ABSTRACT

Among heavy drinkers with liver disease, the development of severe alcoholic hepatitis (AH) is a serious complication. Prognosis is grave and associated with high mortality due to liver failure, hepatorenal syndrome or intractable sepsis. Clinically, AH presents as a syndrome of progressive inflammatory liver injury in patients with recent or ongoing heavy alcohol consumption. Although approximately 20% of alcoholics undergoing liver biopsy reveal histological features of AH, only a minority progress to severe AH with markedly elevated serum liver enzymes, jaundice and impaired liver function. To establish the diagnosis of AH, histology is recommended but not mandatory. Prognostic scores include the Maddrey's discriminant function, the model of end-stage liver disease, the Glasgow Alcoholic Hepatitis score, and the ABIC score. While the former scores identify patients at risk of death or the need for corticosteroids, the response to corticosteroid therapy can be assessed using the Lille model. Treatments include abstinence and enteral nutrition, while pharmacotherapy using corticosteroids either with or without N-acetylcysteine may be indicated for patients with severe AH. Pentoxifylline was found to reduce the risk of hepatorenal syndrome, but data on mortality are limited. Although considered a contraindication in most transplant centers, recent evidence indicates that carefully selected patients with AH could be good candidates for liver transplantation with a prognosis comparable to other indications.

Key words: acetaldehyde – corticosteroids – endotoxins – enteral nutrition – liver failure – liver transplantation – pentoxifylline – tumor necrosis factor

INTRODUCTION

Alcoholic liver disease (ALD) represents the largest proportion of chronic liver diseases in Western countries, and promotes the progression of non-alcoholic causes of chronic liver injury [1]. Hospital admissions for ALD increased significantly in several countries in recent years [2, 3], and remained high in others [4].

The term “ALD” comprises a continuum of rising liver damage encompassing steatosis with or without fibrosis in virtually all subjects with an alcohol consumption of >40g/day, alcoholic hepatitis (AH) characterized by histological necroinflammation of variable severity in approximately one third of patients, liver cirrhosis in 10-20% of patients, and hepatocellular carcinoma in 1-2% of cirrhotics per year.

A small but considerable fraction of heavy drinkers develop severe AH which can complicate any stage of chronic alcoholic liver injury. While the true incidence of AH is unclear, its prevalence is around 20% among subjects who undergo liver biopsy [5], and is suspected to be present in 10-35% of alcoholics hospitalized for liver disease [6]. In 2007, 56,809 patients were admitted as in-patients due to AH in the United States who had a hospital mortality of 6.8% for which older age, presence of sepsis, spontaneous bacterial peritonitis, pneumonia, urinary tract infection, acute renal failure, hepatic encephalopathy and coagulopathy were independent risk factors [7]. Presumably, this figure underestimates the true hospital mortality risk of patients with AH as the study could...
not distinguish between severe and less severe AH, and data on whether the diagnosis was confirmed by histology was not available. Other data, such as from a study in Denmark [8], indicate a higher 28-day mortality of 15%, which however, is still lower than the short-term mortality of >30% patients not receiving corticosteroids reported from earlier trials including only patients with severe AH [9]. An older study by Orrego et al. showed that alcoholic cirrhitics with superimposed AH have the poorest prognosis both short- and long-term, with a five-year mortality rate of 47% [10].

**CLINICAL PRESENTATION AND COMPLICATIONS OF AH**

According to most recent considerations (R. Bataller, personal communication) one has to differentiate between mild AH with only slight elevation of serum transaminases and without any effect on liver function and severe AH. While mild AH is frequently treated successfully by abstinence only, severe AH is clinically characterized by a recent onset of jaundice, and clinical and biochemical signs of impaired liver function. In severe cases, AH leads to liver decompensation with ascites, variceal bleeding, hepatorenal syndrome, hepatic encephalopathy and sepsis with resulting multiorgan failure. Although most patients with AH are active drinkers, it can evolve even after alcohol consumption has been significantly reduced or terminated. Patients are predominantly male although women drinking equal amounts of alcohol are at higher risk for AH [11].

