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### **Treatment of Severe Alcoholic Hepatitis**

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#### Abstract

Alcoholic hepatitis (AH) is a syndrome of jaundice and liver failure that occurs in a minority of heavy consumers of alcoholics. The diagnosis is usually based on a history of heavy alcohol use, findings from blood tests, and exclusion of other liver diseases by blood and imaging analyses. Liver biopsies, usually collected via the trans-jugular route, should be analyzed to confirm a diagnosis of AH in patients with an atypical history or presentation. The optimal treatment for patients with severe AH is prednisolone, possibly in combination with N-acetyl cysteine. At present, only short-term increases in survival can be expected—no treatment has been found to increase patient survival beyond 3 months. Abstinence is essential for long-term survival. New treatment options, including liver transplantation, are being tested in trials and results are eagerly awaited.

Keywords: NAC, alcoholism, cirrhosis, steroid

Alcoholic hepatitis (AH) is a distinct clinical presentation characterized by jaundice and liver failure in patients with prolonged and excessive alcohol consumption<sup>1</sup>. Typically patients have been drinking up to the time of admission or have only stopped drinking within 4–6 weeks of presentation. Recent onset of jaundice helps to distinguish patients with <u>AH</u> from patients with decompensated cirrhosis. A group of patients with severe AH can be defined using Maddrey's discriminant function (DF), which is based on the serum bilirubin and prothrombin time<sup>2</sup>. A DF score of <u>32 or more</u> has been associated with up to <u>30% mortality</u> over a 28 day period after admission.

AH is usually diagnosed based on a patients' histories and laboratory results, and exclusion of other causes of acute liver injury, based on findings from serologic tests and ultrasound analyses of the liver. Characteristic laboratory findings include bilirubin >5 mg/dL (>85 umol/L), level of aspartate aminotransferase (AST) greater than level of alanine aminotransferase (ALT) with AST usually less than 400 IU/mL, and increased white blood cell counts (>10,000/mm<sup>3</sup>, with increase in polymorphonuclear cells). An incorrect clinical diagnosis of AH may be made for up to 20% of patients therefore in cases where there is diagnostic uncertainty patients must undergo liver biopsy.

Rates of alcohol consumption are high in North America, Europe, and some parts of the western Pacific regions. In these areas, the alcohol-related mortality and disability adjusted life years are correspondingly high <sup>3</sup>. There are few data on the incidence of AH; one study from Denmark 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 <sup>4</sup>.

Short-term mortality from AH can be deduced from randomized trials. In studies conducted before 1980, short-term mortality was reported to be as high as 60% <sup>5</sup>. However, in recent trials, mortality among subjects in placebo or steroid treatment groups have invariably been <u>below 20% after 28 days or 1 month</u> <sup>6-8</sup>

#### Who to Treat—Stratification of Patients by Disease Severity

Encephalopathy, renal failure, coagulopathy (based on prothrombin time), and serum levels of bilirubin have served as independent prognostic factors for AH since the early 1970s<sup>5,9,10</sup>. However, Maddrey et al were the first to use discriminant analysis to produce a scoring system that reliably defined individuals at highest risk for death in the short term. In the original study describing the DF, a cut-off value of 93 was used to identify patients who died. Subsequently, the scoring system was changed (to measure the seconds prolonged in the prothrombin time, rather than the actual prothrombin time); a <u>cut-off value of 32</u>, which corresponded to the old cut-off value of 93, was used to identify patients with severe AH. Using the DF, large variations in mortality were observed between patients with DF values of 32 or more compared to those with lower values<sup>9</sup>. Most trials conducted since that time have used this threshold to identify patients who might benefit from treatment. Most trials conducted before 2000 enrolled relatively small numbers of patients, which would make it difficult to detect a statistically significant difference in mortality in patients with low mortality.

Subsequently, model for end-stage liver disease (MELD) scores (a score above 20 indicates that a patient should be treated) and several additional scoring systems specific for AH have assessed risk of death within 1 month in patients with AH <sup>11, 12</sup>. These scoring systems often incorporate the same variables (such as bilirubin, prothrombin time (or INR), creatinine, and age) and appear to have similar efficacy in predicting short-term survival. The Lille score, calculated after 1 week of treatment with prednisolone, includes baseline variables as well as response to treatment, assessed by change in bilirubin after 1 week of prednisolone<sup>13</sup>. In the initial analysis, prednisolone treatment did not increase survival among patients with Lille scores of 0.45 or more; a subsequent analysis suggested that prednisolone was ineffective in patients with Lille scores of 0.56 or more—either of these scores can be used to discontinue prednisolone. Short-term mortality might be better predicted by combining MELD and Lille scores <sup>12</sup>. The MELD score is a strong measure of disease severity at baseline, whereas the Lille score is a strong measure of response to therapy.

#### **Recommended Treatments**

#### Corticoteroids

From 1971 through 2014, 13 randomized trials and 4 meta-analyses investigated the effects of corticosteroids in patients with AH <sup>14-17</sup>. Although these studies produced many results, controversy persisted over the use of corticosteroid therapy in these patients. Advocates cite reductions in short- to medium-term mortality, whereas detractors raise concerns about risks of sepsis and gastrointestinal hemorrhage.

