $p<0.05$ compared with placebo or no treatment. NA, not applicable; ND, not determined.

Table 3. Recommended empirical antibiotic strategies in patients with alcoholic cirrhosis or severe alcoholic hepatitis and bacterial infection

Type of infection	Absence of severe sepsis		
	Community-acquired infections	HCA and nosocomial infections	
		Low prevalence of MDR bacteria	High prevalence of MDR bacteria
Spontaneous bacterial peritonitis	IV 3rd-generation cephalosporins	IV piperacillin/tazobactam	IV meropenem ± glycopeptide or linezolid/daptomycin#
Spontaneous bacteremia			
Urinary infections			
Pneumonia**	IV 3rd-generation cephalosporins **+** oral/IV macrolide or levofloxacin		IV meropenem/ceftazidime +ciprofloxacin ±glycopeptide or linezolid ¶
Soft tissue infections	IV amoxicillin/clavulanic acid		IV meropenem/ceftazidime **+** glycopeptide or linezolid/daptomycin#

Type of infection	Severe sepsis or shock*	
	Low prevalence of MDR bacteria	High prevalence of MDR bacteria
Spontaneous bacterial peritonitis	IV piperacillin/tazobactam	IV meropenem + glycopeptide or linezolid/daptomycin#
Spontaneous bacteremia		
Urinary infections		
Pneumonia		IV meropenem/ceftazidime +ciprofloxacin ±linezolid ¶
Soft tissue infections		IV meropenem/ceftazidime + linezolid/daptomycin#

*: Empirical antibiotic treatment of severe sepsis or shock will be decided considering the local rate of MDR pathogens in order to cover all potential pathogens. Site of infection is not considered.

#: linezolid/daptomycin in areas with a high prevalence of vancomycin-resistant enterococci (VRE); ¶: antibiotics active against MRSA should be added in patients with risk factors: ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage. Consider adding nebulized colistin or amikacin to cover MDR *Pseudomonas aeruginosa* in areas with high prevalence of this MDR bacteria. HCA, healthcare associated; MDR, multi-drug resistant.

Table 4. Characteristics of double-blind, randomized, placebo-controlled clinical trials of an oral quinolone for primary prophylaxis of infection in patients with cirrhosis

Characteristics	**Study Details**			
Reference	Rolachon et al. [179]	Grangé et al. [180]	Fernandez et al. [181]	Terg et al. [182]
Intervention	Ciprofloxacin (750 mg per os, once a week, for 6 months)	Norfloxacin (400 mg per day for 6 months)	Norfloxacin (400 mg per day for 12 months)	Ciprofloxacin (500 mg per day, for 12 months)
Inclusion criteria	AF protein concentration ≤15 g/L	AF protein concentration <15 g/L	AF protein concentration <15 g/L and advanced cirrhosis*	AF protein concentration < 15 g/L
Primary end point	Primary prevention of SBP**	Primary prevention of Gram-negative bacterial infections	3-month and 1-year probability of survival	Primary prevention of SBP
Number of patients				
Quinolone	28	53	35	50
Placebo	32	54	33	50
Proportion of alcoholic cirrhosis, n (%)	55 (92)	93 (87)	36 (53)	NA
Bacterial infection (% of patients)				
Any				

Quinolone	14	13	40	16
Placebo	34	24	58	32**
SBP				
Quinolone	4	0	6	4
Placebo	22*	9	30***	14
Caused by Gram-negative bacteria				
Quinolone	4	0	37	NA
Placebo	0	11	18	NA
Mortality rate (%)				
By 3 months				
Quinolone	-	-	6	-
Placebo	-	-	30***	-
By 6 months				
Quinolone	14	15	-	-
Placebo	19	18	-	-
By 1 year				
Quinolone	-	-	29	14

Placebo	-	-	39****	34***

Abbreviations: AF, ascitic fluid; SBP, spontaneous bacterial peritonitis; NA: Not available.

*Advanced cirrhosis was defined as follows: advanced liver failure (Child–Pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dL) or impaired renal function (serum creatinine level ≥ 1.2 mg/dL, blood urea nitrogen level ≥ 25 mg/dL, or serum sodium level ≤ 130 mEq/L)

**Only 2 patients in the ciprofloxacin group and 5 in the placebo group had had prior episode of SBP.

***$p<0.05$ quinolone vs. placebo

****The Kaplan-Meier estimate of 1-year mortality was 48% in the norfloxacin group and 60% in the placebo group ($p=0.05$).