On physical examination skin alterations associated with liver diseases such as spider angiomata, palmar erythema, chapped lips and gynecomastia may be visible, and the liver is usually tender and enlarged on palpation. Patients with impaired liver function often develop ascites and leg edema. Many patients with AH show clinical signs of malnutrition such as muscle atrophy, weakness, fatigue, diarrhea and often weight loss as a result of concomitant liver cirrhosis complicated by acute necroinflammation of liver tissue [12, 13]. Laboratory findings supporting this suspicion comprise low serum albumin levels, urinary ketone bodies reflecting nitrogen loss, as well as clinical and biochemical features of hypovitaminosis of B vitamins, retinoids, vitamin C, E and zinc [14]. Nonhepatic manifestations of alcohol toxicity including polyneuropathy, cardiomyopathy and a history of chronic pancreatitis may be present [15, 16]. Patients with severe AH frequently present with the clinical picture of a so-called systemic inflammatory syndrome (SIRS) characterized by fever, hypotension, leucocytosis, and elevated C-reactive protein related to the underlying acuteness of liver injury or concomitant infections [17]. Patients with AH are significantly more prone to bacterial infections and should therefore be routinely screened for pneumonia, urinary tract infection, spontaneous bacterial peritonitis and dental infections, particularly, when corticosteroids deem indicated [18].

Liver-related laboratory markers such as serum aminotransferase levels are usually raised 5 to 8-fold, less than in acute viral hepatitis, characteristically with aspartate aminotransferase (AST) outweighing alanine aminotransferase (ALT). This enzyme elevation pattern of AST/ALT >1 is termed De Ritis ratio, and distinguishes AH from acute viral or autoimmune hepatitis. The rise of AST over ALT relates to an alcohol-related deficiency of pyridoxal 5'-phosphate (vitamin B6) and alcohol-induced mitochondrial damage, but may also merely reflect the presence of cirrhosis [19]. Most patients with AH have some degree of coagulopathy with an increased international normalized ratio (INR) and prolonged prothrombin time indicating impaired liver function, and/or low platelet numbers due to splenomegaly from portal hypertension. An amber sign indicating poor prognosis is the presence of impaired kidney function, particularly when progressive, since this may indicate looming hepatorenal failure [20]. Two types of hepatorenal syndrome (HRS) are distinguished with type 1 HRS, being a rapidly progressive impairment of renal function often triggered by infections, and type 2 HRS a rather stable or slowly progressive renal insufficiency [21]. If left untreated, HRS type 1 has a median survival of about 2 weeks, whereas type 2 has a median survival of about 6 months [22]. Evidently, successful treatment of either condition would have a strong impact on the prognosis of patients with AH complicated by HRS.

**HISTOLOGY OF AH**

The three histological key features of AH are: 1. steatosis as a result of alcohol-mediated disturbances of lipid metabolism by inhibition of fatty acid oxidation and increased lipogenesis, 2. pronounced necro-inflammation characterized by neutrophilic infiltrates which often surround eosinophilic inclusion bodies termed Mallory-Denk bodies, and 3. scarring by more or less fibrotic tissue with a typical perivenular distribution as opposed to periportal fibrosis in chronic viral hepatitis. In addition, significant hepatocellular ballooning and a “chicken wire”-like pattern of fibrillar collagen deposition is regularly found [23]. For systematic reasons and morphologic similarities, many clinical pathologists apply a classification recently validated for non-alcoholic steatohepatitis [24]. A liver biopsy can be helpful to confirm the diagnosis of alcoholic steato-hepatitis (ASH) and is recommended in the newly released practice guidelines issued by the American Association for the Study of Liver Disease (AASLD); however, it is not mandatory [25]. The recently issued clinical practice guideline by the European Association for the Study of the Liver (EASL) proposes to perform a liver biopsy only in patients at a high risk of dying without pharmacotherapy (see below Assessment of Prognosis and Response to Pharmacotherapy) to confirm or reject the suspicion of AH [26]. Due to clotting abnormalities or ascites, liver biopsies often cannot be performed percutaneously in patients with AH, and should therefore be performed via the transjugular route, also in order to gather information on the severity of portal hypertension.

Diagnosis of AH is predominantly based on clinical findings rather than imaging results; however, the latter remain part of the routine work-up of patients with suspected AH, mainly to rule out other causes of recent onset hepatitis with jaundice. Regarding AH, neither ultrasound nor computed or magnetic resonance tomography unravel specific findings, but they can exclude obstructive jaundice or acute vascular
abnormalities. Recently, transient elastography obtained by the use of Fibroscan® has been widely used in the assessment of liver fibrosis in ALD [27], but results are significantly skewed by elevated liver enzymes and cholestasis [27, 28].

