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Infections in severe alcoholic hepatitis

Eleni Karakike[a], Christophe Moreno[b,c], Thierry Gustot[b,c,d]

CHU Brugmann; C.U.B. Erasme, Université Libre de Bruxelles; Université Libre de Bruxelles, Brussels, Belgium; Centre de Recherche sur l'inflammation (CRI), Paris, France

Abstract

Severe alcoholic hepatitis (sAH), defined by a modified discriminant function ≥32, is the most severe form of alcohol-induced liver disease and is associated with a 1-month mortality rate of around 30%. Corticosteroid treatment remains the only therapeutic option that improves short-term survival. Infectious complications, occurring in approximately 50% of patients, are the main causes of death, even in patients who benefit from corticosteroids. Liver failure, recent alcohol consumption and immunosuppressive drugs contribute to this infectious risk. Although infection is a well-described feature of cirrhosis, little is known about the characteristics of infections in sAH. Infection is mainly of bacterial origin and frequently affects the respiratory tract. Pathogens classically observed in cirrhosis, such as gram-negative bacilli, are frequently involved, but opportunistic pathogens, such as fungi (*Aspergillus fumigatus, Pneumocystis jirovecii*) or viruses (Cytomegalovirus, Herpes simplex) may appear, mainly related to corticosteroid treatment. A high level of suspicion with systematic screening and prompt, adequate treatment are warranted to improve outcomes in these patients. Prophylactic strategies in this high-risk population should be assessed in well-designed trials.

Keywords Alcoholic hepatitis, infection, corticosteroids, aspergillosis

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Introduction

Severe alcoholic hepatitis (sAH) is a clinical entity identified as the most severe form of alcoholic liver disease and presents high incidence rates among young people. The diagnosis of sAH requires a recent or ongoing excessive alcohol intake (minimal thresholds for women ≥40 g per day [3 drinks], for men ≥50-60 g per day [4 drinks]), recent onset (<3 months) of severe jaundice (total bilirubin ≥5 mg/dL) and ideally a liver biopsy showing typical histological lesions, macrovesicular steatosis with at least one of the following: ballooning hepatocytes, Mallory-Denk bodies and neutrophil infiltration, and intrasinusoidal fibrosis [1]. The true prevalence of sAH is currently unknown, given the lack of systematic biopsy-driven diagnosis, but it has been reported to be as high as 20% in hospitalized alcoholic patients [2]. In Europe, a more recent Danish study over a decade found an incidence of nearly $40/10^6$ inhabitants per year [3]. In those population studies only clinical criteria were used, and the number of AH diagnoses may have been under- or overestimated. Severity stratification in AH is crucial, for prognostication as well as for treatment purposes; sAH is classically defined by a Maddrey (modified) discriminant function (mDF) of ≥32 and is associated with a poor prognosis (28-day and 1-year mortality rates 30% and 50%, respectively) [1,4,5].

Although the treatment for AH continues to be debated, corticosteroids (prednisone 40 mg per day), the most widely used treatment, showed a 14% reduction in 1-month mortality in sAH (defined by mDF ≥32) based on a meta-analysis of 5 randomized controlled trials (RCT) [4]. On the other hand, pentoxifylline, compared with placebo in a small trial, has shown encouraging results in reducing mortality, mainly by preventing hepatorenal syndrome [6]. Recently, a large-scale RCT (STOPAH) showed that corticosteroids significantly improved survival at 28 days when compared to placebo and after adjustment for different severity factors, whereas pentoxifylline had no significant effect. The survival benefit from corticosteroids was not maintained at 90 days or 1 year [7]. Although discrepancies persist, current guidelines

[a]Department of Infectious Diseases, CHU Brugmann (Eleni Karakike); [b]Department of Gastroenterology and Hepato-Pancreatology, C.U.B. Erasme, Université Libre de Bruxelles (Christophe Moreno, Thierry Gustot); [c]Laboratory of Experimental Gastroenterology, Université Libre de Bruxelles (Christophe Moreno, Thierry Gustot), Brussels, Belgium; [d]Inserm Unité 1149, Centre de Recherche sur l'Inflammation (CRI), Paris, France (Thierry Gustot)

