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Review Article

Infections in Alcoholic Hepatitis

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Abstract

Severe alcoholic hepatitis (sAH) is defined by a modified discriminant function ≥32 or model for end-stage liver disease (MELD) >20. Patients with sAH are in an immunocompromised state attributed to cirrhosis-related immunoparesis and corticosteroid use. Individuals with sAH often develop severe infections that adversely impact short-term prognosis. Currently, the corticosteroid prednisolone is the only treatment with proven efficacy in sAH; however, the combination of corticosteroid treatment and altered host defense in sAH has been thought to increase the risk of acquiring of bacterial, opportunistic fungal, and viral infections. Newer studies have shown that corticosteroids do not increase occurrence of infections in those with sAH; unfortunately, the lack of response to corticosteroids may instead predispose to infection development. Prompt and appropriate antibiotic treatment is therefore essential to improving patient outcomes. This review highlights common infections and risk factors in patients with sAH. Additionally, current diagnostic, therapeutic, and prophylactic strategies in these patients are discussed.

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Introduction

Alcoholic liver disease (ALD) involves a range of injury from simple steatosis to frank cirrhosis. Over the last decade there has been a rapid rise in the prevalence of ALD in the USA, particularly among patients younger than age 30.[1] These trends have intensified since the start of the coronavirus disease 2019 (COVID-19) pandemic with a notable increase in incidence of alcohol use disorder, ALD, and alcoholic hepatitis (AH).[2]

AH is considered the most severe form of alcohol-related liver disease. Clinical presentation typically includes recent or ongoing excessive alcohol intake, with a minimal threshold for women being 3 drinks (≥40 g per day) and for men 4 drinks (≥50–60 g per day).[3,4] The severity of AH is classically determined by a Maddrey (modified) discriminant function (mDF) of ≥32, based on a combination of prothrombin time and bilirubin levels.[5] More recently, the model for end-stage liver disease (MELD) has been utilized to identify severe AH, with a score >20 signifying severe AH.[6] In certain cases, patients may develop multiorgan failure (MOF) and the 3-month mortality rate can approach 40%.[7] The prevalence of severe AH has been reported to be as high as 20% in hospitalized patients.[8]

Certain patients with severe AH may require corticosteroid treatment with prednisolone, which is the only therapeutic option demonstrated to improve short-term survival for this condition. Currently, the use of steroids in AH is controversial, as studies have shown conflicting results.[9–11] In a meta-analysis of 11 randomized controlled trials (RCTs), which ultimately included 2,111 patients with sAH, it was demonstrated that corticosteroid treatment significantly reduced mortality at 28 days compared with placebo, with an overall 36% risk reduction.[9] However, the largest double-blinded placebo RCT regarding treatment of sAH, the STOPAH trial, did not demonstrate a statistically significant survival benefit at 28 days in patients receiving corticosteroids compared with placebo, while in a *post hoc* multivariable analysis, corticosteroids were associated with improved 28-day survival (odds ratio [OR] 0.609; p=0.015) but not at 90 days (OR 1.02) or 1-year (OR 1.01).[10] Despite these discrepancies, guidelines recommend that a MDF ≥32 or MELD score >20 indicate the need for treatment with corticosteroids.[11,12]

Patients with sAH, however, are at high risk of developing bacterial and fungal infections, due to immunoparesis related to disease pathogenesis and the immunosuppressive effects of corticosteroids.[13] A meta-analysis of 12 randomized trials found a cumulative incidence of infection of 20% in patients with AH during corticosteroid therapy.[14] Additionally, a cohort study found an infection incidence of 53% in 162 patients with biopsy-proven severe AH during a 90-day follow up.[15] The incidence of bacterial infection in the setting of severe AH is variable, ranging from 30% to 80% of cases,[16] leading to a significantly greater risk of mortality.[17]

The purpose of this review is to highlight common infections and risk factors in patients with sAH. Additionally, current prevention strategies in these patients will be summarized and discussed.

