Alcoholic Hepatitis: Pathogenesis and Approach to Treatment

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This is to acknowledge that Mack C. Mitchell, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mitchell will be discussing off-label uses in his presentation.

Biographical Information

Dr. Mack C. Mitchell is Professor and Vice-Chairman of Internal Medicine at U.T. Southwestern Medical School. He attended Davidson College and received his B.A. and M.D. from Johns Hopkins. He completed residency in internal medicine at the Johns Hopkins Hospital and a fellowship in gastroenterology and clinical pharmacology at Vanderbilt University. Dr. Mitchell was a member of the faculty at the Johns Hopkins School of Medicine until 1996, when he became Chairman of Internal Medicine at Carolinas Medical Center. In 2004, he returned to Hopkins to direct the division of gastroenterology at Johns Hopkins Bayview. He joined the faculty at Southwestern in 2011. Dr. Mitchell has had a long-standing interest in alcohol and drug-induced liver injury and has served on the study section and Advisory Council of the National Institute on Alcohol Abuse and Alcoholism. In collaboration with colleagues at University of Massachusetts, University of Louisville, the Cleveland Clinic and UT Southwestern, Dr. Mitchell is involved in two clinical trials studying treatment of alcoholic hepatitis.

Purpose and overview:

Excessive consumption of alcohol is one of the major causes of cirrhosis. Although a majority of heavy drinkers develop fatty infiltration of the liver, only 20-25% develop cirrhosis. Over the last 25 years, a number of important observations, including several made at U.T. Southwestern, have furthered our understanding of the pathogenesis of acute alcoholic hepatitis, an inflammatory disorder that often leads to fibrosis and eventually cirrhosis. This discussion will review the clinical features of alcoholic hepatitis, the potential mechanisms that underlie liver injury in alcoholic hepatitis, and therapy for this condition. Although corticosteroids reduce short-term mortality in patients with acute alcoholic hepatitis, many patients are not treated, because of concerns about adverse events. Recognizing the importance of the innate immune system in the pathogenesis of alcoholic hepatitis led to the design of a clinical trial for treatment of alcoholic hepatitis. The rationale and design of the clinical trial will be discussed.

Objectives:

1. Review the clinical and laboratory features of acute alcoholic hepatitis and how these features are used to establish diagnosis and prognosis.
2. Review risk factors for alcoholic hepatitis and the pathogenesis of alcoholic liver injury.
3. Review current and future novel treatments for alcoholic hepatitis.
4. Review contributions to understanding the pathogenesis and treatment of acute alcoholic hepatitis made at U.T. Southwestern Medical Center over the last 25 years.

Introduction

Alcoholic hepatitis is an inflammatory disorder of the liver characterized clinically by jaundice, tender hepatomegaly and abdominal pain and histologically by macrovesicular steatosis and necroinflammation. Short-term mortality from alcoholic hepatitis may be as high as 50% in a subset of patients with deep jaundice and profound coagulopathy. The histological spectrum of alcoholic liver disease includes fatty liver, steatohepatitis, cirrhosis and hepatocellular carcinoma. Although abstinence is the cornerstone of therapy for alcoholic hepatitis as it is for all stages of alcoholic liver damage, a number of interventions are beneficial in treatment of patients with alcoholic hepatitis.

Risk factors for alcoholic liver disease

The absolute risk of developing liver damage from alcohol is relatively low, ranging between 6-20% of those drinking more than 40 g of ethanol daily (approximately 2.5 standard drinks).[1,2] Most studies have reported an increased risk of serious liver disease including cirrhosis that is related directly to daily intake of alcohol.[1] The estimated amount of daily alcohol intake required to cause alcoholic hepatitis varies considerably among individuals.[1,2] The risk for development of alcoholic cirrhosis increases with daily intakes of more than 40 gm/day, although it is puzzling that only a minority of alcoholics, many of whom ingest considerably more alcohol, develop alcoholic hepatitis. On average, the amount of alcohol ingested was more than 200 grams/day in one study.[3] A number of risk factors other than the amount of alcohol consumption have been identified. The pattern of drinking may be important as some studies suggest that a pattern of binge drinking with consumption of large amounts of alcohol per occasion is associated with a higher risk of developing significant alcoholic liver disease.[2] Although men with cirrhosis due to alcohol greatly outnumber women, women may have an increased risk of liver damage at lower levels of consumption than men.[2,4] Many theories, such as a possible relation to an autoimmune phenemonon, have been postulated to explain this observation, but evidence in support of any one theory is inconclusive. In most studies hard liquor was the preferred beverage in those who developed cirrhosis[2,4] and in one study, wine consumers appeared to be less likely to develop serious liver damage than other drinkers, suggesting a possible favorable relationship to the pattern of consumption with meals.[2] Cigarette smoking is often identified as a risk factor for alcoholic cirrhosis, but the relationship between heavy drinking and smoking is difficult to disentangle in population studies.[4] Curiously, consumption of coffee is inversely related to the development of both alcoholic and non-alcoholic cirrhosis.[4] A complex interaction between genetic susceptibility and environment is considered most likely, as suggested by twin-twin concordance studies. Since only a minority of heavy drinkers develop advanced alcoholic injury, genetic polymorphisms are likely to play a role in the etiology of disease. For example, Hispanics and African Americans may be more susceptible. Although several genetic polymorphisms have been found to be associated with an increased risk of ALD in small studies,[5] the level of association has not been robust enough to be of interest, with the exception of PNPLA3.[6,7] Hepatitis C has become one of the leading causes of advanced liver disease in Western populations. Patients with a history of chronic heavy alcohol abuse who have concurrent hepatitis C infection are likely to have more severe disease

than patients with hepatitis C alone. Multiple studies have demonstrated that patients who consume more than 50 grams of alcohol per day, and perhaps even as little as 30 grams per day, in the setting of hepatitis C infection, will have more fibrosis and be more viremic than age-matched, non-alcoholic hepatitis C patients.[8]

The role of obesity in alcoholic liver disease

Early studies of hospitalized patients with alcoholic cirrhosis found malnutrition in a significant percentage leading to the concept that malnutrition increased the risk of ALD. However, studies from France called attention to the role of obesity as a risk factor for alcoholic cirrhosis as well as alcoholic hepatitis and steatosis.[9] These observations were confirmed in larger population studies.[1,2] Of note, the relative risk of cirrhosis was increased in both subjects who were underweight (BMI < 20; RR 2.2) and in those who were obese (BMI > 30, RR 2.2).[2]

Clinical features of alcoholic hepatitis

Although histologic evidence of alcoholic hepatitis may be present in the absence of any symptoms, clinically significant acute alcoholic hepatitis is an icteric illness accompanied by abdominal pain, anorexia, nausea, and constitutional symptoms including fatigue, weight loss and low-grade fever. Tender hepatomegaly is common and ascites and hepatic encephalopathy occur in more severe cases of alcoholic hepatitis. Less common features that may be seen with alcoholic hepatitis include enlargement of the parotid and lacrimal glands. Spider nevi, gynecomastia, and evidence of temporal wasting occur in those individuals who have more advanced liver disease including cirrhosis. Since heavy alcohol consumption is a significant contributor to alcoholic hepatitis, the patient with alcoholic hepatitis may exhibit signs and symptoms of alcohol dependence and withdrawal when initially hospitalized.