The largest placebo-controlled study of the effects of corticosteroids, in 90 patients with AH, found prednisolone to provide no benefit compared with placebo<sup>9</sup>. This study was hampered by its inclusion of patients with moderate and severe AH or end-stage alcoholic liver disease. In studies that required histological confirmation of AH, prednisolone was associated with a short-term decrease in mortality, but there was no reduction in mortality over 6 months <sup>18, 19</sup>. Systematic reviews of these clinical trials generated conflicting results. A Cochrane meta-analysis reported a trend toward, but not a not statistically significant, increase in survival. However a re-analysis of the 3 largest studies indicated that corticosteroids significantly increased survival of patients with AH <sup>16</sup>. In this study, 15% of patients with DF values of 32 or more given prednisolone died within 28 days, compared to 35% of patients given placebo.

In an attempt to resolve the controversy over the use of steroids or pentoxifylline, a double blind, factorial 2 x 2, multicenter trial was conducted in the United Kingdom between 2011 and 2014 in patients with a diagnosis of AH (the STOPAH trial)<sup>20</sup>. This study reported a borderline reduction in mortality at 28 days for patients given prednisolone 40 mg daily for 28 days compared with control patients <sup>8</sup>. However, survival curves converged after 28 days such that prednisolone therapy provided no benefit to patients after 90 days or 1 year. Data from this trial and previous studies were incorporated into a network meta-analysis, which confirmed that corticosteroids do not benefit patients beyond the first month of treatment <sup>17</sup>.

Two factors potentially limit the efficacy of corticosteroid use: increased susceptibility to infection and recidivism. In the STOPAH trial, incident infections classified as serious adverse events were more common among subjects given prednisolone than controls <sup>8</sup>. Infections of the respiratory tract were particularly more common. However, in the meta-analysis of Singh et al, infection was not any more common among patients treated with vs without corticosteroids <sup>17</sup>. This apparent discrepancy could have been caused by different methods of trial reporting. On the other hand, a study comparing corticosteroids with intensive enteral nutrition found that the short-term gains in survival in the steroid group were lost after the first month due to an increased incidence of infections, which resulted in patient deaths <sup>21</sup>.

#### **Nutrition**

Deficiencies in protein, vitamins, and minerals have been described in patients with alcohol use disorders but these are not specifically associated with liver disease. High body weight and arm muscle area are associated with AH and cirrhosis, indicating a role for obesity alongside alcohol consumption in the etiology of these conditions. <sup>22</sup> Nevertheless, protein calorie malnutrition, assessed using 8 nutritional parameters, is associated with significantly higher 30 day, 6 month, and 12 month mortalities <sup>23</sup>

A number of trials have attempted to assess the therapeutic value of nutritional supplementation using either enteral or parenteral routes. In a small randomized study where both groups were offered 3000 kCal/100g protein orally, the effect of supplementing the diet with 70–85g intravenous amino acid supplement was evaluated in the treatment arm. Patients receiving the supplemented diet had lower mortality and lower rates of ascites and encephalopathy, and greater improvements in serum levels of albumin and bilirubin, than controls. <sup>24</sup> However, in a smaller study of 15 patients with AH, 5 were given amino acids and glucose and 10 given glucose alone. Patients given the amino acids had improved nitrogen balance and reduced hepatic steatosis, compared with controls, but did not have better clinical outcomes than controls <sup>25</sup>. Similarly, when a standard oral diet of 2500 kCal and 100 g protein was supplemented with peripheral parenteral nutrition, with an additional 1000 kCal and amino acids, the additional

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nutrition did not improve results of liver function tests or reduce complications or mortality <sup>26</sup>.

Oral supplementation of calories and protein decreases the risk of line sepsis associated with intravenous treatment, but many patients with severe AH have profound anorexia. Tolerance of nasogastric feeding is poor, particularly among patients with hepatic encephalopathy. In a trial of 64 patients with AH, those randomly assigned to the group given supplemental calories (2000 kCal/day) and protein-either in the standard form or as branched chain amino acids—did not survive any longer than controls <sup>27</sup>. In the Veterans Affairs Cooperative study, enteral supplementation with 1600 kCal and 60 g of protein/day, administered with the anabolic steroid oxandrolone, led to a significant reduction in mortality at 1 month and 6 months in patients with moderate protein calorie malnutrition. However, mortality was not reduced for patients with severe malnutrition <sup>28</sup>. A study of patients randomly assigned to receive either prednisolone or oral (or nasogastric) supplements of 2000 kCal/day found no difference between these groups in overall mortality. However, mortality was higher in the feeding group in the early phase of the study, whereas the group given steroids had increased mortality due to infections <sup>21</sup>. In a follow-up study, mortality was low among patients given a combination of steroids and enteral nutrition, but no findings form randomized controlled studies of this approach have been published <sup>29</sup>.

