REVIEW ARTICLE

MEDICAL PROGRESS

Alcoholic Hepatitis

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Excessive alcohol consumption is the third leading preventable cause of death in the United States.[1,2] Alcohol-associated mortality is disproportionately high among young people, and approximately 30 years of life are lost per alcohol-associated death — or, in the aggregate, 2.3 million years of potential life lost in 2001 in the United States.[1] Excess consumption of alcohol is associated with both short-term and long-term liver damage, several types of cancer, unintentional injuries both in the workplace and on the road, domestic and social violence, broken marriages, and damaged social and family relationships.[3]

The association between alcohol intake and alcoholic liver disease has been well documented, although cirrhosis of the liver develops in only a small proportion of heavy drinkers.[4] The risk of cirrhosis increases proportionally with consumption of more than 30 g of alcohol per day; the highest risk is associated with consumption of more than 120 g per day.[4] The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 g of alcohol a day and up to 5.7% in those consuming 120 g daily. It is presumed that other factors, such as sex,[4,5] genetic characteristics,[6] and environmental influences (including chronic viral infection),[7] play a role in the genesis of alcoholic liver disease.

Chronic alcohol use may cause several types of liver injury. Regular alcohol use, even for just a few days, can result in a fatty liver (also called steatosis), a disorder in which hepatocytes contain macrovesicular droplets of triglycerides. Although alcoholic fatty liver resolves with abstinence, steatosis predisposes people who continue to drink to hepatic fibrosis and cirrhosis.[8] This review focuses on alcoholic hepatitis, a treatable form of alcoholic liver disease. Since up to 40% of patients with severe alcoholic hepatitis die within 6 months after the onset of the clinical syndrome, appropriate diagnosis and treatment are essential.

Clinical Presentation of Alcoholic Hepatitis

Alcoholic hepatitis is a clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day).[9] Not uncommonly, the patient will have ceased alcohol consumption several weeks before the onset of symptoms. The typical age at presentation is 40 to 60 years. Although female sex is an independent risk factor for alcoholic hepatitis, more men drink to excess, and there are more men than women with alcoholic liver disease.[8] The type of alcohol consumed does not appear to affect the risk of alcoholic hepatitis. The incidence is unknown, but the prevalence was approximately 20% in a cohort of 1604 patients with alcoholism who underwent liver biopsy.[9]

The cardinal sign of alcoholic hepatitis is the rapid onset of jaundice. Other common signs and symptoms include fever, ascites, and proximal muscle loss. Patients with severe alcoholic hepatitis may have encephalopathy. Typically, the liver is enlarged and tender.

Laboratory studies characteristically reveal serum levels of aspartate aminotransferase that are more than twice the upper limit of the normal range, although rarely above 300 IU per milliliter, whereas serum levels of alanine aminotransferase are lower. The ratio of the aspartate aminotransferase level to the alanine aminotransferase level is usually greater than 2, although this finding is neither specific nor sensitive.[10] The proposed mechanisms accounting for this high ratio are reduced hepatic alanine aminotransferase activity, alcohol-induced depletion of hepatic pyridoxal 5′-phosphate, and increased hepatic mitochondrial aspartate.[11-13] The peripheral-blood white-cell count, neutrophil count, total serum bilirubin level, and international normalized ratio (INR, which is the ratio of the coagulation time in the patient to the normal coagulation time) are elevated. An increased level of serum creatinine, if present, is an ominous sign, since it frequently portends the onset of the hepatorenal syndrome and death.[14]

Microscopy in patients with alcoholic hepatitis reveals hepatocellular injury characterized by ballooned (swollen) hepatocytes that often contain amorphous eosinophilic inclusion bodies called Mallory bodies (also called alcoholic hyaline) surrounded by neutrophils (Fig. 1).[15] The presence in hepatocytes of large fat globules — also known as steatosis — is common in alcoholic hepatitis. Intrasinusoidal fibrosis (i.e., fibrosis evident in the space between the endothelial cell and the hepatocyte) is a characteristic lesion of alcoholic hepatitis. Perivenular fibrosis, periportal fibrosis, and cirrhosis, which are typical features of alcoholic fibrosis, often coexist with the findings of alcoholic hepatitis. Additional histologic findings associated with alcoholic hepatitis may include foamy degeneration of hepatocytes and acute sclerosing hyaline necrosis.