Laboratory findings commonly associated with alcoholic hepatitis include elevation in the serum bilirubin and aminotransferases. The AST is usually elevated two to three times that of the ALT, with both enzyme levels being less than 400 IU/l.[10] The low level of the ALT has been shown to be due, in part, to deficiency of pyridoxal 5-phosphate, a necessary cofactor for both AST and ALT.[11] The AST is more significantly elevated because of the direct toxicity of alcohol to the mitochondria, a source of serum AST. Other important laboratory findings include more nonspecific indicators of alcoholism, such as an elevated MCV or thrombocytopenia. Elevation of the serum GGT and carbohydrate deficient transferrin (CDT) correlate with heavy alcohol consumption although there is no direct correlation between the level of GGT or CDT and severity of liver disease due to alcohol hepatitis. Serum bilirubin may be impressively elevated, with levels above 20 mg/dl in patients with severe alcoholic hepatitis. Low-level hemolysis, as evidenced by the presence of anisocytosis on the peripheral smear, is relatively common in patients with alcoholic hepatitis and may contribute to the elevated serum bilirubin. Unfortunately, none of the laboratory features is specific enough to establish a diagnosis of alcoholic hepatitis so it is necessary to exclude other potential causes of liver disease, particularly chronic viral hepatitis, hemochromatosis, and alpha 1-antitrypsin deficiency, using specific serological, biochemical and genetic tests.

Table 1. Clinical and laboratory features of acute alcoholic hepatitis

Clinical features	Laboratory features
• Jaundice • Nausea and anorexia • Abdominal pain • Hepatomegaly • Fever	• Leukocytosis • Elevation of AST & ALT < 400 I.U./ml • AST > ALT, usually ratio > 2; > 3 is diagnostic • Prolonged protime • Elevated bilirubin, predominantly conjugated • Elevation in serum IgA level • Elevation of GGT, CDT, RBC MCV

Diagnosis

Successfully diagnosing alcoholic hepatitis can sometimes be difficult, as there are other diseases that can mimic alcoholic hepatitis. A careful assessment of alcohol intake is essential. Most patients with active alcoholic hepatitis and jaundice have been drinking more than 60 grams of alcohol daily (4-5 drinks) within the previous 1-2 weeks.[3] Consumption of less than this amount or verified abstinence for more than 1 month should raise questions about the clinical diagnosis of alcoholic hepatitis. Separating alcoholic hepatitis from non-alcoholic steatohepatitis may be challenging in obese patients who are heavy drinkers. The Alcohol/Non-alcohol Index has been proposed as a way to distinguish the two, based on BMI, MCV, AST/ALT ratio and gender (www.mayoclinic.org/gi-rst/mayomodel10.html). In patients with a presumptive diagnosis of alcoholic hepatitis based on history and laboratory findings, biliary obstruction due to stones or strictures of the distal pancreatic duct in a patient with occult chronic pancreatitis, drug-induced liver damage, viral hepatitis, and autoimmune hepatitis must be excluded. Cholestasis of sepsis superimposed on cirrhosis is one of the most difficult diagnoses to exclude. This possibility should be considered particularly in those patients without a history of recent heavy alcohol consumption.

Appropriate laboratory testing including drug toxicology screens, anti-nuclear and smooth muscle antibodies, iron studies, and viral serologies including PCR evaluations for viral hepatitis, Epstein-Barr, and cytomegalovirus should be obtained if appropriate. Significant elevations in aminotransferases (> 500 IU/L) are inconsistent with a diagnosis of alcoholic hepatitis alone and other causes for the elevation should be explored. Marked elevation of aminotransferases greater than 5000 IU/ml in an alcoholic should prompt consideration of accidental poisoning from acetaminophen. Alcoholics are predisposed to hepatotoxicity of acetaminophen due to induction of cytochrome P450 2E1 and reduction in hepatic glutathione stores by chronic heavy alcohol ingestion.

In those patients with serological evidence of hepatitis C or hepatitis B infection or in whom the diagnosis remains unclear after a non-invasive evaluation, liver biopsy is usually necessary to determine the relative contributions of each to the liver disease. Studies have indicated that the clinical diagnosis of alcoholic hepatitis may not be confirmed by histology in

25% of cases.[12] Biopsies may need to be obtained via the transjugular route in those patients with severe coagulopathy. Histologic findings of ballooning degeneration of hepatocytes, Mallory's hyaline, steatosis, and neutrophilic infiltration are helpful features that aid in diagnosis. A biopsy can also help to identify the severity of underlying fibrosis or cirrhosis. Making the diagnosis of alcoholic hepatitis or instituting specific therapy for alcoholic hepatitis should be delayed until potential confounding disease processes have been excluded.

Complications

Morbidity and mortality from alcoholic hepatitis are related to the severity of underlying hepatic dysfunction. Complications in patients with alcoholic hepatitis include those related to portal hypertension, coagulopathy, infections, and medication effects, among others. The development of hepatorenal syndrome is an ominous prognostic factor in patients with severe alcoholic hepatitis. Hepatorenal syndrome is related to circulatory disturbances induced by hepatic failure, and is classically described as the onset of oliguric renal failure with a low urinary sodium in the absence of other causes of acute renal insufficiency or evidence of pathologic injury to the kidneys. The prognosis for patients with hepatorenal syndrome and alcoholic hepatitis is very guarded. A variety of therapeutic interventions has been attempted with varying success.

