Clinical Practice Guidelines

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EASL Clinical Practice Guidelines: Management of alcohol-related liver disease☆

European Association for the Study of the Liver*

Summary

The harmful use of alcohol has been estimated to cause approximately 3.3 million deaths every year, corresponding to nearly 6% of all deaths globally. Therefore, the effective management and treatment of alcoholic liver disease is a pertinent public health issue. In the following Clinical Practice Guidelines, the latest data on the treatment and management of alcohol-related liver disease will be reviewed and up to date recommendations for clinical management will be provided.

Guideline development process

A panel of clinicians with an interest in liver disease and alcoholic liver disease (ALD), approved by the European Association for the Study of the Liver (EASL) Governing Board, wrote and discussed this Clinical Practice Guidelines (CPG) document between November 2016 and March 2017. The guidelines were independently peer reviewed, and all contributors to the CPG disclosed their conflicts of interest by means of a disclosure form provided by the EASL Office prior to work commencing. The EASL Ethics Committee reviewed the composition of the panel to eliminate the potential for real or perceived bias. The CPG panel conflict of interests are declared in this submission.

Methods

These guidelines have been produced using evidence published before 1 October, 2017. Where possible, the level of evidence and recommendation are cited (Table 1). The evidence and recommendations in these guidelines have been graded using methods adapted from the grading of recommendations assessment development and evaluation (GRADE system). The strength of recommendations thus reflects the quality of underlying evidence. The GRADE system offers two grades of recommendation: strong or weak (Table 1). The CPG thus consider the quality of evidence: the higher, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted. Where no clear evidence exists, guidance is based on the consensus of expert opinion in the literature and the writing committee. Recommendations must also be interpreted in a context specific manner.

Terminology

The term alcoholic is stigmatising and undermines patient dignity and self-esteem. For this reason, these guidelines will use the following terms (Box 1):

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

*However, at this point the term alcoholic hepatitis has become too standardised to change but may be reviewed in future guidelines.

Public health aspects

Alcohol-related morbidity and mortality

According to the World Health Organization's (WHO) 2014 report on noncommunicable diseases, harmful use of alcohol causes approximately 3.3 million deaths every year, corresponding to 5.9% of all deaths. Furthermore, 139 million disability-adjusted life years, or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption. The proportion of global deaths attributable to alcohol differs based on gender, with 7.6% of deaths among males and 4.0% of deaths among females attributable to alcohol.[1]

Alcohol-related morbidity and mortality has a wide geographical variation, with the highest alcohol-attributable fractions reported in the WHO European Region.[1] Within each country there is an excellent correlation between the level of alcohol consumption and the prevalence of alcohol-related harm. In fact, although mean alcohol consumption in the World is 6.2 litres of pure alcohol per person per year, the consumption in Europe is 10.9 litres/year.[1] According to data from the OECD report 2017, alcohol consumption in the OECD countries, averaged nine litres of pure alcohol per person per year. This

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products of the non-oxidative metabolism of ethanol. Furthermore, in comparison to direct determination of ethanol in blood or exhaled air, they have a much longer detection window, which is often critical in order to uncover alcohol intake.[162] To date, determination of the ethanol conjugate EtG in urine (uEtG) is widely applied in many European countries for proving recent alcohol abstinence in forensic settings or for regular monitoring of patients in alcohol addiction programmes and prior to listing for liver transplantation. Depending on the level of alcohol intake, EtG remains in the urine for up to 80 hours. For screening purposes an inexpensive immunoassay is recommended with the possibility of confirmation of positive results via the more expensive liquid chromatography tandem spectrometry.[163] If a cut-off of 0.1 mg/L is used, consumption of very small amounts of alcohol (<5 g) can be detected, so that accidental alcohol intake via, for example, sweets, sauces, alcohol-containing mouth solution *etc.*, may cause a positive test result. Therefore, a higher cut-off is often used resulting in a slightly lower, but still very high sensitivity.[154] Notably, uEtG is not influenced by the presence of compensated or decompensated cirrhosis. So, in a cohort of 141 liver transplant candidates and recipients the sensitivity and specificity of uEtG of 89% and 99%, respectively, outperformed all other indirect alcohol markers, including GGT, AST, ALT, MCV and CDT, in predicting alcohol consumption.