Nonalcoholic steatohepatitis, a condition associated with obesity and insulin resistance, shares many histologic findings with alcoholic hepatitis, including ballooned hepatocytes, steatosis, Mallory bodies, inflammation, intrasinusoidal collagen, and fibrosis or cirrhosis. However, the severity of these changes is usually greater in alcoholic hepatitis, and cholestasis, a frequent finding in alcoholic hepatitis, is not present in nonalcoholic steatohepatitis. The findings in a liver-biopsy specimen typically cannot be used to identify the primary cause of steatosis, Mallory bodies, and fibrosis in obese patients who drink excessively.

Recovery from alcoholic hepatitis is dictated largely by abstinence from alcohol, the presence of a mild clinical syndrome, and the implementation of appropriate treatment. Within several weeks after discontinuation of alcohol intake, jaundice and fever may resolve,[16] but ascites and hepatic encephalopathy may persist for months to years. Either continued jaundice or the onset of renal failure signifies a poor prognosis.[14,17] Unfortunately, even when patients adhere to all aspects of medical management, recovery from alcoholic hepatitis is not guaranteed.[18]

ESTABLISHING THE DIAGNOSIS OF ALCOHOLIC HEPATITIS

The combination of an aspartate aminotransferase level that is elevated (but <300 IU per milliliter) and a ratio of the aspartate aminotransferase level to the alanine aminotransferase level that is more than 2, a total serum bilirubin level of more than 5 mg per deciliter (86 μmol per liter), an elevated INR, and neutrophilia in a patient with ascites and a history of heavy alcohol use is indicative of alcoholic hepatitis until proven otherwise. In some cases, it may be necessary to interview family members or companions to confirm alcohol use.[19,20]

The differential diagnosis of alcoholic hepatitis includes nonalcoholic steatohepatitis, acute or chronic viral hepatitis, drug-induced liver injury, fulminant Wilson's disease, autoimmune liver disease, alpha-1 antitrypsin deficiency, pyogenic hepatic abscess, ascending cholangitis, and decompensation associated with hepatocellular carcinoma.

The findings on liver biopsy may confirm the features described above and may help rule out other causes of liver disease, but a biopsy is not required to make the diagnosis. The risk of bleeding during or after the biopsy can be reduced with the use of the transjugular route. A liver biopsy is not recommended to confirm or refute abstinence, since it is difficult to assess the timeline of the resolution of the histologic features.[21]

Patients should be screened for bacterial infections such as pneumonia, spontaneous bacterial peritonitis, and urinary tract infection with the use of blood and urine cultures, cell count, culture of ascitic fluid if present, and chest radiography. Hepatic ultrasonography is useful in identifying hepatic abscess, clandestine hepatocellular carcinoma, and biliary obstruction, each of which may mimic alcoholic hepatitis. Ultrasonography can

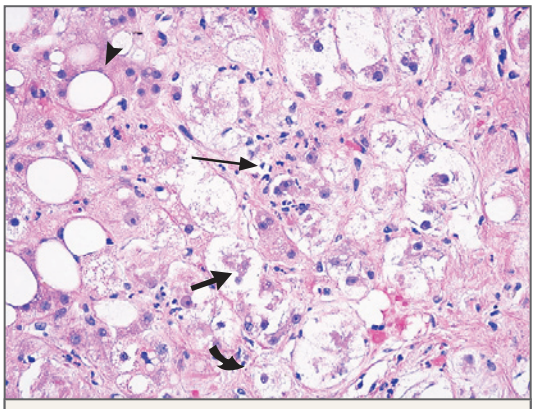


Figure 1. Histopathological Features in a Liver-Biopsy Specimen from a Patient with Alcoholic Hepatitis.