A meta-analysis of 9 trials of enteral feeding and 4 trials of parenteral nutrition found that these approaches produce a modest (20%) reduction in mortality <sup>30</sup>. This strategy also reduced risk of encephalopathy and infection, but for each outcome, significant results depended on the type of statistical analysis performed. Although clearly there is room for further, well-conducted randomized trials of nutrition, it is reasonable to conclude that patients with severe AH should be given enteral supplementation of 1600–2000 kCal/day with 60-100g protein, preferably with administration of an evening snack of ~500 kCal.

# Therapeutic Approaches With Unclear Benefits <u>Pentoxifylline</u>

Pentoxifylline, a phosphodiesterase inhibitor, is believed to inhibit production of tumor necrosis factor (TNF). The efficacy of pentoxifylline monotherapy in patients with AH has been compared with that of placebo and prednisolone (see Table 1). The efficacy of the combination of prednisolone and pentoxifylline has been compared with that of prednisolone or pentoxifylline monotherapy. These studies have produced conflicting results.

Five randomized controlled trials have compared the efficacy of pentoxifylline (1200 mg/day) with that of placebo in patients with AH (see Table 1). A study conducted at a respected liver center reported that 24.5% of patients (12/49) died within 6 months, compared with 46.1% of patients (24/52) given placebo—a significant reduction <sup>31</sup>. Patients given pentoxifylline also had marked reductions in hepatorenal syndrome. Two smaller studies, from India, reported non-significant increases in survival among patients given pentoxifylline compared with those given placebo—also with reduced incidence of hepatorenal syndrome among subjects receiving pentoxifylline <sup>32</sup>. A multicenter study of placebo vs pentoxifylline in 335 patients with a Child-Turcotte-Pugh score of C (255 alcoholic, 133 with AH) reported no significant difference in short-term mortality between patients given pentoxifylline vs placebo, in the overall study and in subjects with AH <sup>33</sup>.

In the **STOPAH** trial, fewer patients given pentoxifylline, compared to patients who received prednisolone or no or other treatment, survived for 1 month; there were no differences in survival at 3 and 12 months. Acute kidney injury occurred in 1.65% of patients (9/546) receiving pentoxifylline vs 2.56% of patients (14/546) who did not receive pentoxifylline. In 3 studies, pentoxifylline did not increase patient survival, compared with prednisolone <sup>8, 34, 35</sup>.

The combination of prednisolone and pentoxifylline was evaluated in four studies. It was proposed that since these drugs have different mechanisms, two might be more effective than one. However, results from these trials did not support this hypothesis. Fewer subjects receiving pentoxifylline with prednisolone died in 1 month (10.5% in the Corpox

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study and 13.5% in the STOPAH study) than subjects receiving prednisolone alone (12.4% in the Corpox study and 16.7% in the STOPAH study), although these differences were not statistically or clinically significant. The combination did not increase survival of patients at 3–6 months in either study <sup>6, 8</sup>. Two small studies reported that patients receiving the two-drug combination had similar survival times as patients given prednisolone or pentoxifylline alone <sup>36, 37</sup>.

In summary, pentoxifylline appears to increase survival compared with no treatment, but does not increase survival compared with prednisolone. Pentoxifylline, in combination with prednisolone, could slightly increase survival, compared with prednisolone alone, although the potential benefit is small (2%–3% at 1 month, but no increase at 6 months). Pentoxifylline reduced the incidence of hepatorenal syndrome in clinical trials in which it increased survival, although the benefit of pentoxifylline on renal function was unclear in larger studies of drug combinations. The overall effects of pentoxifylline on hepatorenal syndrome are therefore unclear.

Table 1. One-month Mortality in '	Trials Comparing Pentoxifylline Alone or in
Combination with Prednisolone	

Study	Survival	Survival with	Survival with	References
Location	with	Prednisolone	Prednisolone and	
	Placebo	0	Pentoxifylline	
US	24.5%	46.1% (24/52)		Akriviadis <sup>31</sup>
	(12/49)			
	28.6%	43.8% (7/16)		Paladugu
	(4/14)			
India	25.0%	40.0% (10/25)		Sidhu <sup>32</sup>
X	(5/25)			
UK	16.7%	19.4%	13.5% (35/260)	Thursz <sup>8</sup>
	(45/269)	(50/258)		
US	5.9%			Akriviadis <sup>31</sup>
	(2/34)			

	24.2%		Paladugu
	(15/62)		
India			Sidhu <sup>36</sup>
		27.8% (11/36)	
US		10.5% (14/133)	Akriviadis <sup>31</sup>
	10%	3.3% (1/30)	Paladugu
	(3/30)		

#### **Therapeutic Approaches That Require Confirmation**

#### N-acetylcysteine (NAC) and antioxidants

Oxidative stress increases in livers of patients with AH, and levels of antioxidants such as glutathione or NAC are decreased in patients with hepatic failure. Several studies have therefore tested the safety and efficacy of NAC, either alone or in combination with other antioxidants, in patients with AH (see Table 2).

