ALCOHOL-INDUCED LIVER DISEASE

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The chain of events that culminates in alcohol-induced liver disease fascinates clinicians and clinical investigators.[1-4] Excessive use of alcohol remains the most important cause of cirrhosis in the Western world and is a leading cause of death and mortality in individuals in mid-life. Alcohol-induced liver disorders present in many disguises and combinations.

The most important alcohol-induced intermediate injury on the path to cirrhosis is designated as alcoholic hepatitis which is a necrotizing, toxic process. Cellular injury develops predominantly as a consequence of the direct cellular toxicity of alcohol [1-5], although there are undoubtedly important contributions from the often-associated nutritional deficiencies in determining the type, rate of progression and extent of injury.[6-10] In addition to toxic effects to hepatocytes, alcohol and its metabolites (especially acetaldehyde) are important in injury to many other cells and in the stimulation of fibrogenesis.

Several aspects of alcohol-induced liver injury are worthy of special note, focusing on what is known with regard to specific cellular and subcellular abnormalities and how these might be important in promoting the progression of the liver injury towards cirrhosis. In addition, a number of therapeutic approaches which have been suggested to be effective in reducing the number of early deaths from alcoholic hepatitis and in some situations possibly preventing the progression of the injury to cirrhosis will be discussed.

PATHOGENESIS OF ALCOHOLIC HEPATITIS

The principal cause of alcohol-induced liver injury is cellular toxicity resulting from acetaldehyde which is produced from ethanol predominantly by the enzyme alcohol dehydrogenase.[1-5] Recognition that acetaldehyde is the most important toxin has led to studies as to how damage occurs and has fostered searches for ways to limit production of acetaldehyde, speed its elimination, or minimize its effects. Acetaldehyde is a highly toxic and reactive intermediate. Among its effects are binding to phospholipids in membranes and formation of adducts with components of cell membranes.[5]

A generation ago many clinicians and investigators believed that alcohol ingestion led to liver disease in large measure because of the often-associated nutritional deficiencies.[6] Subsequently, important observations established a dose-related toxicity of alcohol and its derivatives which initiates the series of events that leads to cirrhosis.[3,4] During the past decade, there has been renewed interest in a contributory role of deficiencies of dietary proteins, calories, and vitamins in the pathogenesis of alcohol-induced liver injury.[7-10]

Major efforts have been undertaken to determine the amount of alcohol that must be ingested to cause liver injury.[11-14] These studies are all beset by the daunting problems in obtaining an accurate history of how much alcohol has been ingested and for how long.[15] In addition, there appear to be other factors that determine whether, and to what extent, an individual chronically ingesting alcohol will develop liver injury. Epidemiologic studies in alcoholic patients indicate that only approximately 1 in 12 chronic alcoholics develop cirrhosis suggesting that there must be many other factors which affect the likelihood that cirrhosis will develop.[3,13,14]

There is increasing scientific support that alcoholism is at least in part inherited.[16] Clinicians have long known that taking a family history in a patient who is an alcoholic with or without alcoholic-induced liver disease often yields information that other members are affected. The idea of an alcohol dose response curve in causing liver injury only gets us so far. Of particular importance to hepatologists is the additional question of whether the likelihood of developing liver injury from alcohol is influenced by heredity. The observation that only one in twelve alcoholics develops evidence of severe liver injury, while interesting, can be turned around to stimulate consideration as to why other heavy users do not develop tissue damage. Inherited differences in preference (even need) for alcohol, metabolism by isoenzymes, and altered responses to metabolic products of alcohol all offer areas for study.[16] One possibility is that specific metabolic products resulting from metabolism by variants of alcohol dehydrogenase may variably cause injury.[17]

Clinicians around the world are convinced that females are at greater risk of developing alcohol-induced liver disease than are males even when such factors as body weight and amount of alcohol ingested are considered.[18-20] There is some evidence that females may have relatively less alcohol dehydrogenase in the gastric mucosa, thereby allowing more of a given amount of alcohol to reach the liver. [4] It has been suggested that metabolism of alcohol by gastric alcohol dehydrogenase affects the concentration of alcohol absorbed into the portal venous system. The initial observations need to be further evaluated and their importance confirmed. We should recall that drug-induced liver injuries from many agents appear to be more often and more fully expressed in females.

Factors that might identify individuals susceptible to the development of alcohol-induced injury have been sought with studies directed towards seeking both characteristic HLA patterns and biochemical abnormalities.[16] Also, there have been studies of the rates of metabolism of alcohol and the characteristics of the various enzymes involved in metabolism of alcohol.[16,17] However, thus far there are no conclusive data that reliably identify a susceptible group.

In addition there have been efforts to identify coexistent factors that may affect the rapidity of onset or progression of injury.[14] Patients who are obese may be at increased risk although no mechanism for progression has been suggested.[21] Various

immunologic abnormalities have been found in chronic alcoholics, suggesting that altered immunologic responses may have a role in the initiation or perpetuation of the liver injury.[22-24] Acetaldehyde derived from ethanol readily forms adducts with components of hepatocyte membranes, and these adducts may serve as an antigenic stimuli contributing to injury. In addition, acetaldehyde adducts may attract polymorphonuclear cells. The production of free radicals by invading cells attracted to the neoantigens may cause damage.[25] It has been suggested that Mallory's hyaline, which is a coalescence of intermediate filaments within the hepatocyte, may serve as a target for immunologic reactions.[26]

Attention has been directed toward the effects of malnutrition on the immune system and on factors that promote increased susceptibility to infection.[9,10] In addition, chronic alcohol ingestion impairs the ability of the liver to regenerate, although the mechanism(s) of inhibition is (are) not well-characterized.[27]

WHAT TRIGGERS THE ONSET OF LIVER INJURY IN A PATIENT WHO IS A CHRONIC ALCOHOLIC?

Surely, there is more than just duration of heavy alcohol use that leads to the onset of liver injury. Changes in nutrition or superimposition of some other disease process may tip the scales.

There has been much interest in, and investigation of, the role of co-existent viral infections in initiating or worsening underlying alcohol-induced liver injury. An interaction between alcohol-induced liver disease and concomitant chronic viral hepatitis has been suggested. There is evidence that patients who ingest large amounts of alcohol and who also have chronic viral hepatitis are more likely to progress to cirrhosis than is an individual with only one of these conditions. The situation with hepatitis C is especially pertinent since this is a common disease throughout the Western world.[28-31] Studies have shown that patients with alcohol-induced cirrhosis have evidence of concomitant chronic hepatitis C in 30 to 40%.[31] The additive nature of the injuries in these individuals may promote the progression to cirrhosis. Furthermore, there are reports which indicate that chronic alcoholics who have ongoing hepatitis B infection are far more likely to develop progressive liver disease that leads to cirrhosis and portal hypertension than are chronic alcoholics who do not have chronic hepatitis B.[32-35] Possibly concurrent or former hepatitis B infection serves as an additive insult to the liver. The intriguing possibilities of viral/toxin interactions need to be further explored.

WHAT ARE THE ROLES OF CYTOKINES IN THE PATHOGENESIS OF ALCOHOL-INDUCED LIVER INJURY?