Patients with severe alcoholic hepatitis often have manifestations of portal hypertension such as ascites. In some instances, portal hypertension may be due to fibrosis and/or cirrhosis with alcoholic hepatitis, though there is evidence that active alcohol use and fatty infiltration may result in portal hypertension in the absence of fibrosis in some patients. Variceal bleeding is a major cause of morbidity and mortality in patients with alcoholic hepatitis. Coagulopathy and thrombocytopenia may worsen the extent of bleeding. Variceal hemorrhage should be managed by endoscopic banding or injection sclerotherapy. Measures to prevent future bleeding such as nonselective beta blockers should be used in long-term management.

Portosystemic encephalopathy (PSE) may develop in the absence of precipitating causes such as infection or bleeding in patients with severe alcoholic hepatitis and its presence in fact defines severe alcoholic hepatitis. However, a careful search for occult gastrointestinal bleeding, infections including spontaneous bacterial peritonitis, use of sedatives for prevention or treatment of alcohol withdrawal and electrolyte disturbances should be conducted as each can precipitate PSE. Treating or eliminating precipitating factors is the best initial management of encephalopathy. Lactulose and rifaximin can be used to manage patients with encephalopathy although they are only marginally effective in patients with severe alcoholic hepatitis in the absence of gastrointestinal bleeding. Although protein restriction has been advocated in the treatment of spontaneous encephalopathy in patients with stable cirrhosis, it should not be used to manage encephalopathy in patients with acute alcoholic hepatitis. A high protein, high calorie diet improves prognosis without worsening encephalopathy in patients with severe alcoholic hepatitis, suggesting that limiting dietary protein is not warranted in this setting.[13] Nutritional deficiencies are common in alcoholics and thus need to be addressed early in the treatment of alcoholic hepatitis. Supplementation with thiamine and folate should be administered at the time of diagnosis and continued through the period of recovery.

Alcoholic hepatitis should be considered an immunocompromised state, both as a result of the disease process itself as well as a result of medical therapy. Common infections include, but are not limited to, spontaneous bacterial peritonitis, bacteremia, urinary tract infections and pneumonia. Pancreatitis may accompany the presentation of alcoholic hepatitis as a result of chronic alcohol consumption. Standard risk assessment criteria, such as Ranson's or Apache III, should be applied so that the patient may be appropriately risk-stratified. Standard therapy for pancreatitis including fasting, intravenous fluids, and analgesia should be instituted. Chronic pancreatitis or benign bile duct and pancreatic duct strictures may require further evaluation with ERCP. However, ERCP should be performed with caution since complications may be devastating in patients with severe alcoholic hepatitis.

Prognosis

A number of studies have demonstrated the importance of the level of the serum bilirubin and the degree of prolongation of the prothrombin time (or INR) as indicators of the severity of alcoholic hepatitis and predictors of the short-term mortality rate. Through analysis of patients with a clinical diagnosis of alcoholic hepatitis, prothrombin time and bilirubin level elevations were found to be independent predictors of mortality.[14] These two laboratory findings were combined mathematically in the Maddrey discriminant function, which is used to predict those patients whose short term mortality rate was 50% or higher. The modified formula utililizes the prothrombin time corrected by subtracting the control value (measured in seconds), multiplied by 4.6 and added to the serum bilirubin measurement [$4.8*(PT_{actual} - PT_{control})$ + total bilirubin (measured in mg/dl)]. A value above 32 indicates a 28 day mortality rate of 50%. Although this measure is a continuous variable, the value of 32 has been used to dichotomize the patient population with alcoholic hepatitis into those with more severe disease and those less severely affected. The Mayo End Stage Liver Disease (MELD) scoring system mathematically combines the serum creatinine level (measured in mg/dl) with the prothrombin time (measured as INR) and the serum bilirubin level (measured in mg/dl). It has also been shown to predict short-term mortality in alcoholic hepatitis and has been touted as potentially being superior to the discriminant function.[15] Use of these models for predicting severity of alcoholic hepatitis may be more difficult in patients with chronic renal insufficiency in the case of the MELD score or in patients with chronic hemolysis, such as sickle cell anemia, not related to the underlying liver disease.

During recovery from alcoholic hepatitis, the serum bilirubin, aminotransferases and prothrombin time improve over several weeks. A decrease in AST with an increase in ALT is a favorable prognostic sign. Improvement in hyper-bilirubinemia may be delayed, though trials from the UK and France determined that a fall in the bilirubin level of 25% or more within 9 days of the institution of corticosteroids heralded a sustained and significant improvement in outcome.[16]

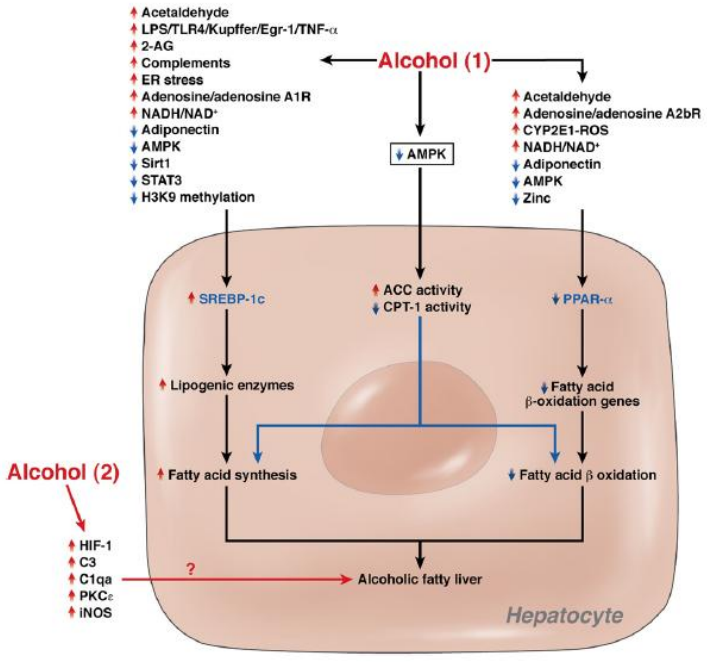
Pathogenesis

The exact pathogenesis of alcoholic liver injury remains unclear. Since many heavy drinkers have only hepatic steatosis without alcoholic hepatitis or fibrosis, the first step in injury is likely fat accumulation within the liver followed by inflammation and fibrosis. The

identification of a genetic polymorphism in the gene encoding patatin-like phospholipase domain-containing 3 (*PNPLA3*), a triacylglycerol (TAG) hydrolase, as a genetic risk factor for NAFLD stimulated similar analyses in patients with alcoholic liver injury. Several studies have now confirmed that individuals who carry this polymorphism in *PNPLA3* are also at increased risk for alcohol-induced liver injury and cirrhosis, although the underlying mechanism has not yet been delineated.[6,7] Previously, many studies have shown that patients with only hepatic steatosis have a much lower risk of progressing to cirrhosis than those with both steatosis and alcoholic hepatitis. For that reason, the focus of treatment is directed toward the inflammatory component of alcoholic liver injury.