In contrast to urinary EtG, determination of EtG in the scalp hair (hEtG) of patients is a powerful tool for monitoring not only short-term, but long-term abstinence from alcohol over a period of up to six months. Thereby each hair segment of 1 cm length reflects alcohol consumption over approximately one month. However, if samples less than 3 cm or greater than 6 cm are used, the results should be interpreted with caution (www.soht.org). In individuals with short hair, incorporation of EtG from sweat into hair after recent alcohol consumption is a concern.[164] In individuals with long-hair, treatments, such as dying, perming or bleaching, may play an increasing role in reducing EtG concentration in the hair. Also, slower hair growth in sick, cirrhotic patients should be considered when assessing results. Nevertheless, several studies show a high correlation between daily alcohol intake and hEtG concentrations in 3–6 cm long hair segments[165,166] and internationally accepted cut-off values for abstinence (<7 pg/mg), "social drinking" (hEtG 7–30 pg/mg) and chronic excessive alcohol consumption with more than 60 g ethanol intake per day (hEtG >30 pg/mg) have been defined (www.soht.org). Due to its high specificity and sensitivity (Table 5), interest in hEtG testing has grown over the past few years, especially for evaluating alcohol abuse in forensic settings,[167] for example child custody cases, or in confirmation of six-month alcohol abstinence in liver transplant recipients.[168]

To get a comprehensive picture of the true alcohol consumption of a patient, it is best to combine different available methods, *i.e.* questionnaires with uETG and hETG testing. In addition to these already well established direct alcohol markers with high reliability, determination of other direct markers, such as EtS in urine, FAEES in hair and PEth in serum or in dried blood spots may gain increasing recognition in the future, as additional methods for confirming suspected alcohol intake.[28,169–175]

Suggestions for future studies

- Investigations focussed on the mechanisms and prognostic significance of histological cholestasis
- Investigation of the clinical utility of monitoring tests for alcohol consumption
- Investigations to determine the optimal screening tool for liver fibrosis

Recommendations

- Liver biopsy is required where there is diagnostic uncertainty, where precise staging is required or in clinical trials (**Grade A1**)
- Screening of patients with AUD should include determination of LFTs and a measure of liver fibrosis. (**Grade A1**)
- Abstinence can be accurately monitored by measurement of EtG in urine or hair (**Grade A2**)

Management of alcoholic hepatitis

Definition and diagnosis

Alcoholic hepatitis is a distinct clinical syndrome characterised by the recent onset of jaundice with or without other signs of liver decompensation (*i.e.* ascites and/or encephalopathy) in patients with ongoing alcohol abuse.[176] It is not uncommon for patients to have ceased alcohol consumption days or weeks before the onset of symptoms. Underlying this clinical syndrome is steatohepatitis, a disease defined histologically by steatosis, hepatocyte ballooning, and an inflammatory infiltrate with polymorphonuclear neutrophils.[88] However, the clinical features of this syndrome can also result from sepsis, drug-induced liver injury, gallstone migration, *etc.*

The cardinal sign of AH is a progressive jaundice, that is often associated with fever (even in the absence of infection), malaise, weight loss and malnutrition. The laboratory profile of AH reveals neutrophilia, hyperbilirubinemia (>50 μMol/L), serum levels of AST greater than twice the upper limit of normal range, AST >50 IU/ml, although rarely above 300 IU/ml, with an AST/ALT ratio typically greater than 1.5–2.0. In severe forms, prolonged prothrombin time, hypoalbuminemia, and decreased platelet count are frequently observed.