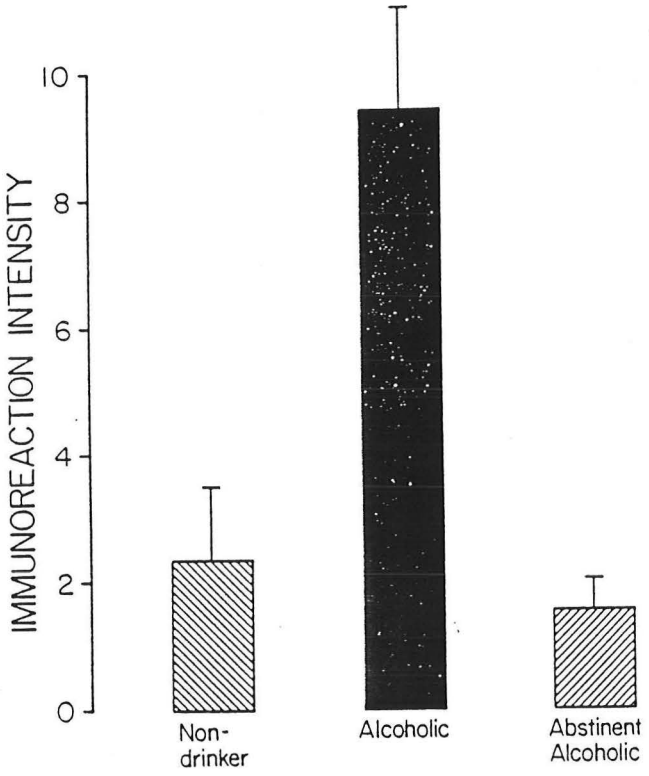
The effects of various cytokines have been studied to determine whether these have a role in promoting liver disease in a chronic alcoholic patient.[36] Exposure to endotoxin has been shown to promote liver damage.[37] Kupffer cells have a greater capacity than other reticuloendothelial cells such as peritoneal macrophages for uptake of endotoxin.[38,39] Endotoxin may affect the hepatocyte directly as a toxin or indirectly through release of additional mediators of injury such as superoxide and tumor necrosis factor (TNF) from Kupffer cells.

The identification and definition of cytokines has been an active, productive, and confusing field.[36-47] Various cytokines are likely of great importance in the pathogenesis of alcohol-induced liver disease. Tumor necrosis factor (TNF), IL-1, IL-6, the transforming growth factors (TGF alpha and beta) and platelet derived growth factor (PDGF), all seem to be of importance in promoting injury. Cytokines may reinforce cellular injury and promote the transformation of lipocytes to fibroblasts leading to collagen production. IL-8 appears to have an important role as a chemoattractant of polymorphonuclear cells.[47] Issues which need definition include to what degree is an alcoholic-induced liver injury augmented by the effects of one or more cytokines. As we learn more in these areas, newer therapies directed towards ways to block the production of specific cytokines or to block the effects of these agents at a cellular level may become relevant. Correlation of serum levels of specific cytokines (e.g. IL-6 and TNF) may be useful predictors of outcome in patients with alcohol-induced liver disease.[36,43-47] Cytokines released by Kupffer cells may also affect protein synthesis by the hepatocyte.[48]

The Interaction of Alcohol and Acetaminophen

The adverse hepatotoxic effects of therapeutic drugs may be important in causing an acute liver injury in a chronic alcoholic or in accelerating the progression of alcohol-induced liver injury.[49,50] The best studied of these potentially toxic drugs is acetaminophen. Chronic users of alcohol have induction of a specific subtype of cytochrome P-450IIE1, which also is the P450 subtype involved in the metabolism of alcohol.[51] Alcohol-related induction of P-450IIE1 subtype may lead to an increased rate of conversion of acetaminophen to a toxic intermediate. Therefore, the toxic metabolite may be present in dangerous quantities even when the dose of acetaminophen ingested has been relatively modest (3-6 g/day) and was not taken with suicidal intent.[49,50] Glutathione is the major hepatoprotectant guarding against the effects of toxic intermediates of acetaminophen. In normal man acetaminophen intermediates are bound by glutathione and excreted in urine as mercapturic acid. An alcohol-related decrease in the rate of synthesis or glutathione is another factor

promoting acetaminophen intoxication in a patient who is a chronic user of alcohol.[52,53]



Hepatic P4502E1 levels in alcoholics and non-drinkers. P4502E1 was quantitated by scanning of western blots of percutaneous liver biopsies, using anti-2E1 antibodies. (51)

CLINICAL MANIFESTATIONS OF ALCOHOLIC HEPATITIS

There is a broad spectrum of clinical manifestations of alcoholic-induced liver disease ranging from individuals with a few or minimal symptoms to those who have life-threatening fulminant liver injury.[1,2] There is often little correlation -- occasionally even considerable dissociation -- between the apparent severity of injury based on the clinical findings and those found on liver biopsy. Patients with severe alcoholic hepatitis may have jaundice, ascites, coagulopathy and hepatic encephalopathy. An additional subgroup of patients has a predominantly cholestatic illness that is clinically similar to that found in patients with bile duct obstruction.[54,55] Alcoholic hepatitis is

often found superimposed on already established cirrhosis, and the clinical manifestations result both from acute alcoholic hepatitis and from problems arising as a complication of cirrhosis.

Alcoholic hepatitis is considered at least partially reversible, whereas the dose-related fatty infiltration caused by alcohol is usually largely reversible. At the stage of alcoholic hepatitis even when there is early fibrosis, the possibility exists that some (if not most) of the injury is reversible. The progression of alcohol-induced injury is not an orderly one. Many patients have co-existence of fatty liver, alcoholic hepatitis, and cirrhosis.

Percutaneous liver biopsy is useful in the evaluation of the chronic alcoholic patient in determining the stage of the illness and providing a guide to prognosis.[56,57] In addition, liver biopsy may provide information of associated disorders such as iron overload, chronic viral hepatitis, and granulomatous inflammation. Liver biopsy remains important in order to assess the relative contributions of fixed liver damage (cirrhosis) as compared with the partially reversible liver damage (alcoholic hepatitis).

LABORATORY EVALUATION OF ALCOHOLIC LIVER DISEASE

The diagnosis of alcoholic hepatitis -- indeed of any alcohol-induced liver disease -- requires consideration in any patient in whom there is history of regular use of alcohol.[1,2] Confirmation of the diagnosis and assessment of the extent of injury is established by performing a liver biopsy. There is no single biochemical test that has proven sufficiently helpful to enable the presence of alcohol-induced injury to be established with confidence. A non-invasive test that would confidently enable the diagnosis to be made without need for liver biopsy would be most useful. Unfortunately, no such test is yet available. The usual biochemical tests of the liver are of scant value in detecting the presence of alcohol-induced injury or in estimating prognosis except in patients with severe disease. An elevated gamma-glutamyltranspeptidase level is often found in patients who have been drinking relatively modest amounts of alcohol, and the extent of the elevation does not correlate with the presence or magnitude of the extent of tissue damage. The greater elevation of AST than of ALT in alcohol-induced injury is of interest; however, the levels of these enzymes do not correlate with the extent of injury.[58] Furthermore, tests for the serum level of type-III procollagen peptides and laminin have been evaluated in patients with alcohol-induced liver disease.[59] Elevated serum levels of type-III procollagen peptide are usually found in patients with alcoholic hepatitis; however, similar elevations are found in patients with other types of alcohol-related diseases.