Moreno et al compared the effect of enteral nutritional support alone with that of nutritional support with intravenous NAC for 14 days in patients with biopsy-proven AH <sup>38</sup>. All patients also received oral supplements of vitamins B1 and B6, folic acid phosphorus, zinc, and magnesium. Mortality was lower, but not significantly, among subjects receiving placebo than among those receiving NAC at 1 month (12.5% vs 32.1%) and at 6 months (39.3% vs 29.2%). Stewart et al studied the effects of NAC with oral antioxidants (vitamins A–E, biotin, selenium, zinc, manganese, copper magnesium, folic acid, and coenzyme Q) or placebo in patients receiving standard of care at that time (prednisolone for patients without infection or recent upper gastrointestinal bleeding) <sup>39</sup>. Mortality at 1 and 6 months was similar in the placebo and NAC groups. Phillips et al compared the effects of NAC and antioxidants (oral vitamins A, C, and E; selenium methionine; allopurinol; and parenteral desferrioxamine) with those of prednisolone <sup>40</sup>. Mortality at 1 month was 46% in the antioxidant group and 30% in the prednisolone group. After adjusting for baseline variables associated with survival (white blood cell count, level of bilirubin, and encephalopathy), risk of death at 1 month was 3-fold higher

(significant) among patients receiving NAC and antioxidants than in patients given prednisolone.

Nguyen-Khac et al compared the effects of the combination of NAC and prednisolone vs prednisolone and placebo<sup>7</sup>. NAC was administered intravenously for 5 days. Mortality at 1 month was 24% (21/89) in the prednisolone group and 8% in the NAC and prednisolone group—a significant difference. Mortality at 6 months was lower among subjects receiving NAC and prednisolone (27%, 23/85 patients died) than among patients receiving prednisolone alone (38%, 34/89 patients died), although this difference was not statistically significant. Importantly, NAC and prednisolone, compared with prednisolone alone, significantly reduced the 6 month incidence of hepatorenal syndrome and infections.

NAC (usually given in combination with other oral antioxidants) does not appear to increase survival compared with standard medical therapy. However, the combination of NAC and prednisolone increased 1 month survival, and reduced infections and hepatorenal syndrome, compared with prednisolone alone<sup>7</sup>. The combination of NAC and prednisolone should be tested in another clinical trial to confirm its efficacy.

Recently, metadoxine, an oral antioxidant with effects on the mitochondria, was tested in combination with prednisolone or pentoxifylline vs either pentoxifylline or prednisolone alone in 135 patients (4 groups, with 30–35 patients/group) with severe AH <sup>41</sup>. Patients were given metadoxine (500 mg, 3 times/day) for 30 days. Survival at 6 months was significantly higher among patients receiving metadoxine in combination with prednisolone or pentoxifylline (approximately 50% survival in each group) than patients receiving prednisolone or pentoxifylline alone (approximately 20% survival in each group). Metadoxine reduced the incidence of hepatorenal syndrome but not infections. These findings should be repeated before metadoxine can be considered for treatment of patients with severe AH. Metadoxine is not available in the United States (US) or Western Europe.

Placebo	NAC	NAC, With	Prednisolone	Prednisolone	Reference
and	and	or Without		and NAC	
Standard	Standard	Antioxidants			
of Care	of Care				R '
12.5%	32.1%	NA	NA	NA	Moreno* <sup>38</sup>
(3/24)	(9/28)				
38%	35%	NA	NA	NA	Stewart** 39
(n=34)	(n=36)				
NA	NA	45.8%	30.2%	NA	Philipps <sup>40</sup>
		(22/48)	(16/53)	$\sim$	
NA	NA	NA	22.5%	8.2% (7/85)	Nguyen-Khac <sup>7</sup>
			(20/89)		

Table 2. One-month Mortality of Patients with AH Given NAC and/or AntioxidantsAlone or in Combination with Standard of Care

\*Standard of care comprised enteral nutritional supplementation with oral supplementation with B vitamins, folic acid phosphorus, zinc, and magnesium.. The NAC group received intravenous NAC for 14 days, whereas the placebo group received 5% dextrose for 14 days.

\*\* Standard of care included prednisolone, if the patient was not infected or had recent upper gastrointestinal bleeding. Approximately 56% of patients received prednisolone. Patients received intravenous NAC for 1 week and oral antioxidants (such as vitamins A– E, selenium, zinc, folic acid, or Coenzyme Q, etc) daily for 6 months. Mortality values were determined after 60 days, based on Kaplan-Meier survival analyses. NA – Not applicable

## Granulocyte colony stimulating factor (GCSF)

GCSF is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and stem cells (CD34+) into the bloodstream. In patients with alcoholic liver disease, GCSF could increase liver regeneration (by stimulating engraftment of CD34+ stem cells in the liver and/or by stimulating regeneration of hepatocytes and progenitor or

intermediate hepatocytes) and by increasing phagocytic function of neutrophils (decreasing infection).

GCSF, given daily for 5 days and then every 3 days through day 30, significantly increased the proportion of patients with acute-on-chronic liver failure (more than half with AH) who survived 60 days, compared with standard treatment <sup>42</sup>. The combination of GCSF and erythropoietin significantly increased the proportion of patients with decompensated cirrhosis (more than half with alcoholic liver disease) who survived 12 months.