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Correspondence to: Thierry Gustot MD, PhD, Associate Professor, Director of the Liver Transplant Unit Department of Gastroenterology and Hepato-Pancreatology, C.U.B. Erasme, Université Libre de Bruxelles, Brussels, Belgium, Tel.: +32 25553714, Fax: +32 25554802, e-mail: thierry.gustot@erasme.ulb.ac.be

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recommend the use of corticosteroids in sAH, in the absence of contraindications such as uncontrolled infection, active gastrointestinal bleeding, or hepatorenal syndrome. The Lille score (freely available calculator on http://www.lillemodel.com/), assessing the response after seven days of corticosteroid treatment, offers an additional prognostication tool by identifying the subgroup of patients who will benefit from a 28-day corticosteroid treatment. Responders to corticosteroids, defined by a Lille score <0.45, have an excellent prognosis (85% survival at 6 months), while non-responders (Lille score ≥0.45), who represent nearly 40% of treated sAH patients, demonstrate substantially lower survival rates (25% at 6 months) [8]. The cessation of corticosteroids is recommended in these non-responders after one week of treatment. Currently, no alternative therapeutic intervention has been effective in reducing mortality in non-responders. A multicenter study showed that highly selected transplanted non-responders had significantly higher 6-month survival rates than non-responder controls (77% vs. 23%, P<0.001) and similar ones to responders [9]. Considering that, using stringent criteria for patient selection, alcohol relapse occurred rarely and the donor pool was minimally affected, this strategy seems to be gaining ground worldwide.

Infections in sAH

Infection is one of the main complications of sAH, as well as one of the major causes of mortality in this setting [3]. Infected patients with sAH suffer from a further increase in mortality of 30% at 2 months. Even responders to corticosteroids, in case of infection, present a survival similar to that of non-responders [10].

Infections accounted for 24% of all deaths in the largest sAH trial to date [7]. In another study, which included 162 patients with sAH, systemic inflammatory response syndrome (SIRS) at admission and in-hospital infection were independently associated with multiple organ failure, which in turn was associated with higher mortality, independently of different severity scores for liver dysfunction and responses to corticosteroids [11].

Reported mortality attributable to infection is probably underestimated, because even other causes of mortality in sAH, such as liver failure or related events and gastrointestinal bleeding, may be precipitated by or concomitant with an unidentified infection [7,12].

Incidence of infections in sAH

The incidence of infections has been evaluated in previous therapeutic trials as part of the secondary outcomes or adverse events of the studied intervention. A meta-analysis of 12 randomized trials found a cumulative incidence of infection of 20% in patients with sAH during corticosteroid treatment (28-day follow up in 1062 patients without infection at baseline) [12]. The heterogeneity of these studies, though, prevents safe conclusions from being drawn.

Very few studies are designed to address the issue of infection in sAH in clinical practice. Louvet *et al*, in a cohort of 246 patients, found that 26% of patients presented an infection at the time of sAH diagnosis, while another 22% were infected during the 2-month period of follow up and treatment, for an overall incidence of infection of nearly 50% [10]. Michelena *et al* reported an incidence of 53% in a cohort of 162 patients with biopsy-proven sAH during a 90-day follow up [11]. Finally, a study that included 79 patients with sAH, followed up for 3 months in our institution, reported even higher rates of infection, which was present in 81% of cases, 37% of which were infected at admission [13]. Table 1 summarizes the reported incidences in different published cohorts with sAH.

Risk factors for infection in sAH

Liver-associated immunodeficiency

The high incidence of infections may be partly explained by underlying cirrhosis, frequently present in biopsy-proven sAH (82-100%)and cirrhosis-related defects in the immune system [18,30]. Cirrhosis-associated immune dysfunction (CAID) involves a state of immunodeficiency, and in parallel a state of persistent activation of the immune system cells, especially monocytes, with increased production of pro-inflammatory cytokines and SIRS [31]. CAID is a complex, multifactorial process, resulting from bacterial overgrowth, dysbiosis and increased translocation, which is responsible for continuous stimulation of immune system cells by microbial-associated molecular patterns and hypersplenism, and splenic pooling of immune system cells [32]. This continuous interaction of gut bacteria with the immune system may lead to exhaustion of the immune response and "immune paralysis". The immune dysfunction is present at multiple cell levels (neutrophils, monocytes, T and B lymphocytes and natural killers) and was recently reviewed by Albillos *et al* [33].