Diagnosis of AH is based on clinical (*i.e.* recent onset of jaundice) and typical laboratory findings mentioned earlier in a patient with a history of heavy alcohol use. Liver biopsy (performed by transjugular route to reduce the risk of bleeding) can be useful to confirm the diagnosis, rule out other diagnoses found in 10–20% of cases,[72,99] and for prognostication.[84,110,111] The main restrictions on the use of liver biopsy in routine clinical practice are access to transjugular liver biopsy, risks and the costs of the procedure. Therefore, the decision to perform biopsy has to take into account the availability of the procedure and experience of the team. Biopsy must only be performed in cases where there is diagnostic uncertainty. In the absence of a liver biopsy more stringent clinical and laboratory criteria should be applied to avoid the misdiagnosis of alcoholic hepatitis, particularly amongst patients with cirrhosis.[83]

The incidence of AH remains largely unknown. A retrospective Danish study based on diagnosis codes revealed an increasing incidence, from 37 cases/million in 1999 to 46 cases/million in 2008 in men and 24 cases/million rising to 34 cases/million in women.[177] Although female sex is an independent risk factor for AH, it is more frequent in men. Excess weight is another risk factor for AH.[178] Although no clear threshold for the amount of

Table 6. Variables incorporated in the five prognostic scores most commonly used in alcoholic hepatitis.

Score	Bilirubin	PT/INR	Creatinine/urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
Maddrey	+	+	–	–	–	–	–
MELD	+	+	+	–	–	–	–
GAHS	+	+	+	+	+	–	–
ABIC	+	+	+	–	+	+	–
Lille	+	+	+	–	+	+	+

Maddrey, Maddrey discriminant function; MELD, model for end-stage liver disease; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, serum bilirubin, INR, and serum creatinine score.

alcohol consumption has been identified, AH generally occurs after decades of heavy alcohol use (>80 g/day).

Evaluation of severity

Different prognostic models have been developed which aim to identify patients at high risk of early death using baseline and dynamic variables (Table 6). The Maddrey discriminant function (DF) was the first score that reliably defined individuals at the highest risk of death in the short-term, and remains the most widely used in clinical practice and clinical trials. DF was originally developed in 1978,[179] and then modified (mDF) in 1989.[180] In its modified version, a cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy. In the absence of treatment, the one-month survival of patients with mDF ≥32 has improved from 50% in early publication to 85% in recent trials.[181,182] Patients with a non-severe AH (*i.e.* mDF <32) had a less than 10% risk of one-month mortality.[183] However, the long-term prognosis of those patients remains largely unknown.

More recently, several prognostic scores such as the model for end-stage liver disease (MELD), the Glasgow alcoholic hepatitis score (GAHS), and the ABIC (age, serum bilirubin, INR, and serum creatinine) score have been developed in the setting of AH. The MELD score is already a well-validated prognostic score in cirrhosis (www.mayoclinic.org/meld/mayomodel7.html). Its usefulness in assessing the short-term prognosis of AH has been studied in retrospective studies, which suggest that patients with an MELD score above 20 are at a high risk of 90-day mortality.[184] GAHS was derived from five variables independently associated with outcome (age, serum bilirubin, blood urea, prothrombin time, and peripheral blood white blood cell count) and identifies patients at greatest risk of death in the absence of treatment.[185] The GAHS ranges from 5 to 12 and patients with an mDF ≥32 and a GAHS ≥9 have a poor prognosis and an 84-day survival benefit when treated with corticosteroid.[186] The ABIC score classified patients with AH according to low, intermediate and high risk of death at 90 days.[187] These different scoring systems often incorporate the same variables and appear to have similar efficacy in predicting short-term survival.[188,189]

Early improvements in liver function have a major impact on short-term mortality. An early change in bilirubin levels, evaluated at day seven of therapy, was initially proposed to easily identify corticosteroid-treated patients at high risk of six-month mortality.[190] Similarly, an early change in the MELD score in the first week has been shown to predict in-hospital mortality.[191] Subsequently, the Lille model, which is based on pretreatment data plus the response of serum levels of bilirubin to a seven-day course of corticosteroid therapy was developed.[192] This score ranges from 0 to 1; a score ≥0.45 indicates non-response to corticosteroids. A subsequent analysis that re-evaluated the Lille score identified three patterns of response to corticosteroid therapy: complete responders (Lille score ≤0.16), partial responders (Lille score 0.16–0.56) and null responders (Lille score ≥0.56), and strongly suggested that corticosteroids should be discontinued in null responders at day seven of therapy.[193] Recently, the combination of MELD and the Lille model was suggested as an effective predictive algorithm of short-term mortality.[194]