Imaging studies of the liver have been of limited value in the evaluation of alcoholic-induced liver disease. Computed tomography (CT) and magnetic resonance

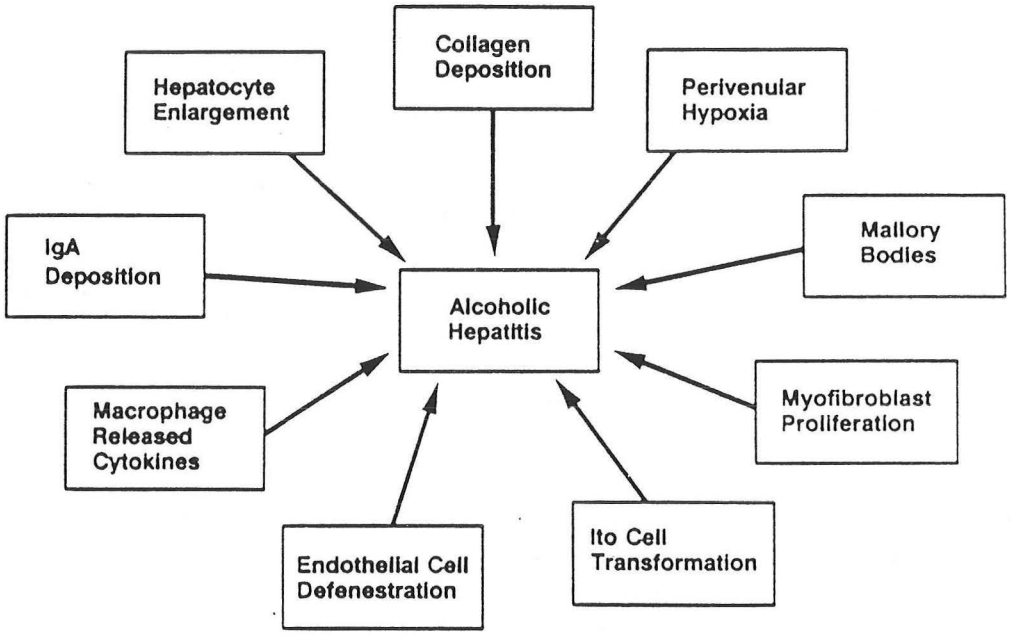
imaging (MRI) readily distinguish a normal liver or minimal fatty change from advanced cirrhosis but are not reliable in distinguishing fatty liver from alcoholic hepatitis. Technetium liver scans are of scant value in detecting early injury.

HISTOLOGIC FEATURES OF ALCOHOLIC HEPATITIS

Which of the several histologic manifestations of alcohol-induced liver disease are predictive of progression to cirrhosis?

One reason we biopsy the liver in a patient with alcohol-induced liver injury is to determine the extent and type of damage.[56] Even with a liver biopsy, we can only make a guess as to the extent of reversible injury. What we are looking for are clues which indicate the process is moving downhill. Undoubtedly, the extent and activity of active and established fibrosis is important.[60,61] Alcohol and its products transform hepatocytes from well-organized, functioning units to somewhat isolated cells with disrupted communications both internally and to the extracellular environment. Nutrients have trouble getting to and through the cell surface as the result of smaller openings between endothelial cells (defenestration) and the baffles presented by accumulation of collagens and other proteins in the space of Disse. At the cell surface, the membrane is disorganized and within the cell multiple hostile microenvironments are found. Variable oxygen availability, pH changes, toxic metabolic products, a decreased pool of mitochondrial glutathione, and damaged microfilaments needed to hold the organelles in place all contribute to the chaos.[1,2,56] Which of these processes signals irreversible injury continues to be an area of active investigation. The cumulative effects of these injuries plus an impaired ability to regenerate damaged cells determines to a large extent the clinical manifestations and the likelihood of a successful outcome even if the patient stops the use of alcohol.

For years it had been concluded that alcoholic hepatitis is a necessary step in the development of alcohol-induced cirrhosis.[1,2] Studies, especially those from Japan, have indicated that in some patients alcohol may stimulate the production of fibrosis and cirrhosis without requiring alcoholic hepatitis as an intermediate lesion.[61] However, sequential liver biopsy studies from the United States and Europe have emphasized the pivotal role of the necrotizing lesion alcoholic hepatitis as the most important precursor lesion in the development of cirrhosis.[1,2]



There are several rather specific cellular and subcellular alterations in patients with alcoholic hepatitis.[62,63] The problem of evaluating the prognostic value of any given subcellular alteration is to determine whether the alteration is itself predictive of a progressive course or just another non-specific result of damage. Characteristically, there is cell necrosis. Inflammation may be scant or plentiful. If inflammation is present, polymorphonuclear cells are usually the predominant infiltrating cells. Often there is an admixture of infiltration of lymphocytes.

Mallory bodies are intracellular eosinophilic inclusions which are located predominantly around the nucleus and are often found in patients with active alcohol-induced liver disease.[64] Mallory bodies represent masses of intermediate filaments.[63-65] Acetaldehyde-induced injury of intermediate filaments may be important in promoting the formation of Mallory bodies. The presence of Mallory bodies in a patient with alcoholic hepatitis suggests a more serious disease than is present in an alcoholic patient who does not have these alterations.[66] Cells containing Mallory

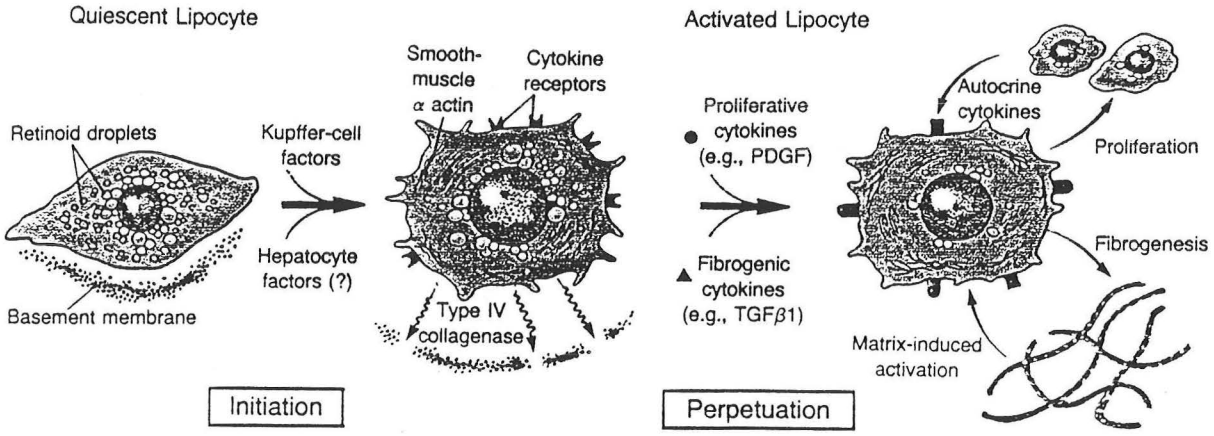
bodies are usually ringed with polymorphonuclear cells indicating imminent cell death. Some studies suggest that immunologic reactions directed against the Mallory's alcoholic hyaline may be important in the pathogenesis of alcohol-induced liver injury.[24]

Much attention has been directed to alcohol-induced changes in the cells lining the hepatic sinusoid and the effects these changes have on sinusoidal blood flow and orderly exchange of constituents between the sinusoids and hepatocytes.[60] In normal man, the area between the hepatocyte membrane and the endothelial cells is designated the space of Disse. Changes in this region are important in determining if free exchanges of constituents from blood to hepatocytes are able to occur. There is evidence of deposition of several types of collagen, non-collagenous proteins, and IgA in the space of Disse in patients with alcohol-induced liver injury.[1-4] Each of these depositions serve to build a barrier to free exchange thereby isolating the hepatocyte from the portal blood. A further consequence of the development of barriers to access in the space of Disse include increase of pressure within the sinusoid.