Metabolism of ethanol occurs primarily in the liver with alcohol dehydrogenase (ADH) accounting for more than 90% of ethanol oxidation and the remainder through cytochrome P-450 2E1 and other minor pathways. The product of oxidation, acetaldehyde, is potentially toxic and is further oxidized via aldehyde dehydrogenase to acetate, which can be used as a substrate for new fatty acid synthesis. Oxidation of ethanol by ADH shifts the cellular redox state: the cofactor NAD+ is reduced to NADH. The change in redox state favors an increase in fatty acid synthesis, a decrease in fatty acid oxidation, and a net accumulation of esterified triglycerides within the hepatocyte. These metabolic reactions may contribute to the steatosis observed in alcoholism but are likely not the entire explanation. Alcohol related changes in cytokines and adipokines may also stimulate fat accumulation. Oxidation of alcohol via cytochrome P450 2E1 can generate free radicals, such as the hydroxyl radical OH-, that can result in oxidative damage.[17] Metabolism of acetaldehyde, the product of alcohol oxidation, by aldehyde oxidase and xanthine oxidase can also result in the production of free radicals. Condensation of acetaldehyde with proteins to form adducts that may act as neo-antigens can potentially activate the immune response

Figure 1. Pathogenesis of alcoholic steatosis (from reference 18)

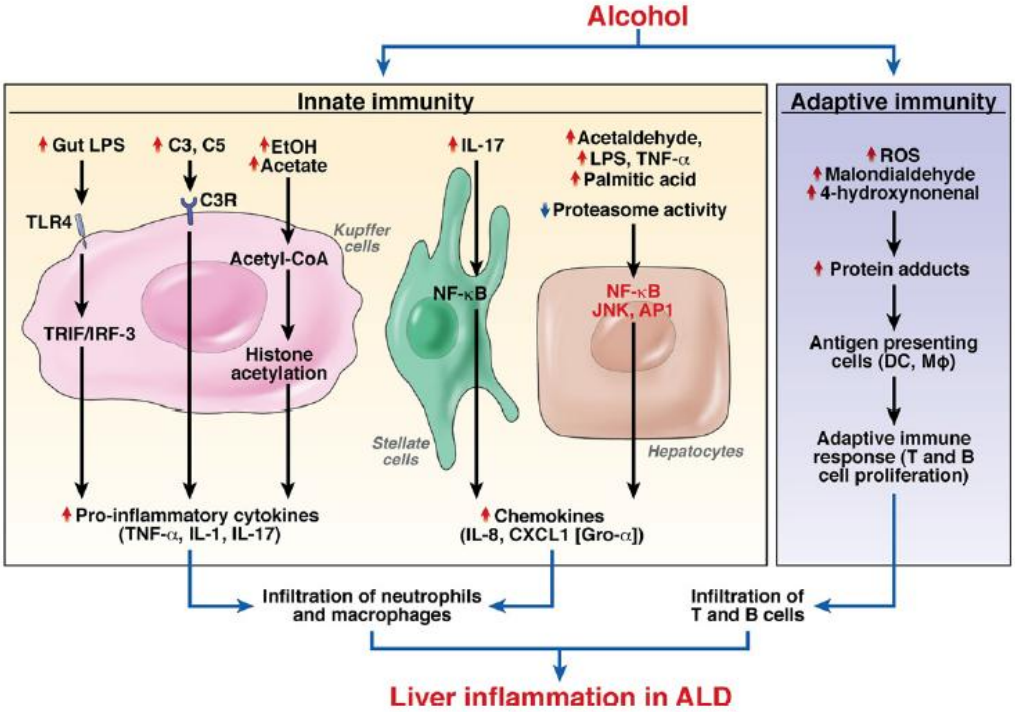


Inflammatory cytokines have been implicated in the pathophysiology of alcoholic hepatitis. A number of studies have demonstrated excess levels of IL-1, IL-6, IL-8, and TNF-α in alcoholics[18-22]. The levels in alcoholics with cirrhosis or acute alcoholic hepatitis are significantly higher than in age-matched controls and in patients with other forms of liver disease. A role for endotoxin in stimulating production of these inflammatory cytokines from Kupffer cells has been postulated.[22-23] Endotoxin (LPS) binds to TLR4 receptors on Kupffer cells with high affinity inducing production of TNF-α through NFκB. Serum levels of endotoxin are elevated in alcoholics with liver disease, possibly due to increased mucosal gut permeability occurring in the presence of alcohol, elevated endotoxin production by existing bacteria, and decreased Kupffer cell-mediated clearance of endotoxin.[22,23] Feeding large amounts of alcohol in animals increases the permeability of tight junctions in the intestinal epithelium, leading to increased gut mucosal permeability.[24] Zinc deficiency may also be an important mediator of the effect of ethanol.[25] Of note, this effect is ameliorated by products of metabolism of probiotics such as lactobacillus rhamnosus GG.[24] As discussed below, enteral nutrition therapy improves the intestinal barrier function which may explain why it is of greater benefit than parenteral nutrition.

The inflammatory nature of alcoholic hepatitis is clearly evident in the histopathology of the lesion. The most common histological features are micro- and macrovesicular steatosis, Mallory bodies, ballooning degeneration of hepatocytes, necrosis, and neutrophil and occasionally mononuclear cell infiltration. The inflammatory cascade in alcoholic hepatitis is a subject of great interest. Alcohol may affect many different cell types within the liver including those of the innate immune system (Kupffer cells, stellate cells) and the adaptive immune system (T cells, NK cells, etc) as well as the hepatocytes (epithelial cells). Stellate cells are thought to be critical in development of fibrosis. Proinflammatory cytokines are released from the Kupffer cells and chemokines are released primarily from stellate cells and hepatocytes. IL-8, which is released by hepatocytes in response to IL-1B and TNF–α, acts as a chemoattractant for neutrophils. As such, IL-8 levels are increased in patients with neutrophil infiltration, with neutrophils releasing additional oxygen radicals and proteases that cause further inflammation and necrosis.[21] These findings may explain why patients with greater degrees of neutrophilic infiltration, as well as high peripheral neutrophil counts, seem to respond better to anti-inflammatory therapy.