Keywords: Alcoholic hepatitis; Infections; Corticosteroids; STOPAH; Antibiotic treatment; Aspergillosis; Immunodeficiency; Alcoholic liver disease.

Abbreviations: ACLF, acute-on-chronic liver failure; AH, alcoholic hepatitis; ALD, alcoholic liver disease; IA, invasive aspergillosis; LPC, lipopolysaccharide; mDF, maddrey (modified) discriminant function; MELD, model for end-stage liver disease; NAC, N-acetylcysteine; RCT, randomized controlled trial; sAH, severe alcoholic hepatitis; SBP, spontaneous bacterial peritonitis; SIRS, systemic inflammatory response system; UTI, urinary tract infection.

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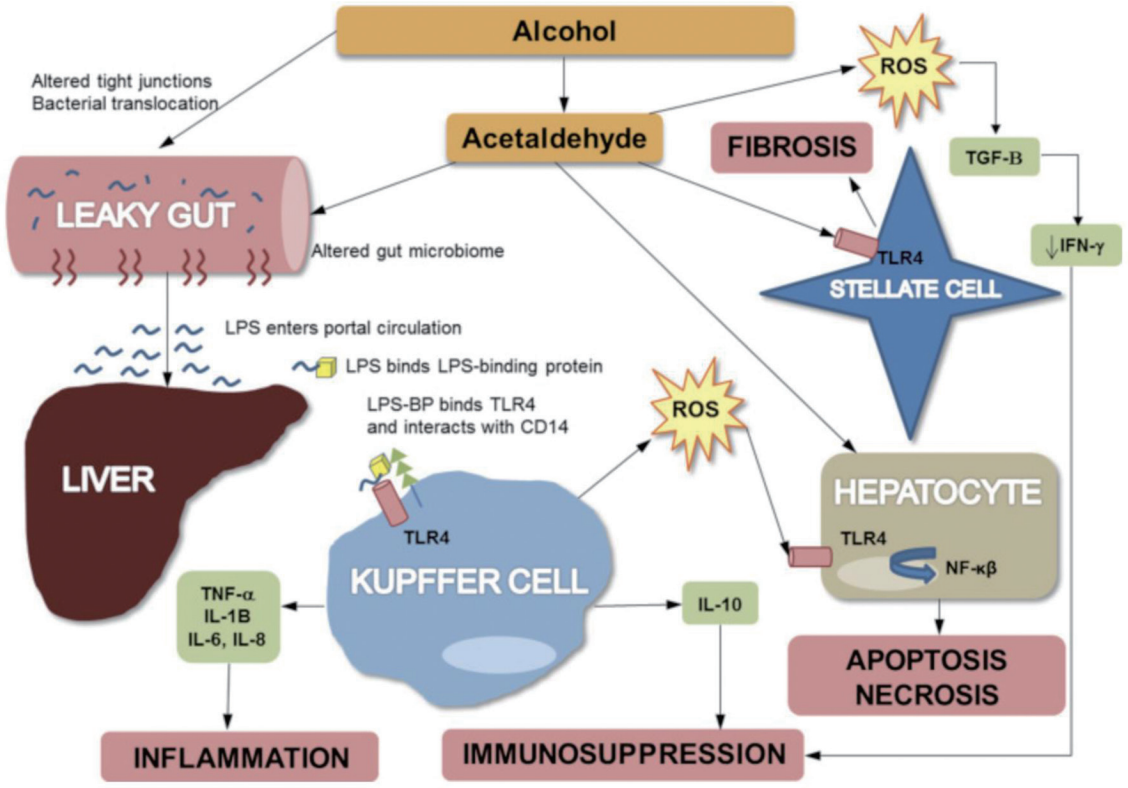

Fig. 1. Alcohol and the innate immune response. Alcohol and its metabolite acetaldehyde alter tight junctions among epithelial cells, leading to increased gut permeability, allowing increased levels of lipopolysaccharide (LPS) to enter the portal circulation. LPS binds toll-like receptor (TLR) 4 and activates a cascade of cytokines and chemokines that lead to a state of both inflammation and immunosuppression. BP, binding protein; IFN, interferon; IL, interleukin; NF, nuclear factor; ROS, reactive oxygen species; TGF, transforming growth factor. Permission has been obtained for reproduction by source: Clinics in Liver Disease, Article: Infection and Alcoholic Liver Disease.