Alcoholic hepatitis is characterized by hepatocellular injury with ballooned hepatocytes (curved arrow). Some hepatocytes contain fat droplets (steatosis, arrowhead), whereas others may contain intracellular, amorphous, eosinophilic inclusion bodies called Mallory bodies (short arrow), which are often surrounded by neutrophils (long arrow) (hematoxylin and eosin). Image courtesy of Dr. Rashmi Agni.

also be combined with aspiration of ascites. Doppler flow studies may be useful, since an elevated peak systolic velocity or an increase in the diameter of the hepatic artery may help confirm the diagnosis.[22]

ASSESSING THE SEVERITY OF ALCOHOLIC HEPATITIS

A variety of scoring systems have been used to assess the severity of alcoholic hepatitis and to guide treatment (Table 1). Maddrey's discriminant function, the Glasgow score, and the score on the Model for End-Stage Liver Disease (MELD) help the clinician decide whether corticosteroids should be initiated, whereas the Lille score (or model) is designed to help the clinician decide whether to stop corticosteroids after 1 week of administration.[23-26] These scoring systems share common elements, such as the serum bilirubin level and prothrombin time (or INR) (Table 1). Maddrey's discriminant function has the advantage of being the test in longest use, but it may be difficult to score when only the INR, and not the prothrombin time (actual and control), is available. The Glasgow score, at least in one study, showed which patients with a high value for Maddrey's discriminant function were likely to benefit from corticosteroids.[27] The MELD score is easy to determine (see www.mayoclinic.org/meld/mayomodel7.html; higher MELD scores indicate worse prognosis), and its usefulness in assessing the severity of alcoholic hepatitis has been suggested in retrospective studies.[28] The validity of the Glasgow score and of the Lille score has yet to be established in populations outside their countries of origin.

Maddrey's discriminant function is calculated as [4.6 × (patient's prothrombin time − control prothrombin time, in seconds)] + serum bilirubin level, in milligrams per deciliter. A value of more than 32 indicates severe alcoholic hepatitis and is the threshold for initiating corticosteroid treatment.[23] In 2005, investigators from Glasgow[24] reported the results of a stepwise logistic-regression analysis identifying variables related to survival 28 days and 84 days after hospital admission in a large cohort of patients with alcoholic hepatitis; on the basis of these results, they developed a new assessment tool, called the Glasgow alcoholic hepatitis score (not to be confused with the Glasgow coma score). With this tool, age, peripheral-blood white-cell count, urea nitrogen and bilirubin concentrations, and prothrombin time or INR are used to identify patients at greatest risk for death in the absence of treatment in order to select those who may benefit from the administration of corticosteroids. One study showed that patients with a Maddrey's discriminant function of 32 or more and a Glasgow alcoholic hepatitis score of 9 or more who were treated with corticosteroids had an 84-day survival rate of 59%, as compared with a 38% survival rate among untreated patients.[27]

Some patients with alcoholic hepatitis will become candidates for liver transplantation. The MELD score, which is based on a numerical scale, predicts a patient's risk of death while waiting for a liver transplant; the score is based on serum levels of creatinine and bilirubin and the INR. In two retrospective studies, the MELD score predicted short-term mortality among patients with alcoholic hepatitis as well as or better than Maddrey's discriminant function.[25,28] A MELD score of 21 or more was associated with a 90-day mortality of 20%; Dunn et al. suggest that a score of 21 is an appropriate threshold for placing a patient in experimental trials that address the use of "potential therapeutic agents."[25]

The Lille score, which is based on pretreatment data plus the response of serum levels of bilirubin to a 7-day course of corticosteroid therapy, can

Table 1. Components of Scoring Systems Used to Assess Prognosis in Alcoholic Hepatitis.*

Scoring System	Components							
	Bilirubin	Prothrombin Time or INR	Creatinine	Age	White-Cell Count	Urea Nitrogen	Albumin	Change in Bilirubin between Day 0 and Day 7
Maddrey's discriminant function†	Yes	Yes	No	No	No	No	No	No
MELD score‡	Yes	Yes	Yes	No	No	No	No	No
Glasgow score§	Yes	Yes	No	Yes	Yes	Yes	No	No
Lille score¶	Yes	Yes	Yes	Yes	No	No	Yes	Yes

* Maddrey's discriminant function, the Model for End-Stage Liver Disease (MELD) score, and the Glasgow score are used to decide whether to initiate corticosteroid therapy, whereas the Lille score is use to decide whether to stop the use of corticosteroids after 7 days or complete a 28-day course. INR denotes international normalized ratio.