Because of its potent pro-inflammatory effects, TNF–α became an early focus of interest in pathogenesis and later treatment of alcoholic hepatitis. Knockout mice that lacked the ability to make TNF–α were resistant to inflammatory effects of ethanol feeding and early studies in animal models suggested that anti-TNF–α therapy could prevent liver injury in animal models. More recently other cytokines have been considered better targets for treatment as discussed below.

Figure 2. Role of cytokines and chemokines in alcoholic hepatitis (from reference 18



Treatment

Abstinence is the cornerstone of therapy for alcoholic hepatitis as it is for all stages of alcoholic liver damage. Although it may be possible to manage some patients with alcoholic hepatitis on an ambulatory basis, hospitalization is often needed to insure short-term abstinence, particularly in those individuals without a supportive family and home environment. Hospitalization allows for a careful evaluation to exclude associated complications such as infection and gastrointestinal bleeding. Because patients are hospitalized for a relatively short period of time, counseling patients and families about the importance of complete abstinence at an early stage in the illness is critical to both short and long term success. During the first few days of hospitalization supportive care including adequate fluids, multivitamins including thiamine, protein and calories is needed. Treatments that are intended to improve the underlying pathophysiology are primarily anti-inflammatory. Experience has shown that patients with mild-moderate alcoholic hepatitis improve with abstinence and supportive care alone. Several studies have evaluated the role of nutritional supplements, specific anti-oxidants and other measures in this population and are detailed below. Those patients with severe alcoholic hepatitis definitely require hospitalization and other interventions because of the extremely high short-term mortality rate that is greater than the mortality in patients with class IV acute myocardial infarction.

Corticosteroids

Because they are anti-inflammatory, corticosteroids were among the first medications studied for the specific treatment of alcoholic hepatitis. There is a considerable amount of data that has shown that corticosteroids do not improve outcome for the majority of patients with mild to moderate alcoholic hepatitis.[26,27] An initial analysis of the results in a single center concluded

that a subset of patients with severe alcoholic hepatitis benefited from treatment.[19] The analysis led to the development of the Maddrey discriminant function which has been used subsequently to define eligibility for a number of randomized, controlled trials of steroids and other medications. No fewer than thirteen randomized placebo-controlled trials of corticosteroids and at least three meta-analyses of the trials of corticosteroids have been reported.[26-30] Outcomes in these studies varied widely (five were favorable and eight showed no benefit) resulting in considerable controversy regarding the use of corticosteroids in treating alcoholic hepatitis.

Three well-designed recent studies that limited patient enrollment to those with a Maddrey score > 32 or spontaneous portosystemic encephalopathy demonstrated improved 28 day mortality in the group receiving corticosteroids. One study demonstrated a durable survival benefit at two months and one year.[29] In each of these trials, patients with a modified Maddrey score greater than 32 (indicating a 50% mortality) were randomized to receive prednisolone or placebo in addition to supportive care and adequate nutrition. Randomization was generally made within the first seven days of hospitalization and treatment was continued for four weeks, with subsequent tapering of the dose of prednisolone.

A subsequent meta-analysis of these three studies alone showed a 30 day survival of 85% in the steroid treatment group as compared to 65% in the placebo group. Based on these findings, the authors concluded that corticosteroids should be first-line therapy for severe alcoholic hepatitis, but not for patients with a Maddrey score < 32. However, a Cochrane review of the role of corticosteroids in alcoholic hepatitis concluded that steroids were not effective. As noted by the authors of the Cochrane review, there is considerable heterogeneity among the studies that have been reported.[30] Heterogeneity in criteria for patient selection, particularly with regard to severity, comorbidities and the ratio of women to men in the trials may partially explain the differences in outcome between the various studies. Since many of the trials were performed before adequate testing for hepatitis C infection was available, patients with chronic hepatitis C were likely included in many of the studies. All of the trials that showed benefits for corticosteroids excluded patients with evidence of active gastrointestinal bleeding. It is also interesting to note that those studies that included a higher percentage of women were more likely to show a benefit of steroids. The explanation for this observation is not fully understood, but young women with alcoholic hepatitis usually have higher levels of bilirubin relative to men for a given level of the Maddrey discriminant function (personal observations).

One important issue that remains unsettled is the optimum duration of treatment with corticosteroids. Most of the RCTs utilized a fixed duration of steroid treatment (28 days), but some investigators have pointed noted that a more flexible duration of treatment could help to minimize infections, which are the most common complication associated with steroid treatment. A group of investigators in France determined that using the early change in bilirubin (ECBL) in combination with age, creatinine, the Maddrey DF and serum albumin could the used to predict those patients who would not benefit from corticosteroids.[16] The Lille model (www.lillemodel.com) can be used as a "stopping rule" for corticosteroids to avoid infections and complications in those with a very low probability of response. The basis for poor response to steroids is a subject of debate.

Although corticosteroids clearly have benefits in a subset of patients with severe alcoholic hepatitis, other therapies have emerged that show also show benefit for certain subsets of patients with alcoholic hepatitis. Further evaluation of these treatments as single agents or in combination is needed to improve the long-term survival of patients with alcoholic hepatitis, particularly those with contraindications to corticosteroids

Anti-TNF therapy:

Plasma TNF–α levels are elevated in patients with alcoholic hepatitis and predict a higher moraltity rate in patients with severe alcoholic hepatitis.[19,22] Because TNF has been implicated in the pathogenesis of alcoholic hepatitis and in experimental models of alcoholic liver injury, there has been considerable interest in treating alcoholic hepatitis with drugs that block production of TNF-α or neutralize its actions.