Hepatocytes are considerably and irregularly enlarged in patients with alcohol-induced liver injury.[67] Enlargement of hepatocytes results from an increase in intracellular lipids and also secretory proteins whose transport from the hepatocyte has been inhibited. The significance of enlargement of the hepatocyte in the pathogenesis of portal hypertension in patients with alcohol-induced liver disease is uncertain.[68-70]

Acetaldehyde has profound effects on the processes leading to orderly production of proteins and their movement to sites for discharge into the blood.[71] Alcohol-related injury of the Golgi apparatus and disruption of the endoplastic reticulum contributes to impairment of secretion of proteins.

Characteristically there is increased collagen in the space of Disse in patients with alcoholic hepatitis.[60,72] The deposition of collagen results from increased fibroblast activity. Deposition of collagen leads to a barrier between the free exchange from blood in the sinusoid and the hepatocyte and may cause the open sinusoidal system to become closed (capillarization) and hence contribute to portal hypertension. In addition, the fat-laden sinusoidal lining cells (Ito cells) are transformed by exposure to alcohol to become fibroblasts.[60,73-76] The Ito cell loses fat granules and develops an endoplasmic reticulum (transitional cells) as part of the transformation to a fibroblast. Lipocytes have also been shown to be a major source of proteoglycans.[77]



Model of Lipocyte Activation

Current evidence suggests that the process of lipocyte activation is a cascade occurring in at least two stages. Initiation is characterized by cellular enlargement, the expression of smooth-muscle actin, and the induction of cytokine receptors; initiating stimuli may include as yet uncharacterized paracrine factors from Kupffer cells, hepatocytes, or both. Initiation may also include the early disruption of the extracellular matrix through the secretion by lipocytes of type IV collagenase, leading to its eventual replacement with fibril-forming collagens. Perpetuation reflects the subsequent effects of proliferative and fibrogenic cytokines on the cells and the additional stimulation in response to the altered extracellular matrix. Adapted from Friedman with the permission of the publisher. PDGF denotes platelet-derived growth factor, and TGF B1 transforming growth factor B1.(60)

It appears that there is more rapid progression towards cirrhosis in individuals in whom there is evidence excessive collagen deposition around the terminal hepatic venule (perivenular) region; zone III).[78-80] Similar findings were present in an animal model of alcohol-induced liver injury in which baboons who had perivenular deposition of collagen early in the course of forced alcohol-induced injury were more likely to progress to cirrhosis.[2,4,79]

An additional finding in alcoholic hepatitis is the increased numbers of myofibroblasts in zone III of the hepatic lobule.[81] These cells characteristically contain microfilaments and alpha-actin. Therefore, in zone III, proliferation of myofibroblasts and transformation of Ito cells may both be important in the production of excessive collagen and in promoting progression to cirrhosis.

Another finding that may relate to the development of a barrier between the blood and the plasma is the fusing of endothelial cells which leads to loss of porosity.[82-84] Normally, there are gaps (fenestra) between the sinusoidal endothelial cells which provide access of plasma within the sinusoid to the space of Disse. Electron microscopic studies in patients with alcoholic hepatitis have suggested that endothelial defenestration is a prominent feature especially likely to be found in zone III, and that the decrease in porosity of endothelial cells may further contribute to closure of the sinusoidal system.

In addition to defenestration of endothelial cells, a basal lamina may be formed underlying the endothelial cells, adding to the barrier to free exchange between blood in the sinusoid and the plasma membrane of the hepatocyte.[85-87] The basal lamina is extracellular and contains various proteins including type IV collagen and fibronectin.

The deposition of IgA along the plasma membrane may also increase the barrier affecting transfer from blood to hepatocytes.[88,89] Elevated serum IgA levels are characteristically found in patients with alcoholic hepatitis and cirrhosis.[90]
It has been suggested that IgA triggers the release of tumor necrosis factor by monocytes in patients with alcohol-induced injury.[91]

Much emphasis has been placed in recent years on the relative zonal distribution of alcohol-induced liver injury.[1-4,62,75,92-94] The most significant alcohol-induced injuries occur in zone III (perivenular region), which is furthest from the entry site for oxygen into the hepatic lobule. There is evidence that zone III receives relatively less oxygen in patients with alcohol-induced liver disease in whom there often is anemia as well as an alcohol-induced generalized hypermetabolic state which leads to an increased need for oxygen.[1-3,95,96] Other characteristics of zone III include a heightened concentration of cytochrome P450 enzymes and alcohol dehydrogenase relative to other parts of the lobule. Therefore, relatively more acetaldehyde is produced in zone III leading to more injury in this vulnerable region.

MANAGEMENT OF ALCOHOLIC HEPATITIS

Are there any therapies other than abstinence and a good diet which may be helpful?

For some patients there is little hope that any treatment will make a difference. Undoubtedly, there is a point beyond which it is just too late to achieve any benefit from abstinence. However, even an extensively remodeled cirrhotic liver may hold on a long time if the assaults cease. We need to develop more specific ways to regulate fibrogenesis and to learn more regarding whether there is a contribution of antibodies to acetaldehyde adducts to progression of injury. It is not known if these antibodies are all short-lived and of little consequence or if the adducts have an important

ongoing role in promoting the development of alcohol-induced liver injury. The answer for now remains maybe. Several investigators have reported that the titers of the antibodies correlate directly with the extent of injury. However, it is uncertain what vital function is impaired by the antibody.

Whether supplemental vitamins affect recovery from liver damage is also unknown. Clearly use of excessive vitamin A may promote additional injury.[97] A role for supplemental polyunsaturated lecithin which has been suggested to decrease the rate of production of collagen by Ito cells exposed to alcohol and to prevent the progression of alcohol-induced injury in the baboon must be further studied before being widely used.[98,99] We need better information to decide if and when a diet is "good."

Once a patient has developed clinical and histologic evidence of alcoholic hepatitis, there is no question that a potentially life-threatening liver disease is present.[100] By this time in the illness, the moment is past during which it is likely that abstinence from alcohol will lead to complete restoration of a normal liver. In fact, many of the patients included within the broad spectrum of alcoholic hepatitis have already moved beyond a considerably blurred line and have an active cirrhosis.

When we consider treatment of alcoholic hepatitis, we need to consider several issues must be considered:

1. Is it likely that the patient already has far advanced cirrhosis with another wave of alcoholic-induced necrosis or are there elements of reversible disease?
2. Is the patient bereft of defenses? If so, the major issues may relate to the need for support or treatment of co-existing problems of gastrointestinal bleeding, infection, ascites, or encephalopathy.
3. Are there co-existing disorders such as iron overload or chronic viral hepatitis that must also be considered when planning treatment? A further consideration in a patient with an acute illness, especially one in when there is a marked elevation in serum aminotransferase levels, is that the patient may have a superimposed injury from the concomitant use of acetaminophen.[49,50]

There have been two decades of clinical trials evaluating several drugs in patients with alcoholic hepatitis.[1,2,100] Goals of these trials have included, in some, reduction of immediate short-term mortality, and in others, interruption of processes that appear likely to lead to cirrhosis.

It remains a safe conclusion that for the great majority of patients with alcoholic hepatitis, there is no definite therapy that will do more than can be achieved by abstinence and a good diet administered in a supportive environment by medical

personnel aware of, and ready to respond to, associated complications. However, hope springs eternal that in some way we can intervene to the patient's benefit. That little progress has been made has not resulted from a lack of trying.