Risk factors for infection development

AH vs. cirrhosis-associated immune dysfunction

AH is physiologically unique, when compared to cirrhosis, and often presents as a state of high-grade inflammation. Dysregulation of the immune system due to acute or recent alcohol use can lead to both an immunocompromised and proinflammatory state.[18] Alcohol and its metabolite acetaldehyde alter tight junctions among epithelial cells, leading to increased gut permeability, allowing increased level of pathogen-associated molecular pattern (PAMP) molecules, including lipopolysaccharide (LPS), to enter the portal circulation.[18,19] LPS binds to toll-like receptor (TLR) 4 on Kupffer cells in the liver to produce increased proinflammatory cytokines, including TNF-α, which activates the cell-death pathway triggering production of reactive oxygen species.[20] Additionally, this cascade of cytokines and chemokines can lead to a state of both inflammation and immunosuppression (Fig. 1).[18,20] One prospective study analyzed serum from 20 patients with acute AH, 16 patients with stable advanced alcohol-related cirrhosis, and 12 healthy controls. Compared to patients with advanced alcohol-related cirrhosis, those with acute AH had markedly greater suppression of T lymphocytes, due to overexpression of inhibitory receptors and reduced neutrophil antimicrobial activities. These alterations seem to be dependent on the higher chronic LPS exposure observed in severe AH.[21] Also, chronic and acute alcohol consumption are associated with a decrease in T cells, B cells, natural killer cells, monocytes, and an increase in proinflammatory cytokines.[13,19,22,23] Ultimately, findings suggest that excessive response of the immune system to PAMPs, including LPS, plays a role in the development of liver damage in AH, which is different from alcohol-related cirrhosis.[18–20,24]

In contrast, in compensated cirrhosis, damage-associated molecular patterns (DAMPS) from stressed/damaged tissue or necrotic hepatocytes activate circulating immune cells.[22] The progression of cirrhosis distorts hepatic architecture and impairs functional capacity. These events compromise the immune surveillance function of the liver and impairment of the bactericidal role of phagocytic cells. This low-grade systemic inflammation is a distinctive feature of compensated and stable decompensated cirrhosis.[19] The degree of systemic inflammation and immunodeficiency intensifies as the course of cirrhosis progresses.

Immunodeficiency is characteristically present in the setting of acute-on-chronic liver failure (ACLF) and often among patients with stable decompensated cirrhosis, contributing to episodes of acute decompensation triggered by bacterial infection.[19] Ultimately, this immunodeficiency increases the risk of infection at any stage of liver disease, with greater risk of infection correlating with higher ACLF grade.[25] In decompensated cirrhosis, gut barrier dysfunction arises from damage at all levels of intestinal barrier defense, which may contribute to the frequency and severity of complications.[26]

In summary, alcohol-induced derangement of the immune system via the LPS-TLR pathway triggers an extended inflammatory response, resulting in immune exhaustion and paralysis.[18,27] This process is offset by a dysregulated

compensatory anti-inflammatory pathway that predisposes patients with AH to infection.[18,27,28]

Corticosteroid-related immunosuppression

Prednisolone, the primary treatment for sAH, may tip the balance between systemic inflammatory response system (SIRS) and compensatory anti-inflammatory response syndrome (CARS) toward CARS, which then results in immune paralysis, nosocomial infections, and multiple organ dysfunction.[13] Cirrhosis-associated immune dysfunction is characterized by increased expression of immune inhibitory markers and decreased phagocytic activity of neutrophils and monocytes, setting the stage for susceptibility to infections.[13,21] Prednisolone may also further exacerbate this diminished adaptive immune response, as it can suppresses cellular (Th1) immunity.[29] At the cellular level, prednisolone inhibits the access of leukocytes to inflammatory sites in several ways, including interfering with the function of leukocytes, endothelial cells, and fibroblasts, while also suppressing the production and effects of humoral factors involved in the inflammatory process.[30]