PATHOGENESIS AND POTENTIAL THERAPEUTIC TARGETS

While ALD develops insidiously over many years to decades of harmful alcohol consumption, AH may evolve comparatively swiftly under certain circumstances. The major difference between other stages of ALD and AH is the presence of necroinflammation in the latter, while ALD is generally devoid of significant inflammatory activity [29]. The reasons why only a minority of alcoholics develop alcoholic hepatitis are not completely understood but likely involve environmental and host, i.e. genetic factors that interact with mechanisms specific to alcohol and its metabolism. Regarding the latter, various factors are considered important in the development of AH.

Premier mediators of alcohol toxicity are metabolites derived from oxidative alcohol degradation via two separate enzyme systems, alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1), located in the cytosol and the endoplasmatic reticulum, respectively. While ADH function remains relatively stable regardless of the extent of alcohol consumption, CYP2E1 is inducible and undergoes upregulation with increasing amounts of alcohol. Both enzyme systems generate acetaldehyde and reactive oxygen species (ROS), both of which are highly reactive, toxic and carcinogenic. Abundant experimental and human data have convincingly demonstrated the premier role of CYP2E1 induction in the increased production of ROS and acetaldehyde in ALD [30, 31]. Particularly, compelling evidence exists that CYP2E1 induction and the consecutive production of ROS and lipid peroxides are major triggers of inflammation in the evolution of AH [32, 33]. Although ROS are central in alcohol-induced organ damage, their scavenging by antioxidants has been disappointing and studies have failed to demonstrate a clinical benefit of various antioxidants on ASH [34, 35].

A milestone finding in the quest for the cause of inflammation in AH was the revelation that alcohol disrupts the mucosal barriers of the small bowel allowing endotoxins (lipopolysaccharides, LPS) derived from gram negative bacteria to enter the portal blood stream and reach the liver where they bind to endotoxin receptors and activate Kupffer cells (KC) [36]. Following LPS-binding, KC express pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) that lead to liver cell necrosis, apoptosis, and inflammation [37]. Patients with AH show elevated plasma levels of TNFα that correlate with mortality [38, 39]. Presumably, elevated TNFα expression contributes to the cachexia observed in patients with AH similar to tumor patients resulting in weight loss and anorexia [40]. In turn, it has been demonstrated experimentally that blockade of Kupffer cells with gadolinium chloride or antibodies raised against TNFα improve ASH [33, 34]. It is very likely that other cytokines are likewise involved in the precipitation and perpetuation of AH as well as in its attenuation, but TNFα has been most widely studied also as a potential therapeutic target.

PROGNOSIS OF ASH

Severe AH has a grave prognosis and high mortality as indicated above, while milder courses often reside with abstinence alone. So, assessment of prognosis aims at separating those who will improve spontaneously from those who likely will not, or may even die without specific therapy. Since no specific test to confirm the diagnosis of AH is available, its presence should be considered in all patients who present with a rapid onset of jaundice in the context of harmful alcohol consumption in whom no other etiology of icteric hepatitis can be identified. Once a clinical diagnosis has been established, a liver biopsy is recommended for confirming the suspicion. However, since neither the degree of liver enzyme level elevation nor liver histology reflect the severity of AH, several composite scores were designed to distinguish patients with a poor prognosis from those in whom simple supportive care together with abstinence would suffice for spontaneous recovery (Table 1).