Superimposed sAH seems to worsen this cirrhosis-induced immunodeficiency. Compared to patients with advanced alcohol-related cirrhosis, sAH patients presented a more markedly immunosuppressive profile of T lymphocytes (higher interleukin-10 expression and lower interferon-γ production) due to overexpression of inhibitory receptors (PD1, PDL1, TIM3 and galectin-9) and reduced neutrophil antimicrobial activities (phagocytosis and oxidative burst in response to *Escherichia coli*). These alterations seem to be dependent on the higher chronic lipopolysaccharide exposure observed in sAH [15]. Thus, it is reasonable to expect a higher incidence of infection in sAH than in cirrhosis. One study compared patients with AH (of whom 81% had sAH and were treated with pentoxifylline) to cirrhotic patients with equally severe disease (based on mDF) and found a higher incidence of infectious episodes in the former group (38% and 25% respectively) [26]. Those data suggest that sAH patients, even more than cirrhotic

Table 1 Incidence of infections in sAH

Study	No. pts	At baseline %	follow-up	Follow-up duration	Sites (% of all infections)	Severity scores
Thursz 2015 [7]*,†	1092	10% ‡	10% §	12 months	Pulm 50% > SB 25% > SSTI 5% > UTI 2%	mDF 62.6 (mean)
Haim-Boukobza 2015 [14]†	84	N/A	38.1% overall 91% bacterial 9% viral	LOS (non-specified)	N/A	mDF 73.3 (mean)
Michelena 2015 [11]	162	19.7% UTI 31% > SB 19% > SB P16% > Pulm 9%	33.3%	3 months	Pulm 27% > UTI 24% > SBP 11%	mDF 43 (mean)
Markwick 2015 [15]	20	N/A	60%	12 months	N/A	mDF 55.4 (mean)
Park 2014 [16]*	121	N/A ‡	8%	6 months	N/A	mDF 66.3 (weighted mean)
Wernlund 2014 [17]	32 (AH+sAH)	0	28%	1 month	Only BSI: SB 33% > UTI=CLABSI 22% > Abdo=Pulm 11%	mDF 76 (mean)
Altamirano 2014 [18]	121	N/A	39%	LOS (non-specified)	Pulm 26% > UTI 23% > SSTI 8% > SBP 6%	ABIC 7.3 (median) MELD 18 (median)
Karakike 2014 [13]	79	30%	51%	3 months	Pulm 40% > UTI 16% > PB13% > SBP11% > SSTI 9%	mDF 62 (median)
Mathurin 2013 [19]*,†	270	N/A ‡	32.6%	6 months	N/A	mDF 56.5 (weighted mean)
Sidhu 2012 [20]*,†	70	N/A ‡	33%	6 months	SB (96%)	mDF 76.7 (weighted median)
Liangpunsakul 2011 [21]	56809 (AH+sAH)	14%	N/A	LOS (6.5±7.7 days)	UTI 68% > SB 15% > SBP14% > Pulm 2.9%	19% HE+
Nguyen-Khac 2011 [22]*	174	N/A ‡	30.5%	6 months	SBP 26% > Pulm=UTI 21% > SB 15% > SSTI 6%	mDF 56.1 (weighted mean)
Moreno 2010 [23]*	47	N/A	36%	1 month	N/A	mDF 52 (weighted median)
Sharma 2009 [24]*	19	N/A ‡	26%	2 months	Pulm 60%, TB 40%	mDF 66 (median)
De 2009 [25]*,†	68	N/A ‡	14.7%	12 months	N/A	mDF 56 (mean)

(*Contd...*)

Table 1 (*Continued*)

Study	No. pts	At baseline %	During follow up	Follow-up duration	Sites (% of all infections)	Severity scores
Louvet 2009 [10]	246	25.6% (SBP/SB 44% > UTI 32%> Pulm 13% > SSTI 11%)	23.2%	2 months	Pulm 40% > SBP/SB 28% > UTI 18% > SSTI 14%	mDF 60.6 (median)
Verma 2006 [26]	99 (AH+sAH)	N/A	38%	2 months	UTI=SBP 35% > Pulm 20% > SB 5%	mDF 48 (median)
Akriviadis 2000 [6]*,†	101	N/A ‡	12%	1 month	SBP 67% > Pulm 17%	mDF 45.6 (weighted mean)
Ramond 1992 [27]*,†	61	N/A ‡	23%	2 months	Pulm 31% >SBP 25% > SB 13%	mDF 55.3 (weighted mean)
Minuk 1992 [28]	97	N/A	21% bacterial-culture positive	N/A	Pulm 50% > UTI 20% > TB 15%	N/A
Theodossi 1982 [29]*,†	55	N/A	24%	LOS (26 days)	SB 100%	62% HE+