The important factors in the management of patients with acute alcohol-induced liver injury include supportive care emphasizing abstinence from alcohol, correction of nutritional deficiencies, and treatment of associated problems such as infections and pancreatitis. For patients with mild alcohol-induced liver disease, abstinence and general support often lead to gradual restitution of the liver towards normal. For extremely ill patients with hepatocellular decompensation, bleeding disorders, and encephalopathy, mortality is high despite support. The patient with alcoholic hepatitis who does not yet have irreversible cirrhosis is at a pivotal stage. There is fibrosis and remodelling of the liver occurring in a setting of disrupted production of proteins, impaired intracellular trafficking and secretion, and impaired exchange of constituents into and out of cells.

Several experimental therapies have been used in an attempt to stabilize the patients with acute alcoholic hepatitis and reduce the short-term mortality from the acute disease and, hopefully, prevent the development of cirrhosis.[1,2,100] These have included the use of corticosteroids because of the established anti-inflammatory and anti-fibrotic effects of these agents; propylthiouracil to decrease the hypermetabolic state and reduce zone III (perivenular) ischemic injury; insulin and glucagon to stimulate hepatic regeneration; and anabolic-androgenic steroids to promote an anabolic state.

There are few areas of agreement about which (or whether) patients with alcohol-induced liver disease should receive one or more of these agents.

CORTICOSTEROID THERAPY

Corticosteroids have been extensively evaluated in several randomized double-blind trials in patients with alcoholic hepatitis [1-3,100,101-112], based in part on the findings of cell necrosis, hepatic inflammation, and evidence of excessive production and deposition of collagen. In addition, corticosteroids may blunt any immunologic processes that may be important in initiation or perpetuation of injury. Acetaldehyde forms adducts with macromolecules in the hepatocyte which apparently serve as neoantigens eliciting an immune response.[24] Furthermore, the evidence that several cytokines (for example TNF) may play a role in the pathogenesis of alcoholic hepatitis provides a further rationale for the use of corticosteroids with hopes of inhibiting their production or minimizing the effects.[36]

Corticosteroids also stimulate the production of albumin and inhibit the production of collagen types I and IV through effects on the genes controlling the

production of these proteins.[113-115] There is evidence that these agents increase albumin production by an effect on the albumin gene which leads to an increase in the mRNA for albumin and that corticosteroid therapy decreases production of type I procollagen by a suppressive effect on the collagen type I gene with a decrease in the mRNA for collagen type I.[113,115] Corticosteroid inhibition of collagen synthesis may blunt some of the acetaldehyde-induced increase in procollagen type I and fibronectin gene transcription which has been reported to occur in rat lipocytes.[116]

Although the exact mechanisms suggesting a favorable corticosteroid effect are not understood, there are ample possibilities justifying therapeutic trials. Of course, the established often serious side effects of corticosteroid therapy, including induction of glucose intolerance and further impairment of host defenses against infection, are important considerations whenever corticosteroids are given.

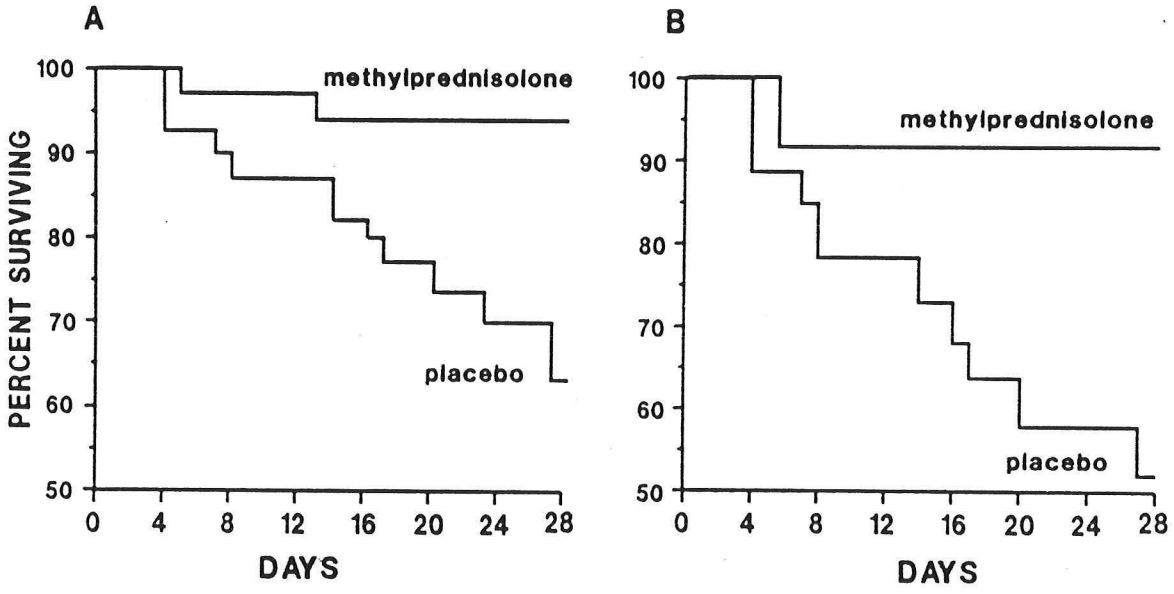
Some studies of corticosteroid therapy have shown an apparently favorable outcome in short-term mortality in patients with severe alcoholic hepatitis.[101-104,112] However, others have shown no benefit.[105-111]

Some areas of agreement regarding what the collective results show seem to be emerging. The first major corticosteroid trial in alcoholic hepatitis study was from the University of North Carolina.[103] Fourteen patients with severe alcoholic hepatitis and hepatitis encephalopathy were included. All six patients who received a placebo died, whereas only one of eight who received prednisolone died. A subsequent study by this group confirmed the initial results in a trial in which all patients received supplemental calories to ensure an intake of at least 1600 kCal/d.[104] All seven patients who received dietary supplement alone died, whereas only two of the seven patients who received corticosteroid therapy did not live until the end of the trial.

In 1978, we reported favorable results of corticosteroids for survival in patients who were severely ill with alcoholic hepatitis.[102] An adverse prognosis correlated with hepatic encephalopathy, prolongation of the prothrombin time, and a serum bilirubin level greater than 10 mg/dl. In 55 patients with alcoholic hepatitis treated for 28-32 days, we found that prednisolone therapy favorably influenced mortality with six of the 24 patients who received placebo dying during the study compared to only one of the 24 patients who received prednisolone. We also found that the presence of hepatic encephalopathy was an important predictor of a poor outcome. In the subgroup of severely ill patients who had alcoholic hepatitis and hepatic encephalopathy, six of 18 (33%) who received placebo died as compared to only one of 13 (8%) who received corticosteroids. A discriminant function (DF) was derived by stepwise regression which took into account the prothrombin time and serum bilirubin. Use of this DF in its initial form was highly predictive of severe disease and in severely ill patients, there was a significant improvement in survival for those who received corticosteroid therapy.

Discriminant function (DF) = 4.6 X prothrombin time (sec.) + serum bilirubin

A DF greater than 92 indicated a poor prognosis. Armed with the DF as a measure of severity, a multicenter trial of treatment was carried out to confirm the value of the DF as a predictor of severity and to seek additional information as to whether corticosteroid therapy was effective. [102] Methylprednisolone (32 mg/day) or placebo was administered in a randomized double-blind trial in which only patients who had severe alcoholic hepatitis as defined by the DF and/or the presence of hepatic encephalopathy were entered. To enable use in multiple centers, the DF was modified to: DF = 4.6 x (prothrombin time of the patient minus the control prothrombin time) plus the serum bilirubin. A DF value of 32 or more indicated severe disease. Sixty-six patients met the criteria, and 59 patients completed the study. Of the 31 patients receiving placebo, 35% died within the 28-day study interval, compared with 2 (6%) deaths of 35 methylprednisolone-treated patients (P = 0.006). When analyzed for survival in relation to the presence of spontaneous hepatic encephalopathy, 9 of 19 placebo patients died (47%), as compared with (7%) death among 14 methylprednisolone-treated patients (P = 0.002).