Table 1. Scores for assessing severity of AH

<table>
<thead>
<tr>
<th>Score</th>
<th>Calculator</th>
<th>Interpretation</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discriminant Function (DF)</td>
<td>DF = 4.6 (patient's PT – reference PT) + total bilirubin (mg/dL)</td>
<td>Prognosis poor when ≥ 32; threshold for corticosteroid therapy</td>
<td>Score longest and most frequently used</td>
</tr>
<tr>
<td>Model for End-Stage Liver Disease (MELD)</td>
<td>MELD = 3.8 x log (bilirubin (mg/dL) + 11.2 x log(INR) + 9.6 x log (creatinine (mg/dL) + 6.4</td>
<td>Prognosis poor when ≥ 18</td>
<td>Neglects kidney function</td>
</tr>
<tr>
<td>ABIC (Age, Bilirubin, INR, Creatinine)</td>
<td>(age x 0.1) + (serum bilirubin x 0.08) + (serum creatinine x 0.3) + (INR x 0.8)</td>
<td>Low risk ABIC ≤ 6.71; Intermediate risk when ABIC &gt; 6.71 and ≤ 9.0; High risk when ABIC &gt; 9.0</td>
<td>Designed for liver transplant allocation; performance equal to DF</td>
</tr>
<tr>
<td>Glasgow Alcoholic Hepatitis Score (GAHS)</td>
<td>Age &lt; 50; ≥ 50; Leucocytes &lt;15; ≥15; Urea (mmol/L) &lt;5; ≥5; INR &lt;1.5; ≥1.5-2.0; ≥2; Bilirubin (mg/dL) &lt;7.3; 7.4-14.6; ≥14.6</td>
<td>Poor prognosis if score &gt; 8 (calculated on day 1 and 7 of hospitalization)</td>
<td>Requires more variables than the other scores</td>
</tr>
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</table>

INR – international normalized ratio; PT – prothrombin time
The first score termed the Maddrey’s discriminant function (DF) was created in 1978 to identify patients in need of corticosteroids in the setting of interventional trials. Since then, DF has been used in most clinical studies which all applied a threshold of 32 for instigating therapy [9]. This figure is based on the initial trial by Maddrey and coworkers in which patients with a score of ≥ 32 revealed a startling mortality of up to 50% [41]. Discriminant function computes serum bilirubin levels and prothrombin time, but neglects age or kidney function (which may be important in patients with HRS). Also, DF can be difficult to calculate if INR instead of prothrombin time is routinely determined.

The Model for End-Stage Liver Disease (MELD) was originally developed to assist the allocation of liver grafts to patients on the transplant waiting list, but has also been used to direct the decision for corticosteroid therapy in patients with AH. Parameters used in calculating the MELD score include serum bilirubin levels, INR, and serum creatinine, and openly accessible calculators (http://www.unos.org/resources/meldpeldcalculator.asp?index=98) render its application simple and fast. Moreover, clinical studies comparing DF vs. MELD have shown an equally good predictive value of both scores indicating a poor prognosis in AH [42, 43].

The ABIC score integrates age, serum bilirubin, INR and serum creatinine which all independently predicted 90-day mortality by multivariate analysis in a clinical study from Spain [44]. The ABIC score allows the stratification of risk of death in patients with AH at 90 days and 1 yr into those with high, moderate and low risk, but provides no threshold for commencing corticosteroid therapy.

Another score, termed the Glasgow Alcoholic Hepatitis Score (GAHS), was established in patients with AH to identify criteria which predict 1- and 3-month survival [45]. The GAHS is derived from age, leucocyte count, urea nitrogen, serum bilirubin and INR, which were all found independently associated with poor prognosis in the index study. Independent validation in a second cohort of AH patients confirmed the usefulness to predict short- (28 days) and midterm (84 days) mortality, irrespective whether the diagnosis of AH was based on clinical grounds or on the results of a liver biopsy.

While the previous scores all aimed to assist the prediction of mortality, the Lille Model has been created to assess a patient’s response to corticosteroids, and to decide whether corticosteroids should be stopped in those not responding to 7 days of prednisolone 40mg/day [46]. The score combines age, renal insufficiency, albumin, prothrombin time, bilirubin, and evolution of bilirubin at day 7 which, taken together, are highly predictive of death at 6 months of follow-up. The Lille model has been validated and replicated repeatedly, and allows for stratifying patients into responders, partial responders and non-responders (Table II). Separating corticosteroid “responders” from “non-responders” is important to avoid ineffective corticosteroid therapy in patients who are often charged with concomitant infections [18], and to consider other therapeutic options (see below, Liver transplantation).

While all authors consider their individual scores as superior to the other scores, a recent post hoc comparison from Denmark of all scores mentioned above in 274 patients with AH revealed no statistically significant differences in the models’ performances to predict 28-, 84-, and 180-day mortality, albeit not as clearly as in the original cohorts in which these scores were established [47].