Treatment of alcoholic hepatitis

General measures

Regardless of the severity, alcohol abstinence is the cornerstone of therapy and early management of AUD is recommended in all patients with AH (Fig. 1). In severe AH, a recent paper demonstrated that severity of liver injury determines short-term survival while alcohol abstinence is the main determinant of long-term prognosis.[195] Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended. Other general approaches include treatment of hepatic encephalopathy (lactulose, rifaximin) and treatment of ascites (salt restriction). Patients with severe AH are at risk of developing acute kidney injury (AKI) which negatively impacts survival.[196] Measures aimed at preventing the development of renal failure are therefore recommended. They include avoidance of diuretics and nephrotoxic drugs and volume expansion if needed. Considering prevention of variceal bleeding, it was suggested that the use of beta-blockers increases the risk of AKI.[197]

Nutrition

Malnutrition is commonly associated with cirrhosis and its severity.[198] Several studies have highlighted that protein energy malnutrition is present in almost every patient with severe AH, and is associated with poor prognosis.[199] The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend a daily energy intake of 35–40 kcal/kg of body weight (BW) and a daily protein intake of 1.2–1.5 g/kg of BW in patients with AH.[198] However, these objectives are often difficult to achieve in clinical practice. Therefore, the use of tube feeding is strongly recommended if patients are not able to maintain adequate oral intake. A randomised controlled trial comparing 28 days of total enteral nutrition to corticosteroid treatment in 71 patients with severe AH suggested that these approaches resulted in comparable one- and six-month survival rates.[200] More recently, a multicentre randomised controlled trial compared the combination of 14 days of intensive enteral nutrition using a feeding tube plus corticosteroids for 28 days to corticosteroid therapy alone, and showed that combination therapy did not improve survival.[201] Tolerance of the feeding tube was an important issue, since nearly half of the patients prematurely withdrew the feeding tube. Interestingly, a *post hoc* analysis of this study demonstrated that, regardless of the allocated therapy, patients with a daily calorie intake below 21.5 kcal/kg of BW had a significantly higher risk of one- and six-month mortality and infections. Thus, it appears reasonable to recommend a careful evaluation of nutritional status and energy intake, to target 35–40 kcal/kg of BW and a daily protein intake of 1.2–1.5 g/kg