Three studies have compared the effects of standard medical therapy with those of standard medical therapy plus GCSF in patients with AH. Eleven patients with biopsyconfirmed AH were given standard medical therapy (prednisolone if DF was above 32) and 13 patients were given a combination of standard medical therapy and GCSF (10 ug/kg/day for 5 days). Analyses of liver biopsies after 7 days demonstrated a marked increase in the number of proliferating hepatic progenitor cells and intermediate hepatocyte-like cells in liver tissues of subjects receiving standard medical therapy and GCSF, whereas the number of proliferating cells had decreased in livers of subjects receiving only standard medical therapy <sup>43</sup>. In another study, 58 patients with biopsy-proven decompensated alcoholic cirrhosis (47 with AH) were randomly assigned to groups given only standard medical therapy (n=30; including prednisolone for DF above 32) or standard medical therapy, GCSF, and autologous transfer of bone marrow mononuclear cells into the hepatic artery (n=28)<sup>44</sup>. After 3 months, 4 patients receiving standard medical therapy died, compared with 2 patients receiving combination treatment. MELD scores were reduced in both groups.

These studies laid the groundwork for a randomized controlled trial to evaluate the effects of pentoxifylline vs a combination of pentoxifylline and GCSF (10 ug/kg/day for 5 days <sup>42</sup>). A significantly larger proportion of subjects who received pentoxifylline with GCSF survived for 90 days (18/23) than those who received only pentoxifylline (5/23). This was because fewer patients receiving the combination therapy died from infection

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and liver failure. These findings indicate that GCSF might increase survival of patients with AH. GCSF is easy to administer and has few adverse effects. However, additional studies should be performed in the West, and GCSF should be tested in combination with prednisolone, before it can be recommended as a treatment for AH.

#### **Meta-analyses of Efficacy**

Results from meta-analyses of studies of patients with AH vary, depending on which studies are included (high quality vs all trials) and who assessed the quality of the study and performed the meta-analysis <sup>45, 46</sup>. Furthermore, until recently, meta-analyses compared 2 treatment options (such as prednisolone vs placebo or pentoxifylline vs placebo). However, a recent network meta-analysis compared outcomes among multiple treatments <sup>17</sup>, based on 22 high-quality studies comprising more than 2500 patients with AH. Based on a direct meta-analysis, compared with placebo, prednisolone, but not pentoxifylline or NAC, decreased short-term mortality. In head to head trials, patients receiving prednisolone did not have greater chances of survival than those receiving a combination of corticosteroids and NAC, but not corticosteroids and pentoxifylline, compared with prednisolone alone. Compared with placebo, no treatment reduced acute kidney injury or was associated with an increased risk of infections.

Results from the network meta-analysis of short-term mortality largely supported those of the direct meta-analysis. Compared with placebo, pentoxifylline, prednisolone, NAC with prednisolone, and pentoxifylline with prednisolone reduced short-term mortality. Pentoxifylline, as well as prednisolone with NAC and prednisolone with pentoxifylline, reduced the risk of acute kidney injury. Prednisolone alone or in combination with pentoxifylline increased risk of infection, compared with pentoxifylline alone. Overall, based on findings from the network meta-analysis, the <u>combination of corticosteroids and</u> <u>NAC</u> was ranked as the <u>optimal (best) treatment for reducing 1 month mortality</u>, followed by the combination of prednisolone and pentoxifylline or prednisolone alone (almost tied for second and third), followed by monotherapy with pentoxifylline, placebo, and NAC (worst).

Although this was a well-performed meta-analysis that allowed for comparison of multiple regimens, there are several points of caution. The STOPAH study supplied approximately 40% of the patients included in the meta-analysis. Also, there were considerable differences in 1 month survival among trials, so it is not clear if all the patients should have been included in a meta-analysis (one of the assumptions is that all patients are drawn from the same population of patients with AH). Finally, only one study has compared the effects of prednisolone and NAC (the optimal treatment) with that of prednisolone<sup>7</sup>. Other studies of the combination of NAC and antioxidants did not find improved outcomes compared with the standard treatment.

The application of these findings therefore requires consideration of each case individually, based on clinical, patient, and physician factors. Finally, no regimen increased the proportion of patients surviving until 6 months.

#### **Liver Transplantation**

Liver transplantation is the ultimate treatment for patients with liver failure. Liver transplantation is accepted for patients with alcoholic cirrhosis, and excessive alcohol consumption is a factor in approximately 20% of transplants performed in the US and 30%–50% of transplants performed in Europe <sup>47-49</sup>. Most countries require 6 months of abstinence before liver transplantation for patients with a history of excessive alcohol use. The problem with requiring prolonged abstinence in patients with severe AH who did not respond to other treatments is that more than 50% die during the first 3 months <sup>13</sup>. Problems with liver transplantation for patients with AH therefore include selection of patients with poor prognoses (i.e., likely to die without a liver transplant) those who are unlikely to return to drinking. Additional problems include selection, listing, and transplantation in a short period of time (few weeks); concerns over the extra burden of evaluating patients with AH for transplantation, the excess demand for livers; and public perceptions of use of organs for patients with alcohol problems.