Several studies have demonstrated increased risk of infection among patients with AH treated with corticosteroids.[10,13,31,32] In the STOPAH trial, prednisolone nearly doubled the risk of infections reported as serious adverse events in patients with AH (13% vs. 7%, p=0.002).[10] In a post-hoc analysis that the STOPAH trial used to evaluate bacterial DNA levels to monitor for infection, it was noted that patients with sAH who were given prednisolone were at greater risk for developing serious infections compared to those who did not receive prednisolone.[31] Based on circulating DNA levels, 12% of patients with sAH were noted to have infection at baseline and 23% developed infection while on prednisolone treatment. The most common serious infections included respiratory tract infections and bacteremia.[31] Another observational study showed that corticosteroid use, along with younger age and higher MELD score, were independently associated with infection, specifically invasive fungal infections (IFIs).[32] However, separate studies have indicated that corticosteroids do not appear to increase the risk of infections in those with sAH, but rather the lack of response to corticosteroids may indicate greater risk of infection. A prospective study by Louvet *et al*.[33] analyzed a cohort of 246 patients and found that the infection risk was significantly greater in steroid non-responders compared to responders, at 42.5% vs. 11.1%, respectively (p<0.000001). Furthermore, that study showed that the development of infection may depend more upon the response to corticosteroid treatment (assessed by the Lille score) rather than the treatment of choice or duration.

Pharmacological interventions

Trials have also investigated the efficacy of other medications for the treatment of sAH, including pentoxifylline, anti-tumor necrosis factor (TNF)-α agents (infliximab, etanercept), and granulocyte-colony stimulating factor (G-CSF) in severe AH. Pentoxifylline has been postulated to exert an anti-inflammatory effect through phosphodiesterase inhibition and increased cAMP levels, with the potential to reduce the risk of hepatorenal syndrome.[20] When analyzing infection risks, a study by Vergis *et al*.[31] demonstrated no association between pentoxifylline therapy and the incidence of serious infection (p=0.08), infection during treatment (p=0.20), or infection after treatment for sAH (p=0.27). In fact, adding pentoxifylline to corticosteroids may reduce the risk of infection compared with corticosteroid monotherapy.[34] Additionally, a network meta-analysis suggested that, in patients with severe AH, pentoxifylline and corticosteroids (alone and in combination with pentoxifylline or N-acetylcysteine [NAC]) can reduce short-term mortality.[35] Contrary to this, the STOPAH trial, along with several other studies, has provided data to support a survival benefit with prednisone but not pentoxifylline; subsequently, pentoxyfilline has not been recommended in the most current American Association for the Study of Liver Diseases (AASLD) guidelines.[9,12,36]

The role of anti-TNF-α, including infliximab and etanercept, in the setting of sAH has been evaluated. These agents inhibit the action of the major proinflammatory cytokine TNF-α, which mediates the immune-induced liver injury. Unfortunately, the anti-TNF-α strategies studied have been ineffective and increased the risk of bacterial infections and mortality, leading to early discontinuation of the trials evaluating these medications.[37,38]

G-CSF has been shown to favorably modify the intrahepatic immune environment and stimulate the regenerative potential of the liver. Under normal physiological conditions, G-CSF mobilizes CD34+ cells, increases hepatocyte-growth factor, and induces hepatic progenitor cell proliferation.[39] A randomized pilot study comparing pentoxifylline plus G-CSF with pentoxifylline alone for treatment of sAH demonstrated marked improvement in survival in the combination treatment group at 90 days (78.3% vs. 30.4%; p=0.001).[40] It is thought that neutrophil function enhanced via G-CSF use may improve the innate immune response to bacteria, diminish the risk of infection, and contribute to an improved outcome in patients with sAH.[41] However, a multicenter, randomized phase II trial showed that G-CSF did not improve patient survival and was unable to reduce the rate of complications including infections in patients with ACLF.[42]