* Therapeutic trial, † Infections were not part of primary or secondary outcome, ‡ Exclusion of non-controlled infections before randomization, § Listed as adverse events, so probably during follow up

Pts, patients; N/A, non-applicable; mDF, modified discriminant function; Pulm, pulmonary infection; SB, spontaneous bacteremia; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infections; SSTI, skin and soft tissue Infections; Abdo, abdominal; TB, tuberculosis; BSI, bloodstream infections; CLABSI, central line-associated bloodstream infections; LOS, length of stay; AH, alcoholic hepatitis; sAH, severe alcoholic hepatitis; HE, hepatic encephalopathy; ABIC, age, bilirubin, international normalized ratio (INR) and creatinine score; MELD, model for end-stage liver disease

patients, are prone to infection, and a preemptive antibiotic strategy may be justified, if there is clinical suspicion.

Infections related to immunosuppressive treatment

A reasonable consideration is that corticosteroid treatment further increases the risk of infection; this is supported by some trials that evaluated corticosteroid treatment [7]. However, a recent network meta-analysis did not show a significant association between infection and either treatment (corticosteroids or pentoxifylline) compared to placebo [30]. Another meta-analysis focusing on corticosteroid treatment and infection found no difference between the corticosteroid and placebo arms in terms of bacterial infection occurrence or associated mortality [12]. Furthermore, it has been implied that development of infection depends more on the response to corticosteroid treatment (assessed by the Lille score) rather than the treatment *per se* or the treatment duration [10]. On the other hand, in the STOPAH trial, the administration of corticosteroids was associated with a greater incidence of infection (13% vs. 7%) [7]. It is of note that the frequency of opportunistic and invasive fungal infections increased among corticosteroid-treated patients [12,34]. The adjunction of N-acetylcysteine to corticosteroid treatment has been shown to decrease the incidence of infections by 23%, compared to corticosteroids alone, but without affecting lethal infections, which occurred equally in both groups [22]. The reason for this decrease is currently unknown.

Investigators explored the potential beneficial effect of specific tumor necrosis factor-α blockade in sAH. In both RCTs (one with infliximab in association with corticosteroids and the other with etanercept alone), the frequency of infections and the mortality rates were greater in the treatment arm compared with placebo [35,36]. This observation seems to be related to a worsening of immunodeficiency, as shown by an alteration in the activation capacity of circulating neutrophils.

Diagnosis of infection

Detecting infections in patients with sAH is challenging, because the SIRS criteria are met in approximately 50% of patients with sAH, whereas infection may be present in only one third of patients with SIRS and in as many as 10% of patients without [11]. Moreover, no clinical and biological parameters are able to distinguish between infected and non-infected patients [10]. C-reactive protein (CRP) and procalcitonin (PCT) levels have been useful for detecting infection in cirrhosis, but have demonstrated variable accuracies in distinguishing infection from SIRS without infection in AH. In a study by Kumar *et al*, CRP, with a cutoff level of 23 mg/L, showed a sensitivity of 82% and a specificity of 75% in detecting infection, while the respective values for a PCT level of 0.57 ng/mL were 79% and 82% [37]. However, another study using the same PCT cutoff value failed to discriminate infected from non-infected patients [38]. In a larger trial, a PCT cutoff of 0.45 ng/mL had positive and negative predictive values of 83% and 71% respectively for infection-associated SIRS (negative predictive value increased to 79% if the cutoff level was lowered to 0.25 ng/mL), while CRP displayed no discriminative capability [11]. In our opinion, these two parameters have a limited utility in clinical practice. Physicians should maintain a high level of suspicion for infection, even in the absence of SIRS or biological inflammatory markers. We recommend that screening exams (blood, urinary cultures, diagnostic paracentesis and chest X-ray) be performed at the time of diagnosis and twice per week during hospitalization, or once weekly when the patient is discharged from hospital during the 28-day corticosteroid treatment.