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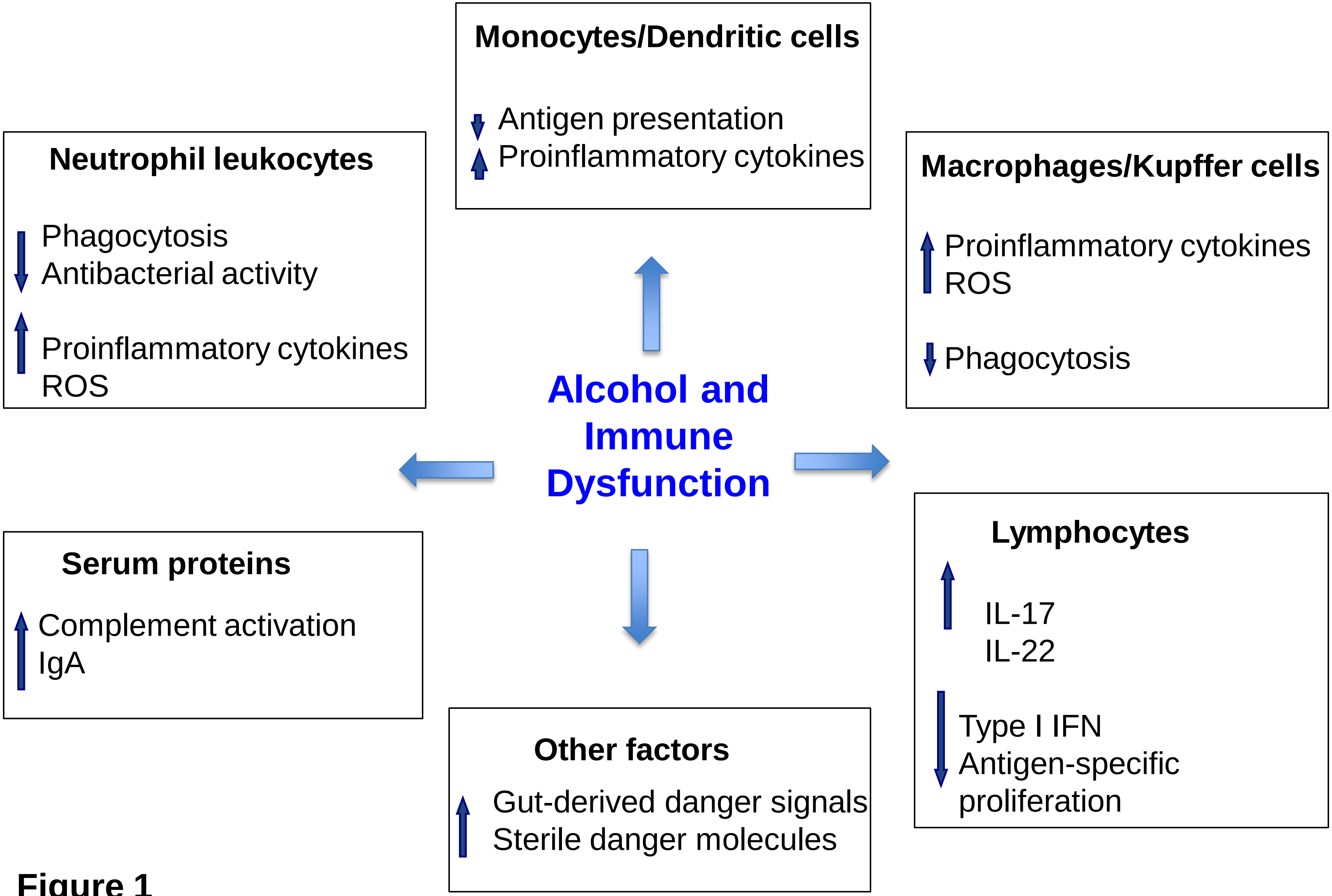