**TREATMENT OF SEVERE AH**

While there are no data as to whether specific treatment apart from alcohol abstinence is required to accelerate remission in less severe forms of AH, vigorous medical therapy of severe AH has been shown to improve survival in a substantial proportion of patients.

**General measures of treating severe liver disease**

Complete abstinence is the therapeutic backbone in patients with AH, but even in those who manage to stop drinking, AH may persist and progress towards liver failure. Clinical trials investigating the effect of abstinence on AH have not been performed so far, but due to the obvious damage continued alcohol consumption would have, abstinence is unequivocally recommended by international expert panels [25, 26]. However, providing a well-balanced review on what treatment to use to achieve abstinence is beyond the scope of this overview. Patients developing severe withdrawal symptoms or delirium tremens can be treated with both short-acting benzodiazepines or clomethiazole but the risk of worsening encephalopathy should be kept in mind. Apart from the specific treatments of AH outlined below, treatment of AH does not differ from that for decompensated liver disease due to non-alcoholic causes. Current guidelines issue evidence-based recommendations for the treatment of ascites and associated spontaneous bacterial peritonitis with paracentesis, and of HRS with the administration of vasoconstrictors such as terlipressin or norepinephrin in combination with albumin [48]. Portosystemic encephalopathy can be treated with lactulose and gut-cleansing antibiotics, and possibly rifaximin [49] although its safety and efficacy in patients with AH has not been investigated. Due to the high prevalence of infections in patients with AH, therapeutic and prophylactic antibiotics, ideally third generation cephalosporines, should be used.

Many patients with significant ALD reveal a certain degree of protein calorie malnutrition and deficiencies of numerous micronutrients [50], and malnutrition is present in nearly all patients with severe AH. Interestingly, nutritional status was part of the initial Child-Pugh-Turcotte score, but was omitted for practicability reasons, and malnutrition constitutes an independent risk factor for reduced survival [51]. Thus, counterbalancing nutritional deficiencies may theoretically improve the prognosis of patients with AH. Several trials have studied the efficacy of oral or total enteral nutritional

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**Table II. The Lille model**

| Lille score = 3.19–0.101 × (age [years]) + 0.147 × (albumin day 0 [g/L]) + 0.0165 × (bilirubin day 1 [μmol/L] – bilirubin day 7 [μmol/L]) – (0.206 × presence of kidney failure y/n) – 0.0065 × (bilirubin day 0 [μmol/L]) – 0.0096 × INR |
| Allows stratification of patients with AH according to response to corticosteroid therapy: complete responders (Lille score ≤ 0.16), partial responders (Lille score 0.16-0.56) and null responders (Lille ≥ 0.56) (from ref. 55) |

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(TEN) support in patients with AH. Particularly interesting is the study by Cabré et al because it emphasizes the potential of sufficient nutritional support [52]. Herein, investigators compared 4 weeks of TEN via a nasoduodenal tube providing 2,000 kcal/day vs. prednisolone at 40mg/day in combination with a diet containing 2,000 kcal/day in 71 patients with severe AH defined by DF >32. While mortality during treatment between groups was similar in both groups, it was significantly higher with steroids during follow-up, mostly due to infections. Based on the evidence derived from this and other studies, TEN by oral nutritional supplements in patients with AH is recommended by the European Society for Parenteral and Enteral Nutrition (ESPEN) since it improves nutritional status and survival in severely malnourished patients with alcoholic hepatitis [53].

**Corticosteroids**

The use of corticosteroids is the most widely studied intervention in patients with AH and a recent meta-analysis included 15 trials with a total of 721 randomized patients [54]. Overall results were inconsistent with only 3 studies reporting a significant improvement of mortality and the remaining 12 trials which did not. However, reanalysis of individual patient data from the five most recent placebo controlled studies with an adequate number of patients and appropriate quality demonstrated that 28-day survival was significantly higher in corticosteroid-treated patients than in non-corticosteroid-treated patients (80 vs 66%). These trials only included patients with severe AH as defined by DF ≥ 32 or encephalopathy, and the survival benefit derived from corticosteroids was predominantly observed in patients classified as responders or partial responders by the Lille model confirming the predictive role of this composite score [55].