Bacterial infections

The term "infection" is commonly used interchangeably with the term "bacterial infection". Indeed, bacterial infections represent the vast majority (86%) of infectious episodes in the setting of sAH. Viral or fungal infections seem to represent 4% and 10% of all infections, respectively [13].

Infectious sites

Urinary tract infections (UTI) and respiratory infections seem to occur more commonly during sAH, in contrast to cirrhosis, where spontaneous bacterial peritonitis (SBP) is predominant [39,40]. Michelena *et al* found UTI to be the most frequent (26%), followed by respiratory infections (21%), SBP (13%) and spontaneous bacteremia (SB, 8%) during a 90-day follow up [11].

Louvet *et al* distinguished infections at admission from those during treatment and follow up. At baseline, SBP or SB occurred more frequently (44%), followed by UTI (32%), respiratory (13%) and cutaneous (11%) infectious episodes. After or during corticosteroid treatment, a shift towards respiratory infections was noted (40% of all episodes), but SBP or SB (28%) and UTI (18%) decreased, while cutaneous infections remained stable (14%) [10]. Concerning in-hospital infections only, Altamirano *et al* reported pneumonia as being the most frequent (26%), followed by UTI (23%), and skin and soft tissue infection (SSTI, 8%), while SBP was present only in 6% of infected patients [18]. Similarly, in a meta-analysis of pooled data from 12 randomized trials evaluating corticosteroids, in-hospital infections during follow up (after exclusion of patients infected at baseline) occurred as follows: pneumonia in 23%; UTI in 10%; SBP in 7%; and SSTI in 2% [12]. In our institution, pneumonia was present in 40%; UTI in 16%; SBP in 13%; SB in 11%; and SSTI in 9% of 95 bacterial infections [13]. Interestingly, the STOPAH trial also found a high prevalence of respiratory infections, representing 50% of all infections during follow up [7]. 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 intensive care unit admission.

Bacterial pathogens

Data regarding pathogens are scarce in sAH studies and are mainly extrapolated from the literature on cirrhotic patients. Briefly, in cirrhosis, Gram-negative bacilli (GNB) are isolated in 30-70% of culture-positive infections and *Escherichia coli* (*E. coli*) is the most represented microorganism. However, Gram-positive cocci (GPC) (i.e. *Enterococcus faecalis* and *Staphylococcus aureus* [*S. aureus*]) emerge as the main bacteria isolated in nosocomial infections, and invasive procedures or admission to the intensive care unit (ICU) increase their isolation [41]. In a large international point-prevalence study on cirrhotic patients admitted to ICU, the most frequently isolated bacteria was *S. aureus* [42]. Moreover, multiresistant bacteria (extended-spectrum β-lactamase–producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, methicillin-resistant *S. aureus,* and *Enterococcus faecium*) become an emergent problem, mainly due to hospitalization, long-term norfloxacin prophylaxis and the wide use of β-lactams [39].

In a small specific study on AH, GNB, mainly *E. coli*, represented 75% of all isolated bacteria, as in cirrhotic patients without AH [26]. In our experience, we observed 67% GNB and 29% GPC out of all bacterial pathogens, *E. coli* being the most frequently isolated organism (33%), followed by *S. aureus* (17%) [13]. On the other hand, another small study, focusing on bloodstream infections only, found a significant prevalence of GPC (44%), while GNB were present in only 22% [17]. Specific pathogens may arise more frequently in the setting of AH. 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 and was associated with increased inpatient mortality [43].

Fungal infections

Fungal disease commonly occurs in immunocompromised individuals. Little is known about the incidence and impact of invasive fungal infection (IFI) in cirrhosis and even less in sAH. In the ICU, cirrhosis seems to be associated with higher fungal colonization and IFI [44]. The rate of fungal colonization reaches 25% in critically ill cirrhotic patients [42]. In one report, the presence of hepatic encephalopathy, concomitant bacterial infection, and a platelet count higher than 150,000/mm^3 are independent predictors of IFI in sAH [45].