Several retrospective studies have suggested that patients with histologic features of AH survive for similar amounts of time after liver transplantation as patients with bland alcoholic cirrhosis. Mathurin et al conducted a prospective study of liver transplantation in 26 patients with AH who did not respond to 1 week of prednisolone therapy (Lille score>0.45; median Lille score, 0.88)  $^{50}$ . Of patients receiving liver transplants, 77% ±8% survived for 6 months—similar to a matched group of patients with AH who responded to prednisolone (Lille score <0.45, 85%±4% survived for 6 months) and significantly better than that of a matched group of patients with AH and Lille score >0.45 who did not receive liver transplants (30%±6% survived 6 months). After 2 years, 71%±9% of transplant recipients were still alive. Three recipients returned to drinking (2 at ~2 years and 1 at ~3 years), with 2 consuming alcohol daily (~30 g/day and >50 g/day). Fewer than 2% of patients with AH received a liver transplant, and 3% of livers were used for transplantation into patients with AH. A larger study of liver transplantation for patients with AH is in underway in France. Guidelines from the Liver Disease Societies in Italy and the United Kingdom permit liver transplantation for select patients with AH without a defined period of abstinence. However, relatively few patients with AH have received livers in these countries. Other countries, including the US, routinely require 6 months of abstinence, which is an unacceptably high barrier for patients with AH to overcome.

#### Abstinence

AH is actually two diseases: a liver disease in patients with alcohol use disorder. Gastroenterologists focus on the liver disease, which is the most frequent cause of death during the first 6 months following the onset of AH. However, alcohol use disorder is the most common cause of death after 6 months. The obvious conclusion that return to alcohol use following an episode of AH would be harmful was demonstrated decades ago and has been confirmed in recent studies <sup>51</sup>. In the STOPAH trial, drinking alcohol at 90 days after enrollment was the only factor associated with survival at 1 year. Importantly, any alcohol use at all at day 90, including less than 2 drinks/day, was associated with a 2to 3-fold increase in mortality. It is therefore critical that physicians inform patients of the need to abstain from all alcohol. Physicians must also explain that slips (temporary return to drinking, often at low levels) or relapse (more sustained resumption of drinking) will

not lead to immediate liver failure, but that persistent drinking, even if years later, will invariably lead to recurrent liver disease and increase patients' risk of death.

Physicians should refer patients to an addiction specialist for longer-term management. Physicians may consider starting treatment with drugs that decrease alcohol craving. In a randomized controlled trial, baclofen (10 mg, 3 times/day) for 12 weeks significantly reduced alcohol use among alcoholic patients with cirrhosis <sup>52</sup>. Confirmatory and longer-term studies are needed.

Other drugs that have been reported to decrease craving include gabapentin, acamprosate, and naltrexone (nalmefene, an opioid antagonist, has been approved in Europe). Acamprosate and naltrexone are not recommended for patients with decompensated cirrhosis. Naloxone has a black box warning by the US Food and Drug Administration for hepatotoxicity and should not be used in patients with significant liver injury.

### **Ineffective Treatment Strategies**

Many strategies that have attempted to alter pathways associated with pathogenesis of AH have failed increase survival (see Table 3). Although most trials enrolled small numbers of patients, the lack of efficacy has reduced enthusiasm for follow-up studies.

Drug	Proposed mechanism of action	References
	in AH	
Colchicine	Inhibits migration of	53, 54
	polymorphonuclear leukocytes	
	and interferes with collagen	
X '	deposition	
Oxandrolone and anabolic	Reverses the catabolic state;	28, 43, 55
steroids	stimulates protein synthesis and	
	regeneration	
Propylthiouracil	Decreases the hypermetabolic	46

Table 3. Drugs Considered	to be Ineff	ective in AH
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	state and related centrilobular	
	(zone III) hypoxia	
S-Adenosyl Methionine	Replaces SAMe deficiency and	
(SAMe)	improves the methionine cycle.	
	Supplies methyl donors to	
	multiple biochemical pathways,	
	including substrates for	
	polyamine synthesis. Provides	
	precursors for glutathione	
	synthesis	
NAC plus other	Increases hepatic antioxidants	40
antioxidants		
Insulin and glucagon	Increases hepatic regeneration	56
Calcium channel blockers	Protects hepatocytes in animal	57
	models	
Penicillamine	Inhibits collage cross linkage	58
	and increases collagen	
	degradation	
Extracorporeal liver support	Supports hepatic functions until	59
	liver recovers	

## Inhibitors of TNF

Strategies to block TNF provide a particular case in point for failed approaches. TNF was believed to be the inflammatory cytokine that made the greatest contribution to development of AH. Infusion of patients with TNF causes several clinical manifestations of AH, including anorexia, fever, wasting, hypoalbuminemia, and leukocytosis <sup>60</sup>. Serum levels of TNF are increased in patients with AH <sup>61</sup>. Administration of anti-TNF agents to animal models of alcoholic liver disease reduces liver injury and portal hypertension <sup>62, 63</sup>. Furthermore, anti-TNF agents are effective as therapies for other inflammatory diseases.

Two small studies indicated that infliximab, a monoclonal antibody against TNF, could increase liver function, but it was also found to increase infections among subjects. Naveau et al conducted a double-blind, randomized study of prednisolone vs the combination of prednisolone and infliximab (10 mg/kg at week 0, week 2, and week 4) in 36 patients with AH (DF value above 32)<sup>64</sup>. The study was stopped early because of increased mortality in the group given prednisolone and infliximab, associated with increased infections.