Although some initial studies have shown encouraging results with G-CSF in patients with severe AH, more work needs to be done to characterize associated risks prior to initiating wide clinical use in the setting of AH.[43]

Bacterial pathogens

The majority of infections among patients with sAH are bacterial, though it is uncertain which species are the most commonly acquired. One small study on AH showed that Gram-negative bacilli (GNB), predominantly *Escherichia coli*, represented 75% of all isolated bacteria.[44] Conversely, another small study analyzed the prevalence of bloodstream infections only in patients with AH. The investigators reported a significant prevalence of Gram-positive cocci (44%) and GNB presence of only 22%.[45] A cross-sectional analysis revealed that, among hospitalized patients with AH, prevalence of *Clostridium difficile* infection (CDI) was 1.6% or about 1.5-fold higher than that among hospitalized patients without AH.[46] Furthermore, CDI in these patients was associated with increased inpatient mortality.[46]

Regarding the site of infection, urinary tract and respiratory systems have been found to be more common in patients with AH.[47] A cohort study analyzed data from 121 patients with AH and showed pneumonia to be the most frequent infection (26%), followed by urinary tract infection (UTI) (23%) and skin and soft tissue infections (SSTIs) (8%), while spontaneous bacterial peritonitis (SBP) was found to be present in only 6% of infected patients.[48] A separate large, retrospective cohort study was conducted to evaluate patients with AH admitted between 2009 and 2014 to seven centers in Europe and the USA.[49] Among the

patients studied, 49% showed clinical or culture-based evidence of infection, primarily involving the lower respiratory tract or urinary tract. Gut commensal bacteria, particularly *E. coli* and *Enterobacter* species, were most commonly isolated in culture. Fungal infection was rarely seen.

Certain studies have shown that the most common infections sites differ before and after corticosteroid administration. For example, Louvet *et al*.[33] reported that prior to steroid treatment, SBP or bacteremia occurred more frequently (44%), followed by UTI (32%) and respiratory infections (13%). After or during corticosteroid treatment, there appeared to be a notable shift towards respiratory infections (40%), followed by SBP or bacteremia (28%) and UTI (18%). A separate meta-analysis from 2016 showed that, in patients with AH, corticosteroids-related infections included pneumonia (23%), UTI (10%), SBP (7%), and SSTI (2%).[14] In the STOPAH trial, respiratory infections accounted for 50% of all infections (both in treated and untreated groups) during follow-up. Lung infections were more common in patients who received prednisolone (7%) vs, those who did not receive prednisolone (3%).[10]

Fungal pathogens

Fungal infection is associated with high mortality in critically-ill patients with cirrhosis.[50,51] However, there are limited studies looking specifically at invasive aspergillosis (IA) in the setting of AH. A meta-analysis demonstrated higher frequency of fungal infection occurrence among steroid-treated AH patients; in these patients, fungal infections were life-threatening, with a high mortality rate (approximately 33% compared to 12% in all steroid-treated infections).[14] In a cohort study of 94 patients with biopsy-proven sAH, IA incidence was 16%. The primary sites of infection included the lungs and central nervous system, while IA was disseminated in two cases. Of note, 13 cases of IA occurred in the context of corticosteroids, and 2 had received no specific treatment for AH.[52] These studies have shown that IA is a frequent complication of sAH and carries a very high risk of mortality. Along with liver disease, other risk factors of IA include neutropenia, hematologic malignancies, HIV, or organ transplantation.[53,54] Early and routine screening for IA may be beneficial.[52,55] Serum galactomannan (GM) has been demonstrated as a good screening test factor for IA in those with severe AH. The classical cutoff of ≥0.5 for serum GM has shown a high diagnostic performance, with sensitivity of 89%, specificity of 84%, positive predictive value of 67%, and negative predictive value of 95%.[52]

Invasive candidiasis incidence has been reported to be between 2% to 8% in patients with sAH.[52] A recent study, from 2021, demonstrated that human neutrophil responses to the fungal pathogen *C. albicans* are significantly diminished in patients with cirrhosis compared to healthy controls. This defect may be due to neutrophil exhaustion in the setting of persistently elevated circulating levels of inflammatory cytokines.[56] Patients with sAH present a more markedly reduced neutrophil antimicrobial activity, including phagocytosis and oxidative burst.[21] This underlying immune dysfunction in patients with AH may explain the lack of neutrophil functioning, thus increased prevalence of candidemia.