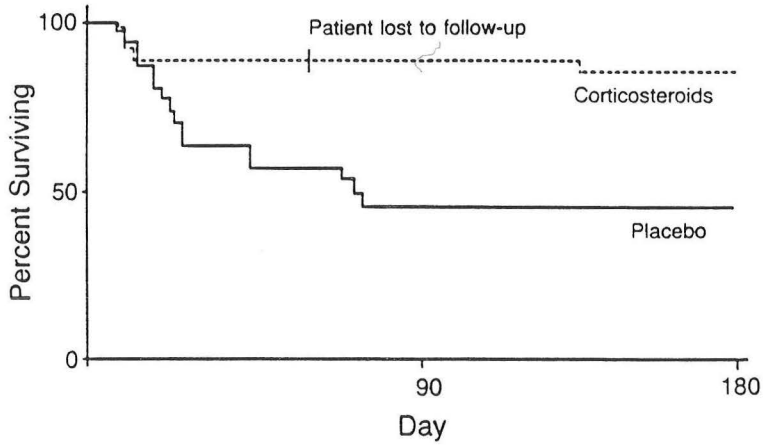


A. Cumulative survival in methylprednisolone and placebo recipients (P = 0.0049). B. Cumulative survival in methylprednisolone and placebo recipients with hepatic encephalopathy at study entry (P = 0.025).(102)

These four favorable studies were reported during two decades in which a number of other investigators found no favorable effects at all.[105-111] Despite many discussions and debates, we do not have answers to explain the discrepancies in the outcomes of the trials. Part of the explanation may be in the exclusion criteria. Patients with recent gastrointestinal bleeding or evidence of infection, both major causes of mortality in such patients, were excluded in all the trials reporting favorable results.

Next came the era of the metanalyses of the studies. [117,118] In an assessment of the results of eleven randomized trials chosen for reasonable comparability, a protective efficacy of 37% (95% confidence interval 20% to 50%) was attributed to the use of corticosteroids.[117] These investigators concluded that corticosteroids did not have a demonstrable protective effect unless the patient had hepatic encephalopathy. Other metanalyses reached similar conclusions indicating support for the concept that a subgroup of patients who benefit from corticosteroids had been found.[117,118]

One further multicenter randomized trial which supports the use of prednisolone in the treatment of alcoholic hepatitis has been reported from France (19%).[112] In this trial, patients were enrolled if there was evidence of hepatic encephalopathy or the DF exceeded 32. Treatment was given for 28 days. By the 66th day after randomization, sixteen of 29 (55%) placebo recipients had died as compared to four deaths in 32 (13%) patients treated with prednisolone (P = 0.001). The survival advantage for prednisolone persisted after stratification for the presence of encephalopathy.



Survival in 61 patients randomly assigned to receive corticosteroid therapy or placebo. Survival rates at six months were 84 ± 6 percent in the corticosteroid group and 45 ± 9 percent in the placebo group (P = 0.002).(112)

Therefore, may well be a small subgroup of patients with severe alcoholic hepatitis in whom the disease is severe enough to cause early death in the acute illness and yet not so severe as to preclude any possible effect of therapy. It is this subgroup who may benefit from treatment. Whether corticosteroids make any difference in long-term survival in alcoholic hepatitis and whether long-term treatment might interfere with the subsequent development of cirrhosis has not been fully evaluated.

PROPYLTHIOURACIL

Propylthiouracil therapy has been reported to be useful in alcohol-induced liver disease.[95,96,119] The evaluation of PTU was based in part on observations that the most severe alcohol-related injury is often in the zone III (perivenular) region and resembles ischemic injury.[1-4] It has been considered that PTU therapy may provide a way to protect the vulnerable zone III from the effects of hypoxia.

In a randomized trial in severe alcoholic liver disease, PTU led to a more rapid rate of normalization of a Complex Composite Clinical and Laboratory Index based on 17 components, eleven of which were clinical features and the rest laboratory variables.[119] No differences in survival were observed during the initial study, and follow-up liver biopsies were not performed. Treatment with PTU had no apparent effect in patients with either fatty liver or inactive cirrhosis.

In a second study from Toronto, PTU was compared with placebo in a trial involving 360 patients with alcoholic liver disease.[96] In PTU-treated patients there was a reduction in mortality at 2 years from 48% to 24.8% and a significant improvement in the Combined Clinical and Laboratory Index. There were no complications from PTU. There was no evidence of a treatment-induced hypothyroidism. However, these favorable results from PTU were not found in another double-blind controlled trial in patients with severe alcoholic hepatitis from Los Angeles.[120]

Therefore, as with corticosteroid therapy, there is evidence both supporting and refuting the use of PTU in patients with alcoholic liver disease.[95,96,119-121] Whether PTU will prove consistently effective in reducing the hypermetabolic state of the patient with alcoholic liver disease, thus limiting injury in zone III, is of great interest and potential importance.

ANABOLIC-ANDROGENIC STEROIDS

Anabolic-androgenic steroids have been used in alcoholic hepatitis to stimulate anabolism and promote hepatic regeneration.[122] There has been intermittent interest

for many years in the use of anabolic-androgenic steroids in the treatment of alcoholic-induced liver disease. Early studies suggested that these agents hastened the resolution of alcoholic-induced fatty liver.[123] However, a study of anabolic steroids in patients with decompensated alcoholic-induced liver disease reported no benefit and interest waned for two decades.[124]

In 1984 the possible role of anabolic-androgenic steroids was reconsidered in a multicenter VA cooperative trial in which there was evaluation of prednisolone, oxandrolone, and placebo therapies in patients with alcoholic hepatitis.[122] All patients were treated for 30 days with one of the agents. Patients were stratified into moderate or severe alcoholic hepatitis categories with the severe group defined as serum bilirubin greater than 5 mg per dl and prothrombin time greater than 4 seconds prolonged. Liver biopsy confirmation of the extent of injury was available in only 31.6% of the patients. There were no differences in survival for the three groups during the study. However, using a statistical method of conditional survival, there was a significant better survival at six months in those who had initially received oxandrolone (96.5%) compared to 80% for patients who had received placebo ($P = 0.02$). The method of analysis (conditional survival) was based on a requirement that a patient survive the acute phase of the illness in order to be considered for analysis in longer follow-up. No ready explanation for these somewhat puzzling findings were available and the results have not been subsequently confirmed.

In a multicenter randomized trial of long-term oral testosterone therapy from Denmark, there was no evidence that the drug was helpful and some evidence that these might have been an increase in mortality in treated patients.[126] In patients followed 8-62 months (median - 28 months), there were 33 deaths in the 134 (25%) patients receiving testosterone therapy (21%) compared to 18 deaths in 87 patients receiving placebo (21%). Fortunately, in an evaluation of all these trials, there is no reason to be concerned that use of these agents promoted the development of hepatocellular carcinoma. We have entered another phase of little enthusiasm for the use of anabolic-androgenic steroids.[127]

INSULIN AND GLUCAGON THERAPY

In many liver disorders it is well-established that following removal of the injurious agent, the liver will undergo a reparative process and effectively restore itself to health. The remarkable regenerative powers of the liver are well-documented and probably account for the rapid recovery which may occur after major injuries such as fulminant hepatitis or hepatic resection. Excessive use of alcohol impairs the ability of the liver to regenerate.[1-3,27] A number of stimulants to regeneration have been identified including insulin, glucagon, epidermal growth factor, glucocorticoids, and parathyroid and thyroid hormones.[128] Of these, infusions of insulin and glucagon

have been most widely studied with benefits seen in the promotion of recovery from murine hepatitis.