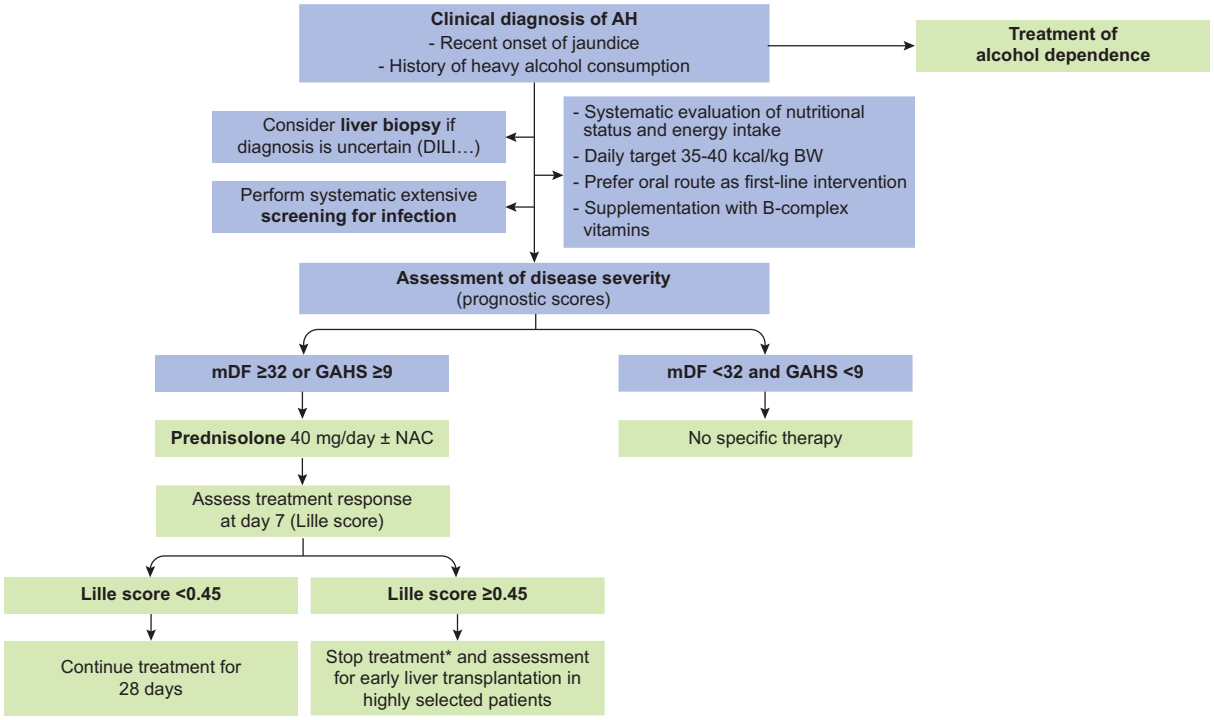

Fig. 1. Treatment algorithm in patients with suspected alcoholic hepatitis. *Particularly in null responders (Lille score ≥0.56). AH, alcoholic hepatitis; BW, bodyweight; DILI, drug-induced liver injury; GAHS, Glasgow alcoholic hepatitis score; mDF, maddrey discriminant function.

of BW and to adopt the oral route as first-line intervention in patients with severe AH.

While parenteral nutrition might circumvent the complications of naso-gastric feeding there is not currently sufficient evidence to support a recommendation, particularly given that parenteral feeding is associated with a high risk of line sepsis.

Corticosteroids

The use of corticosteroids to treat AH has been controversial, owing to the divergent findings of individual studies and meta-analyses.[202–204] A large multicentre randomised trial (STOPAH) was conducted in the United Kingdom between 2011 and 2014, in patients with a clinical diagnosis of severe AH, in order to resolve the controversy over the use of corticosteroids or pentoxifylline (PTX).[181] This study reported a borderline reduction in mortality at 28 days for patients treated with prednisolone 40 mg/day compared with control patients. Importantly, prednisolone therapy provided no benefit to patients after one month, which was subsequently confirmed in a network meta-analysis.[205]

The applicability of corticosteroid therapy is limited by concerns about heightened risks of sepsis and gastrointestinal bleeding. Therefore, early identification of non-responders to corticosteroids is important to define stopping rules and limit unnecessary exposure. The Lille score allows clinicians to predict poor response to corticosteroids at seven days of therapy[192] (see section "evaluation of severity"). In case of poor response, it is recommended that corticosteroids be interrupted, particularly in "null responders" (defined by Lille score ≥0.56).[193]

Practically, prednisolone at a dose of 40 mg per day or methylprednisolone at a dose of 32 mg per day is prescribed for 28 days. At the end of the course of treatment, the prednisolone or methylprednisolone can be stopped all at once, or the dose can be gradually tapered over a period of three weeks.

N-acetylcysteine

Antioxidant therapy is of theoretical interest in the treatment of AH because of increasing evidence that oxidative stress is a key mechanism in alcohol-mediated hepatotoxicity.[206] Ethanol consumption results in depletion of endogenous antioxidant capacities, and patients with AH show evidence of antioxidant deficiencies.[207] Because N-acetylcysteine (NAC) restores the glutathione store and consequently limits oxidative stress, it has been studied, either alone or in combination with other antioxidants, in several trials of severe AH. In those different trials, NAC did not increase survival compared to standard medical therapy.[182,208,209]

A multicentre French trial compared the effects of the combination of NAC and prednisolone to prednisolone and placebo.[210] In this study, NAC was administered intravenously for five days. Mortality at one month was significantly lower in the NAC plus prednisolone group compared to the prednisolone plus placebo arm. Importantly, NAC combined with prednisolone, also significantly reduced the incidence of hepatorenal syndrome and infections. Therefore, the combination of NAC and prednisolone appear to improve prognosis of patients with severe AH, and this combination should be tested in a future large clinical trial to confirm its efficacy.