Similar problems were found in a trial of etanercept, a soluble TNF receptor– immunoglobulin constant fragment (Fc) fusion protein that binds and neutralizes unbound TNF<sup>65</sup>. Mortality at 1 month was similar in the placebo and etanercept groups. However, at 6 months, mortality was significantly higher in the etanercept group than the placebo group (67.7% vs 22.7%). A significantly higher proportion of subjects receiving etanercept developed infections (34.6% vs 9.1% in the placebo group).

These studies demonstrate the complexity of finding new treatments for AH. TNF was considered a major cause of liver injury during progression of AH, based on findings from studies of patients and animals, and anti-TNF are successfully used to treat other inflammatory diseases. However, cytokines have many effects, so it difficult to know if or how they contribute to development of a particular disease in humans. The inflammatory effects of TNF (which are perceived to be harmful) might be outweighed by its positive effects on regeneration. Also, side effects (such as infections) that are not severe or frequent in patients with one particular disease (inflammatory bowel disease) might be more severe or frequent in patients with a different disease.

#### **Future Therapeutic Strategies**

Multiple treatments are being evaluated in patients with AH. Absorbable and nonabsorbable antibiotics could decrease bacterial growth—potentially decreasing absorption of endotoxin and other inflammatory bacterial products. Absorbable antibiotics may also decrease infections or sepsis, particularly among patients receiving corticosteroids. Probiotics may alter the intestinal microbiome to be less hepatotoxic. Binding of endotoxin by use of antibodies to lipopolysaccharide is also being considered. Interfering with inflammation through blockage of interleukin-1 (using already approved drugs) is reasonable given inflammasome activation in experimental and human alcoholic liver disease. A potent immune suppressant (mycophenolate) is under consideration for patients who do not respond to prednisolone. Close monitoring for infection will be necessary when using immune-modulating drugs. Caspase inhibitors may interfere with cell death.

Intervention	Rationale	<b>Clinical Trial Information</b>
<b>Rifaximin</b>	Decreases intestinal	https://clinicaltrials.gov/ct2/show/NCT
	bacteria growth and	02116556
	lowers endotoxin	https://clinicaltrials.gov/ct2/show/NCT
	level in the blood	02485106
Amoxicillin/Clavula	Decreases intestinal	https://clinicaltrials.gov/ct2/show/NCT
nic acid	bacteria growth	02281929
Ciprofloxacin	Decreases intestinal	https://clinicaltrials.gov/ct2/show/NCT
	bacteria growth	02326103
Probiotics	Alters gut	https://clinicaltrials.gov/ct2/show/NCT
	microbiome to	01922895
	decrease intestinal	
	permeability or	
	endotoxin levels	
Bovine colostrum	Binds and removes	https://clinicaltrials.gov/ct2/show/NCT
	endotoxin	02265328
		https://clinicaltrials.gov/ct2/show/NCT
Y.		02473341
		https://clinicaltrials.gov/ct2/show/NCT
		01968382
Obeticholic acid	FXR agonist that	https://clinicaltrials.gov/ct2/show/NCT
	decreases fat	02039219

	synthesis	
Anakinra or	Bind/block	https://clinicaltrials.gov/ct2/show/NCT
Rilonacept	interleukin-1 (anti-	01809132
	inflammatory)	
Mycophenolate	Inhibits	https://clinicaltrials.gov/ct2/show/NCT
	inflammation	01903798
Caspase inhibitors	Inhibits caspase-	https://clinicaltrials.gov/ct2/show/NCT
	mediated cell death	01912404
Interleukin-22	Stimulate hepatic	
	regeneration	

#### **Future Directions**

Infection and septicaemia are common among patients with AH. Some patients have infections at the time of admission, which might have contributed to the development of AH. In other patients, infections develop after admission or after initiation of treatment with corticosteroids; these can increase short-term mortality <sup>66</sup>. A high level of lipopolysaccharide in serum is associated with development of the systemic inflammatory response syndrome, multi-organ failure, and death <sup>67</sup>.

Approximately <u>20%</u> of patients develop <u>bacterial</u> infections during admission and up to <u>20% develop fungal</u> infections <sup>68</sup>. The increased susceptibility to infection in this patient group indicates that AH is associated with <u>immune paresis</u>. Support for this hypothesis comes from reports of innate immune defects. A proportion of patients with AH have a defect in the oxidative burst required to kill phagocytosed bacteria in circulating monocytes <sup>69</sup>. When present at the time of admission, this defect is associated with a 12fold risk of subsequent infection. Defects in neutrophil phagocytosis and oxidative burst have previously been described in patients with AH. Defects in adaptive immunity have also been observed with overexpression of the checkpoint inhibitor pathway PD1–PDL1, resulting in T-cell dysfunction <sup>70</sup>. Because of the immunosuppressive effects of corticosteroids, people have assumed that they increase susceptibility to infection in patients with AH, but there is no strong evidence to support this assumption. In the STOPAH trial, infections reported as serious adverse events occurred in a significantly higher proportion of patients who received prednisolone (13%) than those who did not (7%). A meta-analysis of placebo-controlled trials found no increase in susceptibility to infection among patients receiving prednisolone. This might be because patients who respond to corticosteroids (Lille score below 0.45) are far less susceptible to infection <sup>66</sup>. The risk of infection and the associated consequences forms the rational for several new studies of patients with AH that combine corticosteroid therapy with prophylactic use of antibiotics.