There are now four controlled trials of insulin and glucagon infusions in patients with severe alcoholic hepatitis.[129-132] All the trials were of three week duration with daily 12 hour infusions. The score of studies reporting favorable effects to those which showed no effects is tied at two each.

In the first trial, two groups of 25 patients were given either infusions of insulin and glucagon daily for three weeks or were placed in a placebo group.[129] The duration of the trial was three weeks. The results favored the treatment group with six of the 25 (24%) patients in the control group dying during the study compared to only two deaths in the 25 (8%) who received placebo. There were significant improvements in serum bilirubin and prothrombin levels in the treated patients. One patient in the insulin and glucagon treatment group died of hypoglycemia.

A second published trial also reported favorable results with fourteen of 33 (42%) control patients dying during a three week study compared to only five deaths in the 33 (15%) treated patients.[130] In this study it was also reported that those who received insulin and glucagon infusion had more rapid improvement in serum bilirubin, prothrombin and aminotransferase levels.

However, two additional trials have been reported which do not support the use of insulin and glucagon.[131-132] In a single center study, fifteen (35%) of 43 patients who received insulin and glucagon died within four weeks of randomization.[131] There were 14 (33%) deaths in 43 untreated controls. Hypoglycemia occurred in six of the patients receiving the infusions. When patients who survived the first four weeks were re-counted six months later, there were five additional deaths in those who had received insulin and glucagon infusions as compared to one additional death in a patient who had been in the control group. In addition, these investigators did not find treatment related improvement in any clinical or biochemical parameter. The negative results from the study were soon followed by the results from similarly discouraging multicenter randomized, single-blind trial.[132] Only 44 patients were enrolled before the trial was discontinued. Ten of 37 (27%) patients in the treatment group died within four weeks of beginning the study as compared to five deaths in the 35 (14%) control patients. Fortunately, there were no deaths attributed to hypoglycemia.

Therefore, we are left without a definite answer as regards a role for insulin and glucagon.[133] It stands to reason that stimulation of liver regeneration should help. I doubt insulin and glucagon infusions will prove to be the answer - hypoglycemia is too easy to induce and is too dangerous. There are also issues as to whether these stimulants of regeneration can be successfully taken up and used by injured cells. There is evidence that because of a defect in receptor-mediated endocytosis,

epidermal growth factor is poorly internalized in an animal model of alcoholic-induced liver injury.[134] The stimulant needs to get into a cell which is capable of responding in order to exert an effect.

Other Therapies

Clinicians and investigators readily recognize the multiple evidences of malnutrition often found in patients with alcoholic hepatitis and cirrhosis.[1-3,7,8,10] In earlier days an important role for malnutrition in promoting the development of alcoholic-induced liver disease was widely considered (and often accepted). Following the important studies which showed conclusively that much of alcoholic-induced toxicity was the result of direct toxicity (most likely from acetaldehyde), interest in the role of nutrition in the pathogenesis of alcoholic-induced liver injury waned. However, there have been several relooks at the roles of protein-calorie malnutrition and deficits in vitamins as promoting factors in the development of alcoholic hepatitis and cirrhosis.[7,8,10] Many patients with advanced alcoholic liver disease, especially those with hepatic encephalopathy, have an abnormal serum amino acid pattern characterized by a decrease in the level of branched chain amino acids and an increase in the aromatic amino acids.[135] Whether these abnormalities are important in the pathogenesis of hepatic encephalopathy remains unknown.

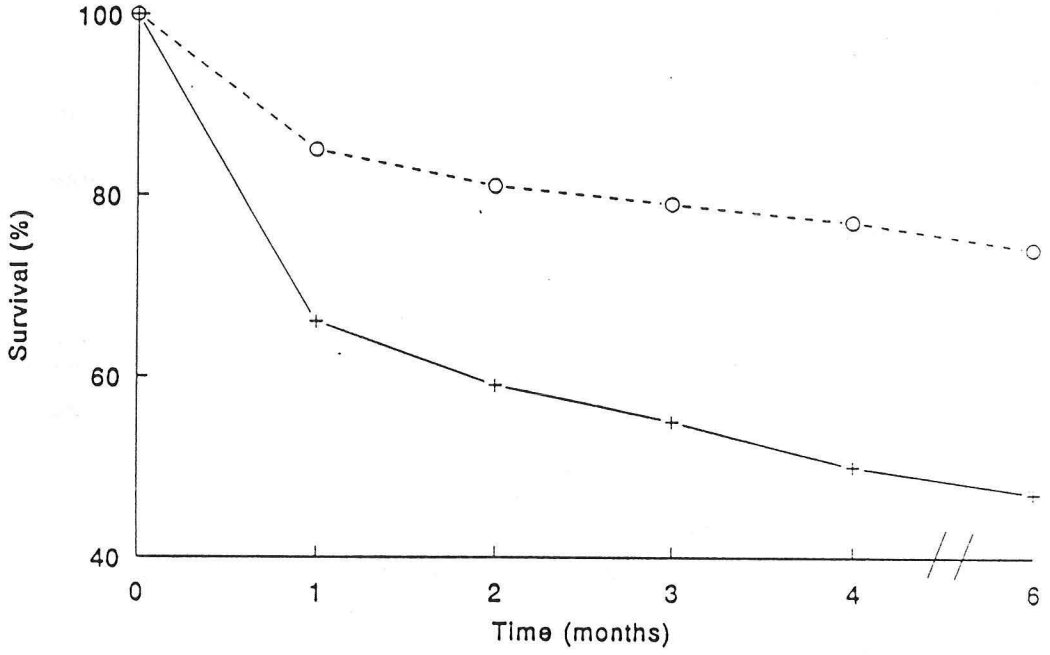
There have been several trials of infusions of amino acids as treatment for alcoholic hepatitis. An early study reported promising results.[136] There were only four deaths in 18 patients in a placebo group compared to no deaths in 17 patients who received a daily supplemental infusion of 70-85 grams amino acids a day. Quite remarkably, the patients tolerated the infusions well with no evidence that the amino acid infusions promoted the development of hepatic encephalopathy.

Subsequently other trials evaluating nutritional therapy in patients with alcoholic hepatitis have generally reported less favorable results.[137-141] In one, 64 patients were randomized to receive either 3 weeks of a controlled diet, diet supplemented with carbohydrate and protein, or a diet supplemented with branched-chain amino acids.[138] Those who were unable to take the diet orally were given the supplement by internal feeding tube or by infusion. There were no differences in survival results from the three groups. However, when mortality was evaluated related to nutritional status, it was concluded that those who were able to achieve a positive nitrogen balance did better. There was a 3.3% mortality in 30 patients who achieved positive nitrogen balance compared with a 58% mortality rate in 19 patients who remained in negative balance. Of course, one consideration is that getting better for whatever reason is likely associated with the development of better nutritional status.

In a multicenter trial, 28 patients received an infusion of 2 l/d of a solution of dextrose and amino acids (25.8 g/l) for one month and a comparable group of 26

patients received only infusions of dextrose.[141] Six patients in the treatment group (21%) died during the study compared to 5 deaths in those receiving the control infusions (19%). Cumulative two year survivals for the two groups were similar (42% for the treated group and 38% for the controls). Despite no evidence of a survival effect, there was ample evidence that the patients who received the infusions benefitted with better nitrogen balance and increases in serum albumin, prealbumin, transferrin and retinol binding protein levels. Evidences of the improved nutritional status appeared to persist well after completion of the course of therapy.