- Infliximab

A single infusion of infliximab, 5 mg/kg, showed a significant reduction in mortality of patients with severe alcoholic hepatitis compared to historical controls.[31] A larger randomized trial in patients with severe alcoholic hepatitis (Maddrey score > 32) used two infusions of infliximab, 10 mg/kg given within the first month, in combination with daily corticosteroids, compared to a standard treatment group that received daily corticosteroids alone. Somewhat surprisingly, the patients who received the combination of infliximab and corticosteroids had a higher short-term mortality rate resulting in the study being terminated prematurely by the data safety monitoring board.[32] Serious infections were the cause of death in all those patients who received the combination. Although severe infections were noted to be more frequent in patients with alcoholic hepatitis treated with anti-TNF–α therapy, the combination does not appear to be inherently more dangerous since patients with inflammatory bowel disease are often treated with steroids and/or anti-metabolites (6-MP or azathioprine) while receiving infliximab.

- Etanercept

TNF–α can be neutralized by etanercept, a p75-soluble TNF receptor:FC fusion protein. This medication has been used effectively in patients with rheumatoid arthritis and psoriasis, two other inflammatory disorders in which TNF–α is thought to play a pathogenic role. Although etanercept improved survival of patients with severe alcoholic hepatitis to 92% in a small pilot study,[33] a larger randomized trial of etanercept in patients with alcoholic hepatitis was stopped prematurely, again because of a worse short term mortality rate in those receiving etanercept.[34] Of note, the trial enrolled patients with a MELD $\geq$ 15, so some did not have severe alcoholic hepatitis as defined by the Maddrey score or spontaneous encephalopathy. The experience with infliximab and more recently etanercept has resulted in an informal moratorium on this approach to therapy in patients with alcoholic hepatitis. These differences have led some to speculate that drastically reducing TNF–α levels may be counter-productive since TNF-α is important in hepatic regeneration.

Table 2. Clinical trials of anti-TNF therapy in acute alcoholic hepatitis

Study	Number patients	Intervention	Outcome
Spahr, et al (2002)	20	Corticosteroids (28 d) +/- infliximab 5 mg/kg X 1	MDF improved d 28 infliximab > steroids
Tilg, et al (2003)	12	Infliximab 5 mg/kg X 1	10/12 survived 1 yr Cytokine profile improved
Naveau, et al (2004)	36	Prednisolone X 28 d +/- infliximab 10 mg/kg X 3	XS infections w/ infliximab
Menon, et al (2004)	48	Etanercept 25 mg X 4 doses	12/13 survived
Boetticher, et al (2008)	48	Etanercept 25 mg X 6 doses (MDF > 15)	1 month similar, 6 mos worse
Sharma, et al (2009)	19	Infliximab 5 mg/kg X 1	XS infections

-Pentoxifylline

Pentoxifylline inhibits the production of TNF-α in cultured cells and *in vivo*. Pentoxifylline, 400 mg orally three times daily, was reported to improve the mortality in patients with alcoholic hepatitis with a modified Maddrey score > 32 compared to placebo.[35,36] The reduction of mortality in patients treated with pentoxifylline appeared to be mediated through a reduction in the number of patients who subsequently developed hepatorenal syndrome. Somewhat surprisingly, there was no demonstrated benefit of pentoxifylline in those patients who had an elevated creatinine at the time of randomization. One significant adverse effect of pentoxifylline, however, is an increase in risk of bleeding complications, particularly in those patients with pre-existing thrombocytopenia and lesions such as varices that may be prone to massive bleeding. The medication should be withheld in those patients who develop significant bleeding. A larger RCT of pentoxifylline is currently underway (clinicaltrials.gov). Other trials have compared PTX to corticosteroids or combinations of PTX + steroids.[37,38] These trials have not shown a benefit to PTX or the combination versus steroids alone. Similar to other studies there appears to be a benefit of PTX in reducing the risk of HRS. Two meta-analyses have failed to demonstrate any benefit of PTX on survival compared to steroids.

Table 3. Clinical trials of pentoxifylline in acute alcoholic hepatitis

Study	N	Intervention	Comparator	PTX
Akriviadis, et al (2000)	101	PTX 400 TID X 4 wks 28 day survival vs placebo (Deaths due to HRS)	24/52 (22)	12/49 (6)
De, et al (2009)	68	PTX vs Prednisolone; 6 month survival (p = .04) (Deaths due to HRS)	12/34 (6)	5/34 (0)
Sidhu, et al (2012)	50	PTX vs Placebo 28 day survival (p = .2) (Deaths due to HRS)	15/25 (7)	20/25 (1)
Sidhu, et al (2012)	70	PTX + Prednsiolone vs Prednisolone; 28 day survival 6 month survival (Deaths due to HRS-28 days)	72% 24% (4)	73.5% 31% (1)

- Nutritional Therapy

A number of studies have reported nutritional deficiencies and malnutrition in patients with alcoholic hepatitis and other forms of alcoholic liver disease. Given the relationship between malnutrition and outcome, many early studies that used supplemental nutrition with or without medical therapy produced mixed results. However, many of these studies used parenteral nutrition or were limited to certain components of nutritional therapy such as amino acids. While these components may have some effect on alcoholic hepatitis, it may be the improvement in the intestinal barrier that is induced by enteral nutrition that is most important. This improvement may decrease the endotoxemia that induces production of TNF–α, and as such there is a new enthusiasm for the use of enteral nutrition. A recent study has suggested that enteral nutrition combined with systemic corticosteroid therapy may produce better outcomes than either therapy alone.[39] Enteral nutrition was begun early in the course of the illness and continued throughout 28 days. Corticosteroid therapy was tapered as soon as there was evidence of improvement in bilirubin and prothrombin time. The study was done as a follow up of prior study comparing enteral nutrition with steroids, in which no significant difference in overall outcome between the two treatment groups was detected, although deaths occurred at an earlier time in patients in the nutrition arm. In the study of combined steroids and enteral nutrition, the number of infections was lower than in the steroid arm of the earlier study. One earlier study using parenteral nutrition reported a reduction in 28 day mortality, which was not confirmed by

other studies. Taken together, these studies and others in patients with alcoholic cirrhosis suggest that enteral nutrition has significant advantages over parenteral nutrition. One possible reason is that enteral nutrition is thought to improve the "leaky gut" in alcoholic patients thereby reducing bacterial translocation, potentially a major source of infections in these patients. Future research directly linking the effects of enteral nutrition to reduction in endotoxemia and subsequent infections is likely to help delineate the role of nutrition in the treatment of alcoholic hepatitis.