Alcohol and Immune Dysfunction

Monocytes/Dendritic cells

↓ Antigen presentation
↑ Proinflammatory cytokines

Neutrophil leukocytes

↓ Phagocytosis
Antibacterial activity

↑ Proinflammatory cytokines
ROS

Macrophages/Kupffer cells

↑ Proinflammatory cytokines
ROS

↓ Phagocytosis

Serum proteins

↑ Complement activation
IgA

Lymphocytes

↑ IL-17
IL-22

↓ Type I IFN
Antigen-specific proliferation

Other factors

↑ Gut-derived danger signals
Sterile danger molecules

Figure 1

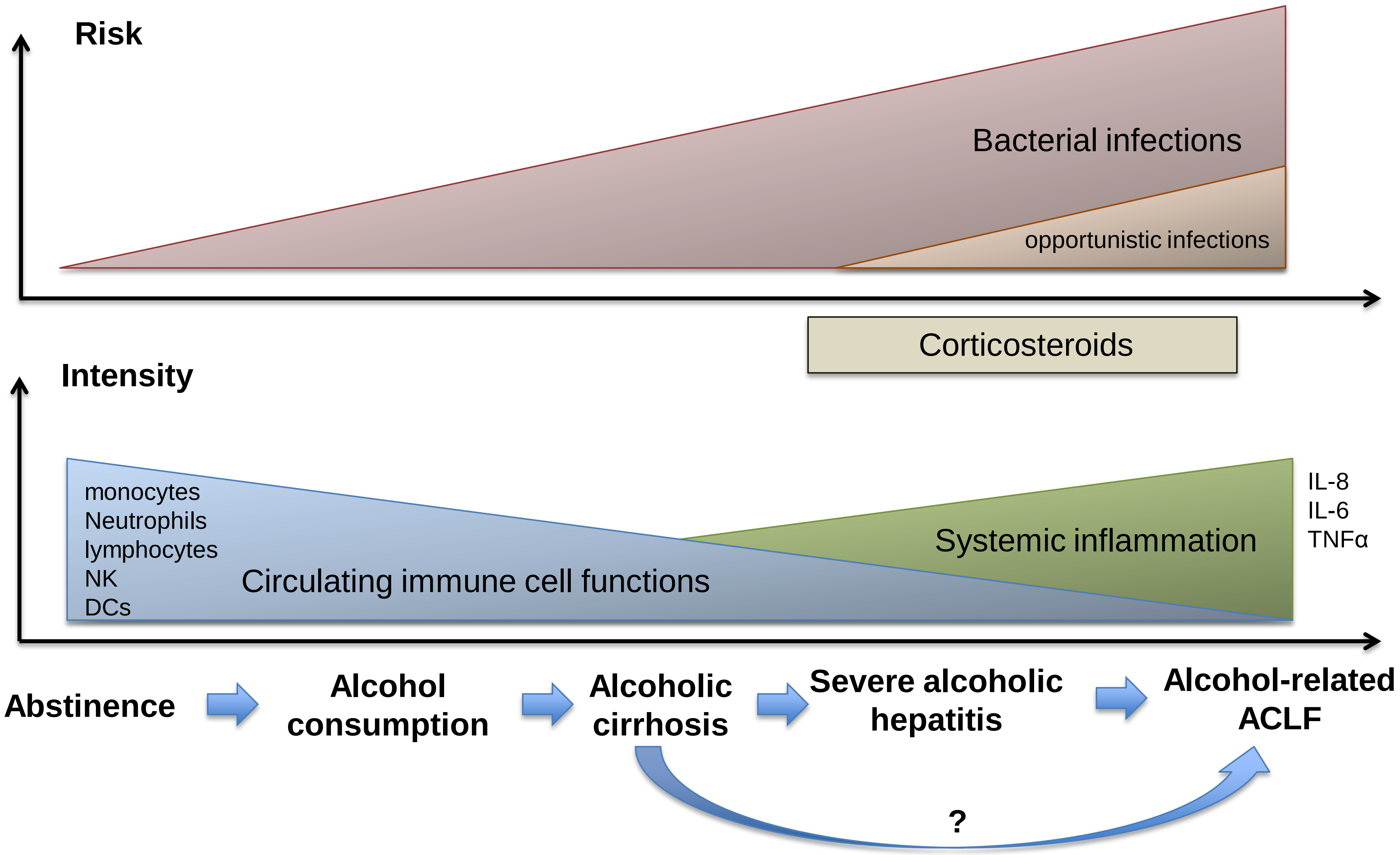
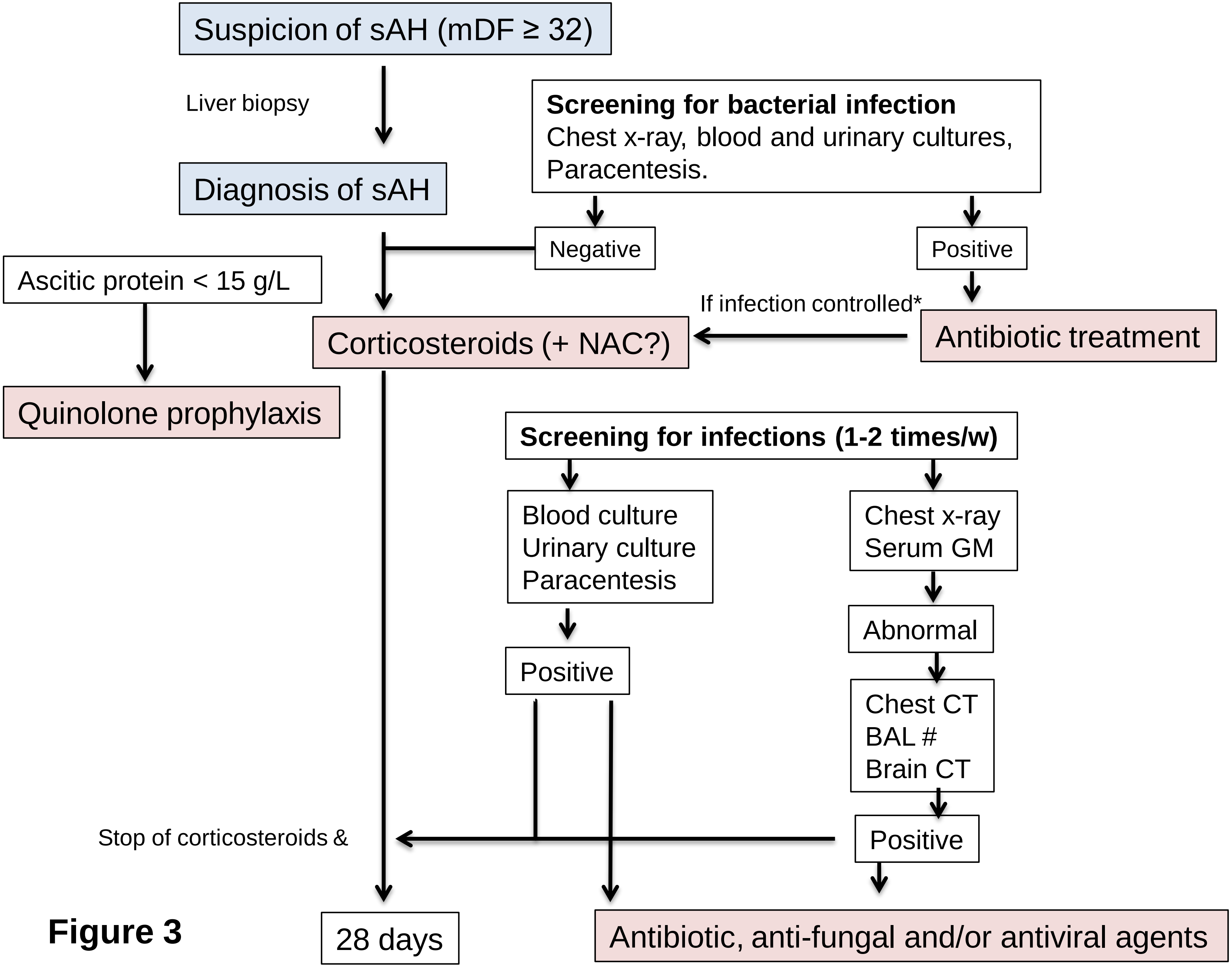

Risk
Bacterial infections
opportunistic infections
Corticosteroids
Intensity
monocytes
Neutrophils
lymphocytes
NK
DCs
Circulating immune cell functions
Systemic inflammation
IL-8
IL-6
TNFα
Abstinence
Alcohol consumption
Alcoholic cirrhosis
Severe alcoholic hepatitis
Alcohol-related ACLF
?

Figure 2



Suspicion of sAH (mDF ≥ 32)
Liver biopsy
Diagnosis of sAH
Screening for bacterial infection
Chest x-ray, blood and urinary cultures, Paracentesis.
Negative
Positive
Ascitic protein < 15 g/L
If infection controlled*
Corticosteroids (+ NAC?)
Antibiotic treatment
Quinolone prophylaxis
Screening for infections (1-2 times/w)
Blood culture
Urinary culture
Paracentesis
Chest x-ray
Serum GM
Abnormal
Positive
Chest CT
BAL #
Brain CT
Positive
Stop of corticosteroids &
28 days
Antibiotic, anti-fungal and/or antiviral agents

Figure 3