In a further large multicenter VA cooperative trial of patients with alcohol-induced liver disease, there was a definite association between the extent of protein-caloric malnutrition, the severity of the alcoholic liver disease, and survival.[8]



Six-month survival analyses of 273 patients with AH. Severity of the AH was effectively stratified on the basis of the level of jaundice (bilirubin [mg/dl] and coagulopathy (prothrombin time [sec]) using a DF (20) where DF = 4.6 (prothrombin time) + bilirubin. 0 = moderately severe AH, DF = 60 to 89; + = very severe AH, DF ≥ 90. Patients with moderately severe AH had significantly better 6-mo survival than did those with very severe AH ($p = 0.0001$; log-rank test).(8)

In a controlled trial of nutritional therapy, 40 patients were offered an oral diet containing 40 kCal per kg per day.[137] Twenty-five of the patients also received

supplemental parenteral nutrition of 40 kCal per kg per day using a central catheter. There were no differences in survival during the 28 day study. The patients who received the amino acid infusions had an overall decrease in serum bilirubin level ($p < 0.02$) and increases in serum transferrin, prealbumin and retinol-binding protein levels. However, these differences were not significant.

Additional studies evaluating fewer patients have shown no effects of infusions of amino acids on short-term survival.[7,140] However, rather consistently, patients receiving the infusions have had more rapid improvement in biochemical tests of the liver and show improvement in the level of serum albumin and other proteins manufactured by the liver. In a detailed metabolic study, 39 patients with moderate or severe alcoholic hepatitis were evaluated in a metabolic unit for 35 days.[142,143] The patients received one of four regimens: either a standard balanced diet plus multivitamins; the diet plus oxandrolone 20 mg orally four times a day; intravenous supplementation of 2 liters a day of 3.5% crystalline amino acids in 5% dextrose; or a combination of oxandrolone and multivitamin supplementation. All the patients survived. Those who received the nutritional supplements with or without oxandrolone had improved serum levels of albumin, transferrin, and a reduction in prothrombin time. In addition, the total lymphocyte count was higher in treated patients. There were also greater improvements in the rates of galactose and antipyrine metabolism in the treated patients. Those patients who received parenteral nutrition had increases in the serum levels of branched chain amino acids and a more favorable ratio of branched chain amino acid to aromatic amino acids.

Colchicine has been reported to be effective in promoting long-term survival in patients with cirrhosis, but a role remains to be demonstrated in the treatment of alcoholic hepatitis.[144] With other agents experience is limited; in some overall results have been disappointing despite early enthusiasm.[1,2,100] Undoubtedly, additional approaches to reduce cell necrosis, inhibit the production of fibrous tissue, enhance collagenase activity, alter immune processes, or minimize the effects of cytokines elaborated by stimulated cells will be introduced and studied.

LIVER TRANSPLANTATION IN THE TREATMENT OF ALCOHOL-INDUCED LIVER DISEASE

The considerable mortality in patients with decompensating alcohol-induced cirrhosis and increasingly favorable results with liver transplantation in patients who have a variety of decompensated liver diseases have led to evaluations and reevaluations of the role of liver transplantation in these patients.[145-151] The issues which have been considered as to whether patients with alcohol-induced liver disease should have equal access to livers for transplantation have been fraught with controversy and emotion. Early in the development of liver transplantation, the majority of the few patients with alcohol-induced injury who received a liver

transplantation procedure died.[147] It was decided by many centers that these patients were not suitable candidates for transplantation and should be excluded.

Several centers, however, pressed forward with liver transplantation in alcoholic patients and important reports from the University of Pittsburgh reported that individuals who had alcohol-induced liver disease had a survival which was similar to that found in patients who did not have a history of alcohol-induced injury.[145,146] Major debates began again. On the one hand, there are those who concluded that in light of the relatively small number of livers available for transplantation, it is not appropriate to use these livers for individuals who had alcohol-induced disease, thereby denying patients with other types of diseases an opportunity to have a transplantation.[151] The alternative argument is that since it has been established that alcoholism is a disease, there is no justification of denying a patient who has an alcohol-induced injury access to what may be a life saving procedure.[148,149] A number of ethicists have become involved in considering and the issue of what should be the weight given to a person's behavior in determining access to a scarce medical resource such as a donated liver.

There are practical issues to be considered even if it is decided that a history of alcohol abuse alone should not exclude a patient from consideration. It has been established that individuals who have a diagnosis of alcohol-induced liver disease and who have maintained a period of abstinence for longer than six months can expect to have an equally favorable outcome following liver transplantation as may a person with another type of disease.[147,148] However, many patients with alcohol-induced liver disease have additional major medical problems. These include cardiomyopathy, pancreatitis, neuropathy, and cerebral atrophy. Any of these conditions or the sepsis often associated with alcohol-induced liver disease would make a patient an unsuitable candidate for liver transplantation.

Most centers now proceed to consideration of transplantation in a person who has proven a dedication to abstinence and have undergone psychiatric evaluations which indicate that the individual is able to participate appropriately in making life decisions which will help insure graft survival.[147] Markers of social stability that have been found to be useful include a steady job, stable residence, a stable marriage (or its equivalent), demonstrated insight into the alcohol relationship to the disease and some evidence of commitment to a long term program of abstinence. Following psychiatric medical evaluations to look for alternative diseases, patients with alcohol-induced liver disease who survive these screens are considered as candidates.

A major issue is whether there should be a documented required interval of abstinence.[147,148] Some centers are proceeding to liver transplantation in individuals who have a relatively acute disease even when there is evidence of alcoholic hepatitis. However, most centers do not consider liver transplantation an appropriate treatment for an individual who has active or very recent alcohol abuse.

Therefore, the status today of liver transplantation for patients with alcohol-induced liver disease is that most centers will evaluate and accept some alcoholics. Selection standards vary greatly. Most require psychiatric evaluation and careful observation of the patient during the waiting period to insure that the individual does not return to drinking. If alcohol is found on spot testing during the pre-transplantation interval, the patient is deemed unreliable and candidacy is reconsidered and usually dropped.

Follow-up studies to look for evidence of recidivism have indicated that approximately 33% of these patients will return to alcohol use, however, only 10-15% return to abusive drinking.[148] The problems from returning to regular and excessive alcohol use are apparent and include the failure to take the necessary immunosuppressive medications, further impairment of the immune system by the alcoholism, which exposes the individual to additional infections, and the emotional effects of a patient who has failed to maintain abstinence on the transplantation team itself.

The general conclusion in 1994 is that liver transplantation should <u>not</u> be considered a treatment for active alcohol-induced liver disease. However, these are ongoing debates and there has been a shift in interest in considering transplantation in early disease.

Risks of Experimental Treatments for Alcoholic Hepatitis

Approach	Risk
Abstinence	None
Corticosteroids	Development of diabetes Promotion of gastrointestinal bleeding Increased susceptibility to infection
Propylthiouracil	Few risks recognized Might induce hypothyroidism
Insulin-Glucagon Infusions	Hypoglycemia
Anabolic-Androgenic Steroids	Long-term use may promote Hepatocellular carcinoma
Supplemental Nutritional Therapy	Risk of long-term indwelling infusion catheters (sepsis) Possible induction of hepatic encephalopathy

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