Invasive aspergillosis (IA)

Liver insufficiency has been suggested as a contributing factor in IA. Indeed, some cases, often with a fatal issue, have been observed in patients with decompensated cirrhosis or acute liver failure [46,47]. In those reports, the occurrence of IA was frequently associated with the use of corticosteroids. We previously reported an IA incidence of 16% in a prospective cohort of 94 patients with biopsy-proven sAH [34]. Risk factors for acquisition of IA were ICU admission and baseline model for end-stage liver disease score ≥24, and the diagnosis is made after 6-80 days from corticosteroid initiation (median of 25 days). The sites of IA were the lungs, in the majority of cases, and the brain. The diagnosis of IA in sAH remains challenging. Indeed, radiological imaging of pulmonary IA revealed mainly non-specific lung infiltrates on chest CT and more rarely (in only 36% of the cases) multiple excavated nodules or "classical" condensations with a halo sign. Serum galactomannan (GM) may be a good screening test for IA in severe AH. In our experience, the classical cutoff ≥0.5 for serum GM had a high diagnostic performance, with sensitivity 89%, specificity 84%, positive predictive value 67%, and negative predictive value 95%. This accuracy seems to be questionable, because lower sensitivity and specificity were reported in another context [48]. Diagnosis of IA depends on the intensity of the screening protocol (frequent GM testing, chest and cerebral CT, bronchoalveolar lavage). To adequately screen for IA, we recommend that a serum GM and chest X-ray be performed twice a week during corticosteroid treatment. Despite this aggressive screening, sAH complicated by IA was associated with a dramatically poor outcome. Like others, we observed a 100% transplant-free mortality rate in our study despite adequate antifungal treatment.

Pneumocystis pneumonia

Sporadic reports have associated sAH and concomitant corticosteroid use with *Pneumocystis jirovecii* pneumonia (PCP), with a 100% case-fatality rate [49-51]. In our cohort, PCP was suspected in 8% of our patients who were positive by polymerase chain reaction testing of bronchoalveolar lavage samples but were negative by direct examination (Giemsa staining) [34]. The distinction between colonization and symptomatic infection was difficult to make, because of the patients' poor general condition and the non-specific CT scan lung lesions.

Invasive candidiasis

The rate of diagnosis of invasive candidiasis, mainly candidemia, in sAH varies between 2 and 8% [34,45]. In our cohort, we observed 2 cases of candidemia with *Candida glabrata*, both with fatal outcomes. One small report described one patient with sAH and candidemia who survived, among 3 patients with this complication [52].

Others

Some reports isolated cases of mucormycosis, cryptococcosis and fusariosis in sAH [45].

Viral infections

Hepatitis C virus (HCV)

HCV, unlike hepatitis B virus (HBV), is frequently associated with alcohol abuse [53]. The prevalence of anti-HCV antibodies in AH reached 25% in an analysis of pooled homogeneous data from 10 studies, while HCV RNA was present in 21% of cases in 4 of those studies [54]. In the United States, the prevalence of HCV in AH was 8%, based on the Nationwide Inpatient Sample dataset of 2007 [55]. It has been suggested that HCV might be an additional independent risk factor for mortality, possibly because of the synergistic hepatotoxic effect and more advanced liver disease [56]. The specific aspects of the treatment of AH in the setting of concomitant HCV infection are currently unknown, because this group of patients was excluded from most therapeutic clinical trials (on corticosteroids or pentoxifylline), because of concerns about an enhancing effect on viral replication. In other contexts, e.g. after liver transplantation, corticosteroids are known to increase the replication of HCV and to accelerate the progression of liver fibrosis. In patients with sAH there are insufficient data to form a conclusion. Currently, HCV replication is not considered as a contraindication for corticosteroids. Based on a large survey, 75% of physicians did not change their approach for the treatment of AH if HCV was present [57]. Given the severity of sAH, we must frequently wait for an improvement in liver function before starting direct-acting agents against HCV.

HBV

The natural course of HBV infection is determined through the interplay between viral replication and the host's immune reaction. Immunosuppressive treatments are able to induce HBV reactivation and a flare of their HBV-related liver disease, leading, in some cases, to acute liver failure and death. HbsAg-positive patients, who must receive prednisone 40 mg per day for 28 days, are considered at high risk of reactivation (11-20%) [58,59]. In this case, it is recommended to start an antiviral agent (ideally tenofovir or entecavir) before initiating corticosteroids. On the other hand, HbsAg-negative anti-Hbc-positive patients on corticosteroids are at low risk of reactivation (<1%). Here, it is recommended to monitor HBV DNA and to treat when a reactivation is observed.