† Maddrey's discriminant function is defined as [4.6 × (patient's prothrombin time − control prothrombin time, in seconds)] + serum bilirubin level, in milligrams per deciliter. A score of more than 32 indicates severe alcoholic hepatitis and is the threshold for initiating corticosteroid treatment.

‡ The MELD score is defined as 9.57 × log creatinine, in milligrams per deciliter, plus 3.78 × log bilirubin, in milligrams per deciliter, plus 11.20 × log INR plus 6.43. The MELD score can be calculated at www.mayoclinic.org/meld/mayomodel7.html. Higher scores indicate worse prognosis.

§ The Glasgow score ranges from 5 to 12. The score for each item is as follows: age, 1 if younger than 50 years or 2 if 50 years or older; white-cell count, 1 if less than 15×10^9 per liter or 2 if greater than or equal to 15×10^9 per liter; urea nitrogen, 1 if less than 5 mmol per liter (14 mg per deciliter) or 2 if 5 mmol per liter or greater; ratio of patient's prothrombin time to control value, 1 if less than 1.5, 2 if 1.5 to 2.0, or 3 if more than 2.0; bilirubin, 1 if less than 125 μmol per liter (7.3 mg per deciliter), 2 if 125 to 250 μmol per liter (7.3 to 14.6 mg per deciliter), or 3 if more than 250 μmol per liter. Higher scores indicate worse prognosis.

¶ The change in bilirubin levels in the Lille model is defined as the difference in bilirubin levels between day 0 and day 7 of corticosteroid treatment. The Lille score is defined as 3.19 − 0.101 × age, in years, plus 0.147 × albumin on day 0, in grams per liter, plus 0.0165 × the change in bilirubin, in micromoles per liter, − 0.206 × renal insufficiency, rated as 0 if absent and 1 if present, − 0.0065 × bilirubin level on day 0 (in micromoles per liter) − 0.0096 times prothrombin time (in seconds). In patients who have received albumin infusions, use the last available albumin value before the infusion of albumin occurred. The Lille score ranges from 0 to 1 with the use of the formula Exp (− R) (1 + Exp [− R]). The Lille score can be calculated at www.lillemodel.com. A Lille score greater than 0.45 indicates a lack of response to corticosteroids.

be used to determine whether corticosteroids should be discontinued because of lack of response.[26]

MECHANISMS OF ALCOHOL-RELATED LIVER INJURY

Alcohol is metabolized in hepatocytes through oxidation to acetaldehyde, and subsequently from acetaldehyde to acetate. The oxidative metabolism of alcohol generates an excess of reducing equivalents, primarily in the form of reduced nicotinamide adenine dinucleotide (NAD) — that is, NADH. The changes in the NADH–NAD^+ reduction–oxidation potential in the liver inhibit both fatty acid oxidation and the tricarboxylic acid cycle and may promote lipogenesis.[29] In addition, ethanol promotes lipid metabolism through inhibition of peroxisome-proliferator–activated receptor α (PPAR-α) and AMP kinase and stimulation of sterol regulatory element-binding protein 1, a membrane-bound transcription factor.[30-32] In combination, these effects result in a fat-storing metabolic remodeling of the liver (Fig. 2). Nevertheless, it remains unclear how alcohol metabolism itself is linked to the genesis of alcoholic liver disease.