Pneumocystis jirovecii pneumonia (PJP) is another opportunistic fungal infection, which may occur in sAH.[57] Faria *et al*.,[58] analyzed seven ICU patients with biopsy-proven AH who developed bronchoalveolar lavage-confirmed PJP. Six of these patients received steroids for AH treatment prior to the diagnosis. All patients progressively developed acute respiratory distress requiring mechanical ventilation, ultimately leading to death despite receiving appropriate treatment. Additionally, two case reports have been published evaluating patients with human immunodeficiency virus (HIV) and steroid-treated AH who subsequently developed severe pneumopathy due to PJP.[59] Lastly, a report highlighted a case of PJP together with cytomegalovirus infection in an HIV-negative alcoholic patient.[60] Although small in sample size, these studies have shown that otherwise rare opportunistic infections, such as PJP, may occur in patients with AH, particularly in the setting of steroid use.

Biomarkers of infection

Determining the presence of infection may be challenging in patients with AH, as cultures may be negative despite the presence of clinical indicators of active infection, such as leukocytosis.[15] One study showed that the SIRS criteria are met in approximately 50% of patients with sAH, even without documented infection.[15] Both C-reactive protein (CRP) and procalcitonin (PCT) have been investigated as potential biomarkers to determine the presence of underlying infection. Although CRP and PCT levels have been useful for detecting infection in cirrhosis, there have been inconsistencies in differentiating infection from SIRS without infection in AH. Among patients with AH, the findings of one study highlighted that a PCT cutoff of 0.45 ng/mL had positive and negative predictive values of 83% and 71% respectively for infection-associated SIRS, while CRP displayed no discriminative capability.[15] Another study found that serum PCT can be a useful marker for diagnosing sepsis in patients with AH and SIRS, and compares favorably with serum CRP levels.[61] On the other hand, in yet another study, PCT cutoff value failed to discriminate infected from non-infected patients with AH.[62] Therefore, although promising, biomarkers for underlying infection need further study, and in clinical settings should be carefully interpreted in combination with clinical assessment and correlation.

Infection treatment and prevention

Management of sAH begins with thorough review of symptoms, physical exam findings, and infection workup, including chest radiography, urinalysis, cultures, ascitic fluid analysis, and viral serology (Table 1). If infection is detected, pathogen-directed therapy should be initiated (Fig. 2). Identification of an infection is critical prior to the initiation of steroids or immunosuppressant therapy to reduce risk of complications from these medications. If infection is unlikely, prevention strategies are focused on early treatment of sAH, based on discriminant function or MELD score. Additionally, the Lille score (which reassesses prognosis, identifies nonresponses, and guides therapy) may be used to determine whether corticosteroids should be discontinued.[12]

In patients with sAH, the development of infection may depend more on the response to corticosteroid treatment as assessed by the Lille score, rather than the treatment of choice or duration.[33] The response to corticosteroids based on the Lille score is significantly associated with improved survival.[63] The addition of intravenous of NAC to prednisolone may be used as a prevention strategy, as it has been reported to decrease the incidence of bacterial infections in patients with sAH. The adjunction of NAC to corticosteroid treatment has been shown to decrease the incidence of infections by 23%, when compared to corticosteroids alone.[64] Other supplementary infection prevention approaches include adequate patient nutrition. A RCT from 2016 showed that a daily caloric intake of fewer than 21.5 kcal/kg/day