Optimal dosage and type of corticosteroid have not been systematically assessed, but prednisolone at 40mg per day for 28 days and then stopped or tapered down over 2 weeks are suggested. The full course of corticosteroids, however, should only be administered in patients who show an adequate response to corticosteroids, whereas patients with a Lille score above 0.45 after 7 days of corticosteroids are unlikely to respond, and more likely to develop corticosteroid-associated adverse effects [26, 46]. The interruption of corticosteroids is particularly recommended in those identified as non-responders as per a Lille score of >0.56 [55].

**Antagonism of TNF-α**

As mentioned above, TNFα is considered a major trigger of alcohol-associated necroinflammation and thus, its neutralization with TNFα antibodies is an attractive therapeutic concept. The most potent anti-TNF substances in this regard are infliximab and etanercept which both have been tested in AH. Regarding infliximab, a monoclonal chimeric TNFα antibody, a placebo-controlled pilot trial testing 5mg/kg of infliximab as a single infusion in 20 patients with biopsy-proven ASH and a DF ≥ 32 with or without prednisolone demonstrated good tolerability and a significant reduction of cytokine levels and mean DF at day 28 of treatment, but no improvement of mortality and histology [56]. While two subsequent non randomized trials confirmed significant improvements of surrogate markers of liver dysfunction following a single dose of 5mg/kg infliximab [57, 58], two more recent trials – of which one was stopped because of side effects – demonstrated a high rate of severe infections and a high mortality in infliximab-treated subjects regardless whether they were treated with 5 or 10mg/kg, or with or without corticosteroids [59, 60].

Similarly disappointing results have been obtained with etanercept, a p75-soluble TNF receptor:FC fusion protein that scavenges and neutralizes soluble TNFα. A short-term, uncontrolled pilot trial in 13 patients with AH as defined by a DF ≥ 15 reported 1 month survival of 92% [61]. However, the subsequent randomized clinical trial carried out by the same investigators in 48 patients with AH reported a significantly higher mortality at 6 months in patients treated with etanercept than in those receiving placebo (57.7 vs. 22.7%, p=0.017), mostly due to renal failure and sepsis [62]. Due to a lack of evidence demonstrating a clear benefit on the outcome of AH, no anti-TNF drug is currently recommended by international guidelines [26] and should therefore not be used outside randomized trials.

Pentoxifylline is an orally absorbed nonselective phosphodiesterase inhibitor initially approved to treat intermittent claudication. It also acts as an anti-TNF agent and has been tested in several trials including patients with AH. Two recent meta-analyses of 5 trials in one [63], and of 10 trials in the other [64] concluded that pentoxifylline reduces the incidence of HRS, but not short-term mortality. This benefit is apparently not restricted to patients with AH, since a large randomized controlled trial of patients (n=335) with decompensated Child C cirrhosis due to variable etiologies randomized to either pentoxifylline or placebo demonstrated a significantly lower rate of complications (infections, kidney failure, hepatic encephalopathy, gastrointestinal bleeding) in those treated with pentoxifylline [65]. However, similar to AH, pentoxifylline does not decrease short-term mortality in patients with advanced cirrhosis.

**N-acetylcysteine**

N-acetylcysteine (NAC) is well-established in the treatment of fulminant hepatic failure due to paracetamol overdose [66], and increases transplant-free survival in early stage non-paracetamol acute liver failure [67]. Two recent trials have tested the efficacy of NAC also in patients with severe AH based on the concept that consumption of large amounts of alcohol causes oxidative stress and depletion of glutathione. Moreno and coworkers randomized 52 patients into either a group receiving adequate enteral nutrition plus intravenous NAC at 100 mg/kg body weight, or enteral nutrition with an intravenous placebo solution for 2 weeks [68]. Survival, surrogate parameters of liver dysfunction and rates of infection at months 1 and 6 were not different between groups, but the study was underpowered due to a small sample size.

The second study randomly assigned patients with severe AH as defined by a Maddrey's discriminant function ≥32, and a liver biopsy consistent with AH to receive either prednisolone at 40mg/day plus NAC at 50-150mg/kg body weight (n=85) or prednisolone alone (n=89) [69]. Both groups received an oral hospital diet with 1800-2000 kcal/day. Mortality at 6 months
was selected as the primary end point, but did not significantly decrease in the prednisolone/NAC group compared to the prednisolone-only group at months 3 and 6. However, mortality was significantly lower at 1 month (8% vs. 24%, P = 0.006), mainly due to a lower frequency of the HRS and of infections in the prednisolone/NAC group.