Recent advances in our understanding of the pathogenesis of alcohol-induced liver injury and the development of new approaches to its treatment are derived from studies in animals, many using direct infusion of alcohol and fat into the stomachs of rats or mice,[33] which results in liver lesions that mimic mild alcoholic hepatitis in humans, albeit with little fibrosis.[34] Endotoxin — the biologic activity of which is associated with lipopolysaccharide (LPS), a component of the outer wall of gram-negative bacteria — is a key trigger of the inflammatory process in this experimental model. Gut permeability, which is the sum of the factors promoting or restricting the translocation, or transfer, of LPS–endotoxin from the intestinal lumen into the portal blood,[35] appears to be altered with long-term exposure to alcohol (Fig. 2A). Pretreatment with antibiotics to cleanse the gut flora, or with lactobacillus to repopulate the gut, may ablate the increase in LPS–endotoxin that occurs with infusions of al-

cohol and fat and may abrogate alcoholic liver injury.[34,36,37] Similarly in humans, both gut permeability and circulating LPS–endotoxin levels are elevated in patients with alcoholic liver injury.[38,39]

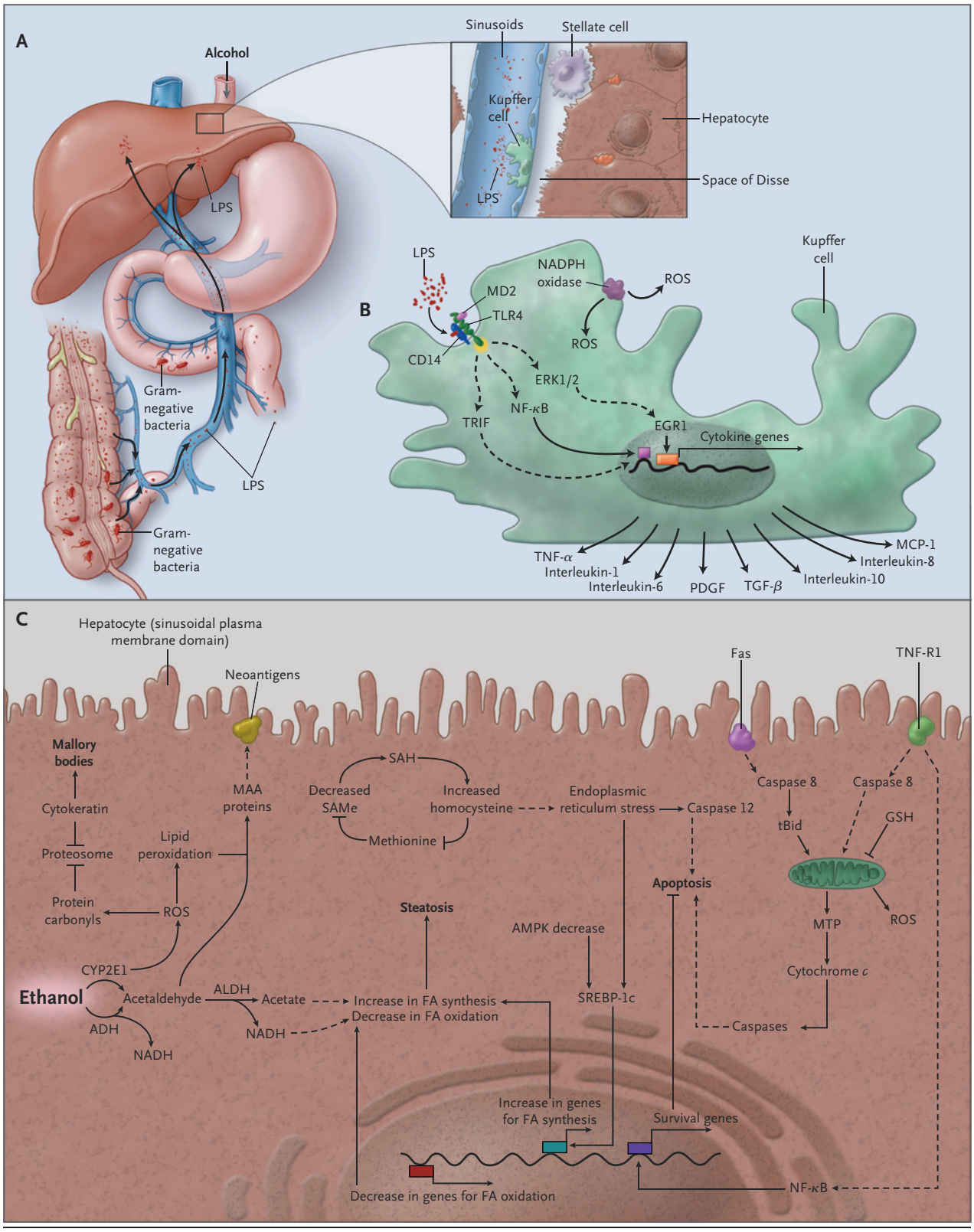
When LPS–endotoxin enters portal blood, it becomes bound to LPS-binding protein, a required step for the inflammatory and histopathological responses to alcohol exposure in experimental models.[40] The LPS–LPS-binding protein complex binds with the CD14 receptor on the cell membrane of Kupffer cells in the liver (Fig. 2B). Kupffer cells are pivotal for the development of alcoholic hepatitis in experimental models.[41] Activation of Kupffer cells by LPS–endotoxin requires three cellular proteins: CD14 (also known as monocyte differentiation antigen), toll-like receptor 4 (TLR4), and a protein called MD2, which associates with TLR4 to bind with LPS–LPS-binding protein.[34,42,43] The downstream pathways of TLR4 signaling include activation of early growth response 1 (EGR1), an immediate early gene–zinc-finger transcription factor, nuclear factor-κB (NF-κB), and the TLR4 adapter known as toll–interleukin-1–receptor domain-containing adapter-inducing interferon-beta (TRIF).[44,45] EGR1 plays a key role in lipopolysaccharide-stimulated TNF-α production; in mice, its absence prevents alcohol-induced liver injury. TRIF-dependent signaling (but not myeloid differentiation factor 88 [MyD88]-dependent signaling) contributes to alcohol-induced liver damage mediated by TLR4.[46] MyD88 is an adaptor protein that participates in many toll-like receptor signaling pathways.