Table 1. sAH assessment and management

History
Recent or ongoing excessive alcohol intake
Women=3 drinks (≥40 g per day)
Men=4 drinks (≥50-60 g per day)
Recent jaundice
Laboratory findings
mDF ≥32 (prothrombin time and bilirubin levels)
MELD >20 (bilirubin, creatinine, international normalized ratio)
Exam findings
Jaundice, icteric conjunctiva
Enlarged liver, ascites, caput medusa
Systemic hypotension, asterixis, confusion
Spider angiomata, palmar erythema
Gynecomastia, gonadal atrophy in men
Proximal muscle wasting, weight loss
Therapeutics
Prednisolone 40 mg/daily
Intravenous NAC+prednisolone 40 mg/day (may improve 30-day survival of patients with sAH)
Of note, pentoxifylline is no longer recommended in the treatment of AH
Duration/Response
Lillie model (albumin, creatinine, and prothrombin time)
Lille score <0.45: Responders to corticosteroids
Lille score ≥0.45: Non-responders
Cessation of corticosteroids after 7 days is recommended in non-responders

MELD, Model for end-stage liver disease; AH, alcoholic hepatitis; mDF, maddrey (modified) discriminant function; NAC, N-acetylcysteine.

was associated with increased rates of infection and mortality at 6 months, when compared to higher intake (65.8% vs. 33.1%, $p<0.0001$).[65]

Antimicrobials

Although patients with sAH are at increased risk of infection, evidence has not yet been reported to support a role for antibiotic prophylaxis. Currently, the use of prophylactic antibiotics in combination with corticosteroids is being investigated in the AntibioCor study.[66] An interim analysis of this study's data, presented as an abstract, revealed that infection rates in patients treated with amoxicillin/clavulanate plus corticosteroids were lower compared to those in the placebo group after 2 months of therapy (29.7% vs. 41.5%; hazard ratio [HR] 0.616, 95% confidence interval [CI] 0.417–0.909; $p=0.015$). Although a 30-day course of antibiotics with prednisolone did not improve 2-month survival in patients with sAH, they did reduce the likelihood of infections.[67] Careful restriction of prophylactic antibiotics to the high-risk populations could reduce the spread of multidrug-resistant bacteria.[47] Additionally, antifungal agents should be considered in patients with risk factors for fungal infections, including comorbid diabetes, acute kidney injury, longer hospital stays, and admission for bacterial infection.[51] Despite management of antibiotics, the presence of infection alone has not been shown to be a driver of short-term mortality. For example, one study observed that the use of antimicrobials early after admission delayed but did not reduce the occurrence of infections in patients with AH, without an effect on mortality.[49]

Conclusions

Patients with AH are in an immunocompromised state, secondary to a combination of cirrhosis related immunoparesis and corticosteroids use, which may predispose them to higher risk of infection. To date, corticosteroids are the only treatment with proven efficacy in sAH. Nevertheless, corticosteroid impact on the occurrence of infection remains controversial. Some studies have shown that corticosteroid use may significantly reduce short-term mortality in patients with sAH.[9,10] Additionally, the combination of corticosteroid treatment and altered host defense in AH has been suggested as a cause of bacterial, opportunistic fungal, and viral infections.[68] Recent studies have shown that corticosteroids do not appear to increase occurrence of infections in those with sAH, though the lack of response to corticosteroids may increase infection risk.[33] However, screening for infections should be performed prior to corticosteroid initiation and during treatment, if clinically indicated. Physicians should be cognizant of recognizing potential infections in patients with ALD, in order to appropriately administer antibiotic therapy that will reduce the associated