Liver transplantation
In many countries, patients with decompensated ALD are only listed for liver transplantation provided they can substantiate a 6-months period of abstinence. This, however, cannot be applied to patients with AH as the majority of these patients will have died prior to this goal. In most countries, AH is still regarded a contraindication for liver transplantation, for reasons which are only in part of medical nature [70, 71]. In fact, more important than medical considerations are moral persuasions that alcoholics are responsible for their dismal situation and as such less eligible for maximum therapies such as liver transplantation. Interestingly, such attitudes do not prevail with regard to individuals who require liver transplantation because of acute liver failure for paracetamol overdose with suicidal intent, or someone who developed decompensated liver cirrhosis due to chronic hepatitis C transmitted by intravenous drug abuse. One medical argument against liver transplantation in AH is certainly the high prevalence of serious infections among this particular group of patients, but this can be ruled out prior to listing, or treated until no longer relevant. Interestingly, retrospective histological analyses of liver explants for criteria of AH showed that AH patients and patients with ALD but without ASH have comparable outcomes [72]. Another reason for denying liver transplantation to patients with AH is that medical therapies such as corticosteroids and nutritional support are available and effective, although only in a subset of patients. The remaining fraction of non-responders to this kind of medical therapy, however, reveals a 6-month mortality of up to 75% and a number will preponderantly die without additional therapeutic options. In fact, a recent French multicenter study showed that liver transplantation could significantly improve the outcome of such non-responders to prior corticosteroid therapy. Mathurin et al selected 26 patients with severe AH with a median Lille score of 0.88 indicating a high risk of short-term death in those who were non-responsive to corticosteroid therapy [73]. The cumulative 6-month survival rate was higher among patients who received early transplantation than among those who did not (77 vs. 23%, p<0.001). This figure is comparable to those for other indications, and was sustained through 2 years of follow-up. Patients were carefully selected based on the following criteria: 1. first decompensation episode; 2. non-response to medical therapy; 3. supportive family background; 4. exclusion of psychiatric illnesses; 5. commitment to lifelong abstinence; 6. complete consensus among team members to select the patient for transplantation. It should be emphasized that only 3 patients returned to occasional or harmful drinking.

As data accumulate showing that patients with AH have similar graft and patient survival as patients with decompensated

![Fig. 1. Proposed algorithm for management of ASH. Crucial switches include the assessment of severity, the presence or absence of malnutrition, and the response to therapy. A liver biopsy is not mandatory, but potentially helpful. Allocating liver grafts to patients with ASH is still controversial. DF, discriminant function; GAHS, Glasgow alcoholic hepatitis score; LT, liver transplantation; MELD, model for end-stage liver disease.](image-url)
alcoholic cirrhosis, liver transplantation should be evaluated prospectively as a possible rescue procedure for patients who do not respond to medical therapy and will likely die [74]. Concerns over the possible impact such a “change of paradigm” may have on the public should not prevent the implementation of equity and fairness towards patients with AH.

CONCLUSIONS

Severe AH is a life-threatening condition requiring intensive hospital treatment. Abstinence is a prerequisite for improvement, but most patients are too sick to drink anyway, and the majority with severe AH will not recover with cessation of drinking alone. Among the treatments investigated, nutritional support providing adequate amounts of calories and protein, corticosteroids with or without NAC in those with a DF >32, a MELD score of >18, and a GAHS of >9, pentoxifylline for those with contraindications for corticosteroids (e.g. sepsis) or with hepatorenal syndrome, and finally liver transplantation in subjects non-responsive to all these measures demonstrate a reasonable body of evidence supporting their implementation. In Fig. 1, an algorithm is proposed how to manage patients with presumed AH.

Remaining problems are the poor overall prognosis of patients with AH even if medical therapy is effective, the restricted availability of liver grafts for transplantation and the limited eligibility of patients for that kind of maximum therapy.

Therefore, research should aim at identifying novel therapeutic targets and, above all, means to reduce harmful drinking to comply with the principle of preventing rather treating a preventable disease.

Conflicts of interest: None to declare.

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REFERENCES


43. Srikureja W, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. J Hepatol 2002:45:700-706.