Alcohol ingestion increases the excretion of markers of oxidative stress, and in humans, the highest levels are observed in persons with alcoholic hepatitis.[47] Studies in rats and mice suggest that activated Kupffer cells and hepatocytes are sources of free radicals (especially reactive oxygen intermediates), which are produced in response to short- or long-term exposure to alcohol.[48,49] Oxidative stress mediates alcohol-induced liver injury, at least in part, through the activity of cytochrome P-450 2E1,[50,51] leading to mitochondrial damage, activation of endoplasmic reticulum–dependent apoptosis, and up-regulation of lipid synthesis.[52,53]

TNF-α, produced by Kupffer cells, appears to play a pivotal role in the genesis of alcoholic hepatitis. Circulating TNF-α levels are higher in patients with alcoholic hepatitis than in heavy drinkers with inactive cirrhosis, heavy drinkers who do

Figure 2 (facing page). Aspects of the Pathophysiology of Alcohol-Induced Liver Injury.

Ethanol promotes the translocation of lipopolysaccharide (LPS) from the lumen of the small and large intestines to the portal vein, where it travels to the liver (Panel A). Normal liver consists of sinusoids lined with endothelial cells. Kupffer cells are located in the sinusoids, whereas hepatic stellate cells are located between the endothelial cells and the hepatocytes (Panel B). In the Kupffer cell, lipopolysaccharide binds to CD14, which combines with toll-like receptor 4 (TLR4), ultimately activating multiple cytokine genes. NADPH oxidase releases reactive oxygen species (ROS), which activate cytokine genes within the Kupffer cells and may have effects on hepatocytes and hepatic stellate cells. Cytokines such as tumor necrosis factor α (TNF-α) have both paracrine effects on hepatocytes and systemic effects such as fever, anorexia, and weight loss. Interleukin-8 and monocyte chemotactic protein 1 (MCP-1) attract neutrophils and macrophages. Platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β) contribute to the activation, migration, and multiplication of hepatic stellate cells, increasing hepatic fibrosis. In the hepatocyte, ethanol is converted to acetaldehyde by the cytosolic enzyme alcohol dehydrogenase (ADH) and the microsomal enzyme cytochrome P-450 2E1 (CYP2E1) (Panel C). Acetaldehyde is converted to acetate. These reactions produce NADH and inhibit the oxidation of triglyceride and fatty acids. ROS released by CYP2E1 and mitochondria cause lipid peroxidation and produce protein carbonyls. Lipid-peroxidation products can combine with acetaldehyde and with proteins to produce neoantigens, which can stimulate an autoimmune response. Inhibition of the proteosome reduces the catabolism of damaged proteins and may contribute to the accumulation of cytokeratin and formation of Mallory bodies. Reduction in the enzymes that convert homocysteine to methionine increases the concentration of homocysteine, stressing the endoplasmic reticulum. Sterol regulatory element-binding protein 1c (SREBP-1c) is released from the endoplasmic reticulum by stress and initiates the transcription of genes involved in triglyceride and fatty-acid synthesis. Decreased binding of peroxisome-proliferator–activated receptor α (PPAR-α) to DNA reduces the expression of genes involved in fatty acid oxidation. Glutathione transport from the cytosol into the mitochondria is reduced. Activation of Fas