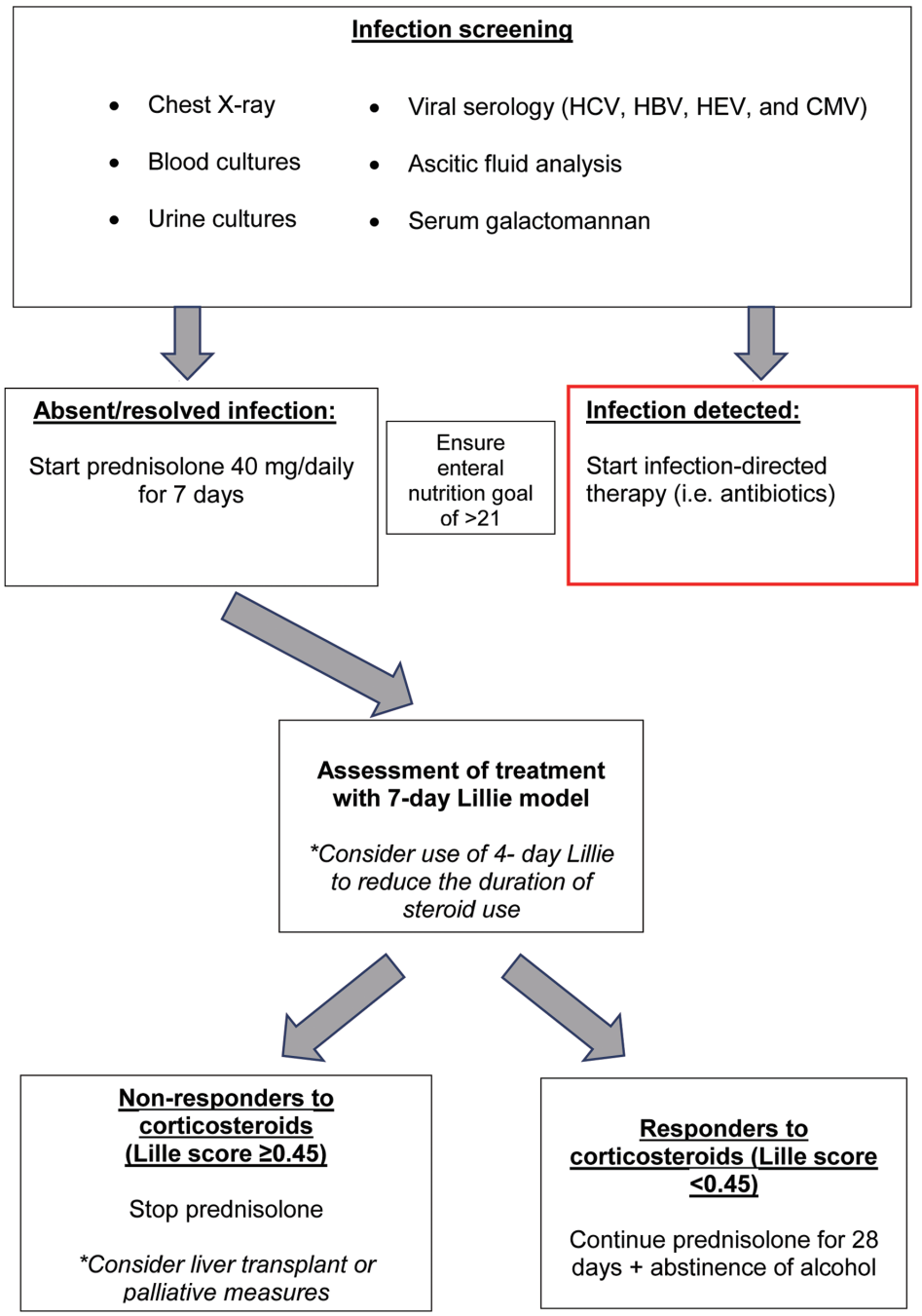

Fig. 2. AH infection management. CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis virus; HEV, hepatitis E virus.

mortality rate. The use of biomarkers such as CRP or PCT to aid in determination of infection development can be useful, though further studies are needed to justify their routine use. We recommend reassessment and potential antibiotic de-escalation at 48 h to reduce the spread of multidrug-resistant bacteria, fungi, or *Clostridium difficile*.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Acquisition of data and drafting of the manuscript (BK, RS, VS), critical revision of the document for important intellec-

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