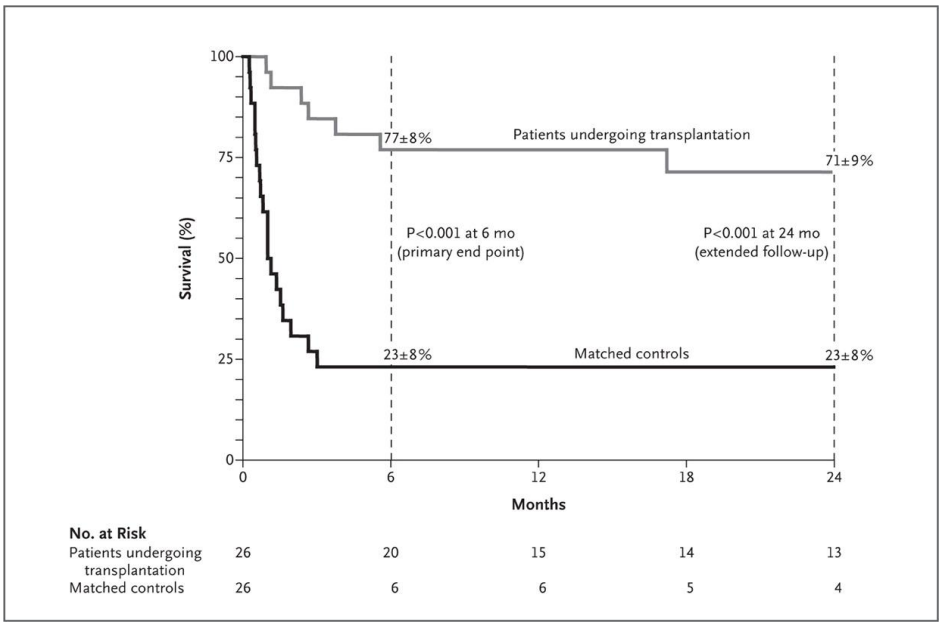
- S-adenosyl-L-methionine and N-acetylcysteine

S-adenosyl-L-methionine (SAMe) is an amino acid that is an intermediate in the transsulfuration of methionine to cysteine, a direct precursor of glutathione, a compound that plays an important role in cellular anti-oxidant defense mechanisms. SAMe has been shown to improve alcohol-mediated injury in an animal model of alcoholic hepatitis. Although several studies have shown that SAMe levels are decreased in patients with advanced liver disease including alcoholic cirrhosis, a pilot study of SAMe in treatment of acute alcoholic hepatitis did not show significant improvements. Another compound, N-acetylcysteine is rapidly converted to cysteine, the rate-limiting precursor of glutathione synthesis. Infusion of N-acetylcysteine for 5 days in addition to treatment with prednisolone improved 28 day mortality in patients with severe alcoholic hepatitis (8%) compared to prednisolone alone (24%) with a trend towards improvement of 90 day (22 vs 34%, p = .06) and 6 month (27 vs 38%, p = .07).[40] Interestingly, the number of patients developing HRS was also reduced at 6 months.

-Liver Transplantation

Liver transplantation is the last resort in the treatment of alcoholic hepatitis. Multiple reports have confirmed that appropriately selected patients without active infections have an equally favorable outcome after liver transplant compared to other liver diseases. The "moral dilemma" in recommending transplantation for severe alcoholic hepatitis is that the majority of patients do not undergo the usual period of abstinence from alcohol before transplantation. Furthermore, many patients have contraindications to transplantation such as concurrent infections. The current shortage of organs for transplantation has led to considerable controversy regarding whether use of a scarce commodity can be justified in patients who are actively drinking and may have a high rate of recidivism following transplant. Nevertheless, several recent studies both from France and from the U.S. have shown clearly that liver transplantation is an effective treatment in carefully selected patients with severe acute alcoholic hepatitis.[41]

Figure 3. Liver transplantation for acute alcoholic hepatitis.[41]



- Other proposed treatments for alcoholic hepatitis

Several medications have been studied in randomized trials that did not consistently improve outcomes in alcoholic hepatitis. These include propylthiouracil, infusions of insulin and glucagon, colchicine, calcium channel blockers, penicillamine, silymarin, vitamin E, cyanidanol, thioctate, malotilate, anabolic steroids, and an antioxidant cocktail. Most of these medications were studied with randomized trials and found to not be efficacious and are no longer recommended. Whether some have potential as part of a combination therapy has not been addressed.

Novel Therapies for Acute Alcoholic Hepatitis

Considerable progress has been made in understanding the pathogenesis of acute alcoholic hepatitis. Alcoholic hepatitis develops in patients with steatosis. The accumulation of fat from heavy alcohol consumption represents the "first hit" in injury from alcohol followed by a "second hit" that probably involves portal vein endotoxemia resulting from increased gut permeability. The severe inflammatory response that is characteristic of acute alcoholic hepatitis is initiated by signaling through TLR4 with release of TNF–α, IL-1, IL-8 and other pro-inflammatory cytokines. The dysregulated cytokine profiles have been shown to correlate with mortality.

Current treatment paradigms typically employ a single agent: corticosteroids, pentoxifylline or anti-TNF–α therapy with neutralizing antibodies or soluble receptors. Few clinical studies have attempted combination therapy to treat alcoholic hepatitis, other than combining corticosteroids with enteral nutrition. In response to an RFA from NIAAA, investigators at the University of Massachusetts, University of Louisville, Cleveland Clinic and

University of Texas Southwestern Medical Center proposed an initial clinical trial that will combine treatments to reduce inflammation, improve gut barrier function and prevent the development of hepatorenal syndrome and other organ failure. Based on data from animal models and observations in patients with alcoholic hepatitis, zinc supplementation will be used to improve gut barrier permeability and reduce endotoxemia.[24,25] Several studies have demonstrated high levels of TNF-α and IL-1β (McClain personal communication). Although pentoxifylline may reduce the production of TNF–α, its main effect in patients with acute alcoholic hepatitis is in preventing development of hepatorenal syndrome (Table 3). Although TNF–α probably plays a role in the inflammatory response in AAH, blocking TNF–α either with infliximab or etanercept led to an increased risk of infections. Other cytokines such as IL-1 likely also contribute to inflammation in AAH. Recent studies using a mouse model of acute alcoholic hepatitis demonstrated a role for inflammasomes in the inflammatory response following alcohol feeding. Furthermore, blocking IL-1 receptors with anakinra reduced the extent of injury.[42] Whereas blocking TNF–α increases the risk of infection in many disease states, blocking IL-1 does not appear to increase the risk of infection in patients with arthritis.