Granulocyte colony stimulating factor

Granulocyte colony stimulating factor (GCSF) is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and stem cells (CD34+) into the bloodstream. Ineffective liver regeneration has been postulated as one of the key factor leading to progressive liver failure and non-recovery in patients with AH.[123] In animal models, the administration of GCSF was able to mobilise the hematopoietic stem cells, induce liver regeneration, and improve survival.[211] Spahr *et al.* demonstrated that GCSF administered subcutaneously for five days in patients with

AH, mobilised CD34+ stem cells, increased circulating hepatocyte growth factor and induced proliferation of hepatic progenitor cells.[212] A randomised placebo-controlled trial from India using GCSF for one month in patients with ACLF (>50% had AH) showed significantly improved short-term survival, and decreased risk of infection and kidney injury in the GCSF group.[213] Another randomised controlled trial from India assessed the effects of PTX *vs.* a combination of PTX and GCSF.[214] A significantly larger proportion of patients who received PTX plus GCSF survived for 90 days than those who received only PTX. Although the sample size was limited, these findings indicate that GCSF might improve the prognosis of patients with severe AH. Moreover, GCSF is easy to administer and is well tolerated. However, a European study of GCSF in decompensated cirrhosis (mostly caused by AH) reported negative results so further trials are required before it can be recommended as a treatment in severe AH.[215]

Pentoxifylline

Pentoxifylline, a phosphodiesterase inhibitor, has been evaluated in patients with AH for its ability to inhibit production of tumour necrosis factor (TNF). In the initial randomised study comparing PTX to placebo in patients with severe AH, patients treated with PTX had an improved six-month survival.[216] This survival benefit was not accompanied by significant changes in liver function, but it was related to a marked reduction in the incidence of hepatorenal syndrome. A large French multicentre trial, which evaluated PTX *vs.* placebo in 335 Child-Pugh C cirrhotic patients (mainly ALD origin, 133 with AH) reported no significant difference in short-term mortality between both arms, in the overall study and in subjects with AH.[217] The combination of corticosteroids with PTX was also evaluated in different trials. In the Corpentox study,[218] 28-day treatment with PTX (1,200 mg/day) plus prednisolone, compared with prednisolone plus placebo in patients with severe AH, did not result in improved short-term survival. Although not significant, incidence of hepatorenal syndrome was lower in patients receiving the combination of PTX and prednisolone. In the STOPAH trial[181] survival (at one month, three months, and one year) was not better in patients receiving PTX compared to those not receiving PTX. Finally, an early switch to PTX in non-responders to corticosteroids did not improve two-month survival compared to matched non-responders treated with corticosteroids only.[219]

In summary, evidence for a survival benefit of PTX therapy in patients with severe AH is very weak, and the drug can no longer be recommended.

Anti-TNF agents

Based on animal models suggesting a key role of TNF-α in the pathogenesis of ALD,[220] and increased liver and serum levels of TNF-α in human ALD,[221] both infliximab and etanercept were evaluated in AH in randomised controlled trials.[222,223] Those studies showed a higher risk of death and of severe infections in AH patients treated with anti-TNF agents. Therefore, those agents are not considered as a treatment option in AH.

Extracorporeal liver support

Extracorporeal liver support procedures can remove some potentially damaging circulating molecules, and are therefore, of potential interest in patients with severe AH. Some encouraging preliminary data with albumin dialysis were reported in patients with severe AH.[224,225] However, to date, no clear benefit has been demonstrated using these extracorporeal liver support devices.[226]

Infection in alcoholic hepatitis

Infection is a frequent and severe complication in patients with severe AH, and is one of the major causes of death. A recent meta-analysis found a 28-day cumulative incidence of infection of approximately 20%.[227] Other trials reported higher incidence of infection in up to 65% during a three-month follow-up.[201,228] Louvet *et al.* reported that patients with severe AH being infected suffer from a further increase in mortality of 30% at two months.[229] In the STOPAH trial, infections accounted for 24% of all deaths.[181] High incidence of infections may be partly explained by underlying cirrhosis, frequently present in biopsy-proven severe AH and cirrhosis-related defects in the immune system. Cirrhosis-induced immunodeficiency is a complex, multifactorial process, resulting from bacterial overgrowth, dysbiosis and increased translocation on one side, and impaired innate and adaptive immunity on the other.[230]