#### Is a liver biopsy necessary?

The diagnosis of AH can usually be made on the clinical history (excessive alcohol consumption and recent onset of jaundice), typical biochemical pattern (level of AST > level of ALT, level of bilirubin > 80uMol/L) and exclusion of other causes of acute liver injury. In histologic analysis, liver tissues from patients with AH display steatosis, ballooned hepatocytes, inflammatory infiltrates, Mallory-Denk bodies, megamitochondria, and pericellular and pervenular fibrosis. Steatohepatitis can be detected in liver tissues from ~80% of patients undergoing liver biopsy for presumed AH <sup>71,72</sup>.

Due to the presence of coagulopathy, liver biopsy invariably needs to be performed by the transjugular route, which is not widely available. As a result, in clinical practice, only around 10% of hepatologists routinely collect biopsies from patients with AH <sup>73</sup>. Histology analyses are essential for patients with uncertain diagnoses (such as possible drug-induced liver injury or ischemia from severe upper gastrointestinal bleeding)— particularly for patients with a long duration of jaundice prior to admission or those without 100% results from serologic tests. European Association for the Study of the Liver guidelines recommend use of histologic analysis in clinical trials; it is important for small exploratory (phase II) studies in which accuracy of diagnosis could affect the results <sup>74</sup>.

#### Designing clinical trials for AH

Well-designed clinical trials needed to identify new treatments for AH. Although reducing short-term mortality is a good indicator of efficacy, the large number of patients required to show that the agent reduces mortality can be an impediment to drug development. Furthermore, mortality is the only accepted endpoint for clinical trials this does not allow for development of therapeutics for patients with moderate disease severity.

Because AH has been associated with a high mortality, and for historical reasons, mortality at 1 month has been the most common primary outcome for clinical trials. Data from several recent studies indicate that mortality at 90 days might be more appropriate for assessing agents that aim to improve liver function. In recent studies, 10%-20% of patients with DF $\geq$ 32 have been reported to die within 1 month after treatment with prednisolone—this considerably less than the ~35% among patients receiving placebo in studies several decades ago. Liver-related causes account for >80% of deaths during the first 90 days. Although analyses of longer time periods (such as 1 year) are important, mortality after 90 days is influenced by return to drinking, a behavior that may not be altered by drugs that improve liver function. So the benefit of a therapeutic agent could be lost in analyses over longer time periods.

Improved liver function is another potential outcome. For patients with moderate or severe AH, liver function could be measured by decompensation events such as infections, hepatorenal syndrome, encephalopathy, etc. However, for phase 2 clinical trials and clinical trials of patients with milder forms of AH, valid trial endpoints instead of mortality are urgently required. Changes in blood tests of liver function could be reasonable outcome measures—especially scores that are associated with survival of patients with AH (such as Lille or MELD scores, etc.). Consensus is needed to select the prognostic factors and the time points for measurement to make this disease area more amenable for drug development.

AH has a spectrum of severity. Survival among patients with mild AH is high. On the other hand, patients with very severe AH (DF>60, MELD>27) or patients who do not respond to initial treatment (Lille>0.56) have poor prognosis no matter what treatment is given. Inclusion of these patients in a clinical trial could obscure benefits to patients with mild to moderate AH. So, stratification of disease severity using an established scale (DF, MELD, or Lille) is recommended.

The role of liver biopsy in clinical trials is an area of debate; some clinical trials require histologic confirmation of liver disease and others do not. AH is incorrectly diagnosed for as many as 20% of patients; inclusion of patients who are unlikely to respond to treatment will reduce the likelihood of efficacy. However, liver biopsies increase costs, risk to patients, and time in hospital. Uniform interpretation of liver histology would need to be assured. It is possible that regulatory agencies will require liver histology analyses before they approve an agent for treatment of AH.

#### Figure 1. Strategy for Treatment of Patients with AH.

Patients must first be accurately diagnosed with AH, based on history, physical examination, and analyses of blood samples and, in some cases, biopsies collected via the transjugular route. Alcohol dependence should be determined and treated initiated at this point. Patients should then be assessed for complications such as infections, upper gastrointestinal bleeding, and renal failure. Patients' nutritional needs should then be addressed; patients should be given 35-40 cal/kg/day orally or enterally, as well as 1.2-1.5 g protein/kg/day. The severity of AH should then be assessed. Patients with a DF  $\geq$  32 and MELD>20 should receive prednisolone (40 mg/day) with or without NAC for 7 days, and then bilirubin should be measured. Patients with Lille scores below 0.45 should continue treatment for 28 days. Patients with Lille scores above 0.45 should stop treatment. There are no specific treatments for patients with DF<32 and MELD>20.

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