Thus, an integrated approach to treating AAH might include combination therapy with zinc to improve gut permeability, reduce inflammation through blocking IL-1 receptors (anakinra) and prevent acute kidney injury with pentoxifylline.

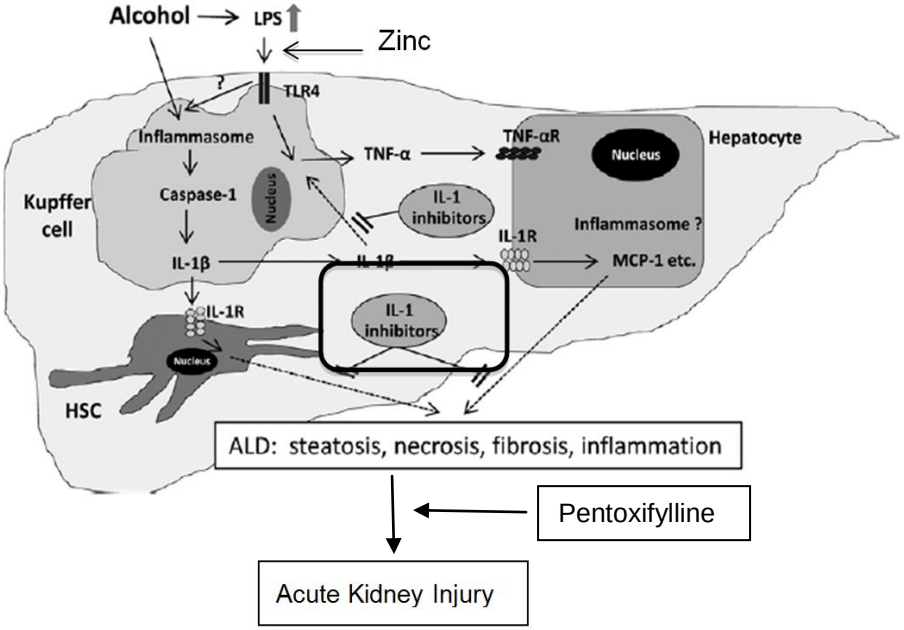


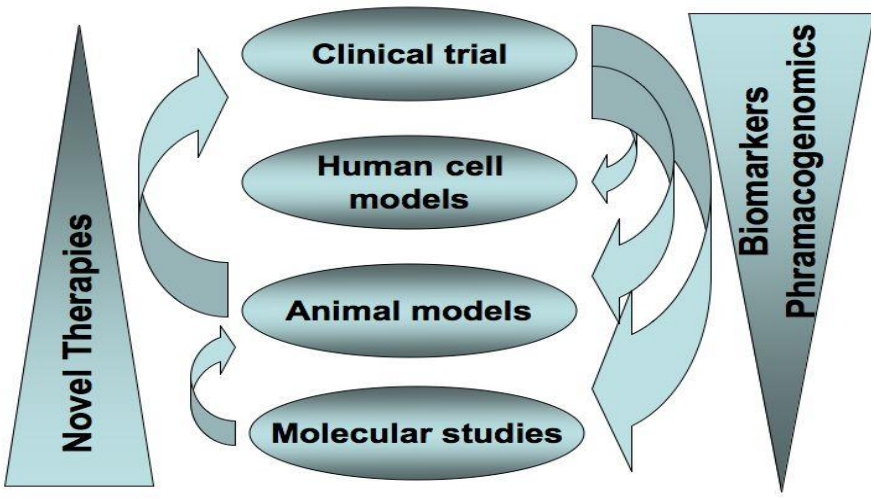
Figure 4. An integrated approach to treating acute alcoholic hepatitis

The clinical trial was approved and will begin at the 4 collaborating centers. Patients will be risk stratified based on the Maddrey discriminant function and the MELD score. The primary outcome for those with severe alcoholic hepatitis defined by MDF $\geq$ 32 and MELD $\geq$ 21 will be 6 month mortality. We will also measure a number of other parameters including changes in gut

mucosal integrity, endotoxin and cytokine profiles. They will receive either methylprednisolone for 28 days or a combination of anakinra (IL-1 receptor antagonist) for 14 days + pentoxifylline for 28 days + zinc supplementation for 6 months. Those with mild to moderate acute alcoholic hepatitis will be randomized to standard of care including advice regarding abstinence and good nutrition or standard of care + lactobacillus rhamnosus GG for 6 months. Outcomes will be 30, 90 and 180 day changes in MELD scores. The study will also collect a number of blood, stool and other samples to inform the design of new animal studies and future clinical trials.

Severe AAH (MELD ≥ 21)	**Moderate AAH (MELD < 21)**
Primary outcome: 6 month mortality	**Primary outcome: 30 day change in MELD**
Secondary outcomes: • 30, 90 day mortality • changes in MELD at 30, 90, 180 days • changes in gut mucosal integrity • endotoxin levels & cytokine profiles	Secondary outcomes: • 30, 90 day mortality • 90, 180 day change in MELD • changes in gut mucosal integrity • endotoxin levels & cytokine profiles

This randomized clinical trial will be the largest NIH-funded clinical trial since the pivotal studies of corticosteroids conducted at Johns Hopkins, MCV, Jefferson and UT Southwestern in the mid 1980's. We hope to have the opportunity to share the data collected with other groups that may help accelerate the development of more effective treatments for a devastating liver disease.



Summary:

Alcoholic hepatitis is an important stage in the overall spectrum of alcoholic liver injury. Multiple histologic and biochemical studies have confirmed the role of an inflammatory cascade

as the basis of its pathophysiology, with TNF-α, IL-1, IL-6, and IL-8 having been identified as the most common cytokines involved. As such, most accepted treatment regimens and future therapeutic interventions are aimed at correcting this inflammatory process. Although corticosteroids represent an effective treatment for many patients with severe acute alcoholic hepatitis (Maddrey DF > 32) without contraindications to corticosteroids, other novel treatments may improve our success in preventing both short term mortality and long-term development of advanced liver disease including cirrhosis in these patients.

The most common causes of mortality are hepatorenal syndrome, gastrointestinal bleeding, and sepsis. Potential reasons for failure of therapy are concurrent hepatic disease, significant fibrosis or cirrhosis, multiple medical comorbidities, and development of complications related to medical therapy. After survival of acute alcoholic hepatitis, alcohol cessation is the cornerstone of long-term survival.

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