One of the major controversies of the past few years is whether corticosteroids, used for the treatment of severe AH, increase the risk of infection. A recent meta-analysis has shown that patients treated with corticosteroids had no increased risk of infection or higher mortality from infection than those treated with placebo.[227] Furthermore, it has been implied that development of infection depends more on the response to corticosteroid treatment rather than the treatment *per se*.[229] However, corticosteroids might enhance infection because they are known to induce infectious events in other fields, mainly by inducing a defect in lymphocyte signalling. In the STOPAH trial, serious infections were more frequent in patients treated with prednisolone. In addition, a higher proportion of patients receiving prednisolone developed an infection after treatment than patients not given prednisolone (10% *vs.* 6%). Importantly, development of infection was associated with increased 90-day mortality only in patients treated with prednisolone, independent of baseline disease severity.[189]

Bacterial infections represent the vast majority (approximately 90%) of infectious episodes in the setting of severe AH. Louvet *et al.* distinguished infections at admission from those during treatment and follow-up. At baseline, spontaneous bacterial peritonitis (SBP) or spontaneous bacteremia (SB) occurred more frequently (44%), followed by urinary tract infections (UTI) (32%), while a shift towards respiratory infections was noted (40% of all episodes) during or after corticosteroid treatment.[229] Therefore, a careful screening for infection is recommended before initiating therapy, repeatedly during corticosteroid treatment, and during the follow-up period.

Interestingly, the presence of an infection at baseline does not appear to contraindicate steroid therapy if the infectious episode is well treated and 'controlled'.[229] In a subsequent analysis of the STOPAH trial,[189] in patients with baseline infection who received prednisolone, there was a significant reduction in 90-day mortality associated with continued antibiotic therapy when compared with those patients in whom antibiotic therapy was stopped before initiating prednisolone (13% *vs.* 52%). Of interest, high circulating bacterial DNA predicted infection that developed within seven days of prednisolone therapy. This could help to better define corticosteroid-treated patients who will benefit from preventive antibiotic therapy in the future. Trials evaluating antibiotic prophylaxis in high-risk patients with severe AH, treated with corticosteroids, are ongoing (NCT02281929).

Invasive aspergillosis (IA) has been reported to complicate severe AH. In a prospective cohort of 94 patients with severe AH, undergoing systemic intensive screening for IA, IA incidence was 16% during a three-month follow-up.[228] In this experience, risk factors for the acquisition of IA were ICU admission and a baseline MELD score ≥24. The diagnosis of IA and the distinction with colonisation in these patients are challenging. Serum galactomannan may be a good screening test for IA (cut-off ≥0.5, sensitivity of 89% and specificity of 84%). Despite adequate antifungal treatment, IA was associated with a dramatically poor outcome.

Sporadic cases of pneumocystis pneumonia (PCP) were described in patients with severe AH and concomitant corticosteroid treatment, with a very high mortality rate. In a prospective cohort, PCP was suspected in 8% of patients.[228]

In view of the non-negligible incidence and the dramatic prognosis of IA and PCP despite adequate therapies in patients with severe AH treated with corticosteroids, aggressive screening strategies should be recommended, and prospective studies should be conducted to evaluate prophylactic strategies.

Suggestions for future studies

- Further studies are required to validate the use of the Lille score at day four.
- New strategies need to be developed to reduce the risk of infection