Hepatitis E virus (HEV)

HEV is causing increasing concern as a cause of rapid decompensation and death in cirrhotic patients [60]. In one report

Table 2 Proposed diagnostic checklist in sAH

At baseline (sAH diagnosis)	During follow up (28-day corticosteroids course)
Blood, urinary and ascitic fluid cultures	Blood, urinary and ascitic fluid cultures (2/week)
Chest X-ray (if abnormalities, chest CT and BAL*)	Chest X-ray (if abnormalities, chest CT and BAL) (2/week) In case of pulmonary symptoms, chest CT
HCV, HBV (Hbs-Ag and anti-Hbc), (HEV) and CMV serologies	CMV PCR (1/week)
Serum galactomannan	Serum galactomannan (2/week)
	In case of neurological deterioration, brain CT (or better MRI) and potentially CSF puncture

*In BAL, the following exams should be performed: direct microscopic examination, Giemsa coloration or immunofluorescence for *Pneumocystis jirovecii*, bacterial and fungal cultures, galactomannan, PCR for *Pneumocystis jirovecii*, cytomegalovirus and herpes simplex virus. Mycobacterial cultures should also be considered according to epidemiological setting

sAH, severe alcoholic hepatitis; CT, computed tomodensitometry; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid

of 93 patients with sAH, 6% patients had serologic evidence of acute HEV and 12% of past HEV. In this report, acute infection showed no impact on outcome, response to corticosteroids, or the need for liver transplantation [61]. Another team reported 4% seroprevalence of acute HEV infection among 84 patients with sAH. The number of patients was too low to draw conclusions concerning the impact on disease course, but total bilirubin and creatinine levels were higher in those patients. Corticosteroids were not contraindicated in acute HEV, and no chronic HEV infection developed after immunosuppression [14].

Others

AH has been associated with sporadic cases of cytomegalovirus pneumonia. 7 cases have been reported, 5 of them concomitantly with PCP, with fatal outcomes [49-51]. Herpes simplex virus pneumonia has also been reported in 3 cases [62,63]. Data remain indicative, but considering the diagnostic challenges of cytomegalovirus pneumonia, its occurrence may be largely underestimated, highlighting the need for systematic assessment of infections in sAH.

Concluding remarks

Patients with sAH are prone to infections, especially of bacterial origin, which are present in 30-80% of cases. A high level of suspicion should be maintained with regard to all admitted patients with a diagnosis of sAH, as SIRS criteria and acute phase proteins are not accurate diagnostic markers for infection. Systematic screening is warranted, including at least blood, urine and ascitic fluid cultures, chest radiography, and other specimens according to clinical suspicion. The control of infection is mandatory before the start of corticosteroids and, in the case of resolution, infection does not impact the patients' outcomes. Under corticosteroids, patients with sAH who develop infections, mainly pneumonia, present a dramatic worsening of prognosis. It is unclear whether corticosteroids, or essentially liver dysfunction, are responsible for an increased risk of bacterial infections. However, opportunistic infections, including invasive aspergillosis, PCP, invasive candidiasis, and cytomegalovirus infection, become emergent problems in sAH related to immunosuppressive treatment. A prompt aggressive diagnostic strategy is needed to reveal these opportunistic infections, which are currently associated with a mortality rate of nearly 100%. Thus, we propose a diagnostic checklist at baseline and during the follow-up period to improve the detection rate of these infectious complications (Table 2) and potentially the outcome. Given the high risk of infections in sAH, preemptive antibiotic treatment is started in most cases. Reassessment and antibiotic de-escalation or cessation at 48-72 h should be part of routine practice, to avoid unnecessary exposure to broad-spectrum antibiotics and the risk of occurrence of infections due to multidrug-resistant pathogens, fungi or *Clostridium difficile*. Currently, the place of prophylaxis against bacteria, fungi or virus in sAH (particularly during immunosuppressive treatment) is unknown and should be assessed in well-designed trials.

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