Recommendations

- A recent onset of jaundice in patients with excessive alcohol consumption should prompt clinicians to suspect AH (**Grade A1**)
- Available prognostic scores should be used to identify severe forms of AH, at risk of early mortality (**Grade A1**)
- In the absence of active infection, corticosteroids (prednisolone 40 mg/day or methylprednisolone 32 mg/day) should be considered in patients with severe AH to reduce short term mortality (**Grade A1**). However, corticosteroids do not influence medium to long term survival.
- N-acetylcysteine (for five days, intravenously) may be combined with corticosteroids in patients with severe AH (**Grade B2**)
- A careful evaluation of nutritional status should be performed and patients should aim to achieve a daily energy intake ≥35–40 kcal/kg BW and 1.2–1.5 g/kg protein, and to adopt the oral route as first-line intervention (**Grade A2**)
- Systematic screening for infection should be performed before initiating therapy, during corticosteroid treatment, and during the follow-up period (**Grade A1**)
- Early non-response (at day seven) to corticosteroids should be identified and strict rules for the cessation of therapy should be applied (**Grade A1**)
- In case of non-response to corticosteroids, highly selected patients should be considered for early liver transplantation (**Grade A1**)

Alcohol-related fibrosis and cirrhosis

Alcohol-related fibrosis

Excessive alcohol consumption may induce a wide spectrum of lesions that include pure alcoholic steatosis, steatohepatitis, progressive liver fibrosis, cirrhosis and HCC.[231] Above a daily consumption of 30 g/day, or a weekly consumption above seven units in women and 14 units in men,[232] the risk of developing ALD is increased.[233] At a daily intake of 100 g/day the relative risk reaches 26.[234] Pure hepatic steatosis, often asymptomatic and overlooked, is almost constant in individuals consuming alcohol in excess (>100 g/day) and may fully reverse following several weeks of abstinence. However, in approximately 10–35% of chronic excessive drinkers, progressive liver injury including AH and liver fibrosis develop and reach the stage of cirrhosis.[231] In excessive drinkers in whom liver biopsy was repeated after four years of follow-up, both steatosis and lesions of AH were independently associated with progression of fibrosis.[106] The presence of mixed macro- and microvesicular steatosis increases the risk of ALD progression.[93] A Danish nationwide registry cohort confirmed an increased risk of cirrhosis at five years in patients with steatohepatitis (16%, 95% CI 7.8–26.8%), with a non-negligible risk of progression in patients with pure steatosis (6.9%; 95% CI 3.4–12.2%).[235] This unexpectedly high rate of progression in a situation accepted as benign should reinforce the need for abstinence in the early phase of ALD. The stage of liver disease in patients with ALD is also a strong predictor of outcome. The liver-related mortality rate at five years is 13% in patients with early alcoholic liver fibrosis but 43% in those with advanced disease.[126]

The progression to advanced ALD (extensive liver fibrosis and cirrhosis) may be influenced by environmental and host factors. Exogenous factors include the amount, type and pattern of alcohol consumption, but also cigarette smoking and coffee drinking. In a population-based study with 20 years of follow-up, smoking ≥1 pack daily tripled the risk of ALD compared to non-smokers, irrespective of alcohol consumption.[236] Conversely, coffee drinking seems to have beneficial effects on the risk of cirrhosis. In a recent meta-analysis, drinking up to two cups of coffee per day decreased by nearly half the risk of alcoholic cirrhosis (relative risk 0.62; 95% CI 0.51–0.73), after adjusting for confounding factors including alcohol consumption.[237] Potential modifiers of natural history of ALD include genetic and non-genetic factors.[231,238] Thus, gender,[239] ethnicity,[240] comorbid conditions such as diabetes and obesity,[241,242] microbial dysbiosis,[243] chronic infection with HBV and HCV[244] and/or human immunodeficiency virus (HIV),[245] α-antitrypsin deficiency, iron overload, and genetic risk factors may influence disease progression.

In addition to the total amount of ingested alcohol, both the type and pattern of drinking seem to influence the development of ALD. A lower risk of alcoholic cirrhosis has been reported in red wine drinkers (relative risk of 0.3) compared to individuals consuming other types of alcoholic beverages.[246,78] Whether this difference relates to some particular composition of wine or if it relates to some confounding factors such as diet is still debated.[246–248] Data from the Dionysos study in northern Italy identified that drinking alcohol outside meals, and consuming more than one type of alcoholic beverage increased the risk of cirrhosis.[233] Drinking frequency influences the risk of cirrhosis. The risk of alcoholic cirrhosis was increased in regular, daily drinkers (HR 3.65; 95% CI 2.39–5.55) compared to those