and TNF receptor 1 (TNF-R1) activates caspase 8, causing mitochondrial injury and opening the mitochondrial transition pore (MTP), releasing cytochrome *c*, and activating caspases, which contributes to apoptosis. Activation of TNF-R1 leads to nuclear factor κB (NF-κB) activation and the expression of genes that promote cell survival. In Panels B and C, solid lines indicate established pathways, and dashed lines indicate indirect or putative relationships between entities. ALDH denotes aldehyde dehydrogenase, AMPK AMP-activated protein kinase, EGR1 early growth response 1, ERK extracellular signal-regulated kinase, FA fatty acid, GSH glutathione, MAA malondialdehyde-acetaldehyde adduct, SAH S-adenosylhomocysteine, SAMe S-adenosyl-L-methionine, and TRIF toll–interleukin-1–receptor domain-containing adapter-inducing interferon-beta.



not have liver disease, and persons with neither alcoholism nor liver disease,[54] and high levels correlate with mortality.[54] The expression of the TNF-α gene was increased in liver tissue from patients with severe alcoholic hepatitis in one study.[55] Liver injury is substantially reduced when alcohol and fat are administered in TNF receptor 1 (TNF-R1)–knockout mice or rats that have been treated with anti–TNF-α antibodies or thalidomide (which reduces production of TNF-α).[56-58]

TNF-α–induced liver cytotoxicity is mediated through TNF-R1 (Fig. 2C).[56] The peroxidative capacity of TNF-α in hepatocytes is restricted to the mitochondria and is exacerbated by alcohol-induced depletion of mitochondrial glutathione, suggesting that mitochondria are the target of TNF-α.[59,60] Long-term alcohol consumption alters the intracellular balance between levels of *S*-adenosylmethionine and *S*-adenosylhomocysteine, resulting in a decrease in the ratio of *S*-adenosylmethionine to *S*-adenosylhomocysteine.[61,62] A decrease in this ratio may contribute to alcohol-induced liver injury, since *S*-adenosylhomocysteine exacerbates TNF-α hepatotoxicity, whereas *S*-adenosylmethionine diminishes it.

Administration of ethanol causes both the release of mitochondrial cytochrome *c* and expression of the Fas ligand, leading to hepatic apoptosis through the caspase-3 activation pathway.[63] In addition, the concerted actions of TNF-α and Fas-mediated apoptotic signals may increase the sensitivity of hepatocytes to injury through an increase in activated natural killer T cells in the liver.[64]

THERAPY FOR ALCOHOLIC HEPATITIS

Treatment of alcoholic hepatitis includes general measures for patients with decompensated liver disease as well as specific measures directed at the underlying liver injury (Table 2). General approaches include treatment of ascites (salt restriction and diuretics) and treatment of hepatic encephalopathy (lactulose and gut-cleansing antibiotics). Infections should be treated with appropriate antibiotics, chosen according to the sensitivity of the organisms isolated. Enteral feeding may be required, as patients are often anorectic. A daily protein intake of 1.5 g per kilogram of body weight is recommended, even among patients with hepatic encephalopathy. Thiamine and other vitamins should be administered according to Dietary Reference Intakes.[80] Delirium tremens and the acute alcohol withdrawal syndrome should be treated with short-acting benzodiazepines, despite their potential to precipitate encephalopathy.[81] The hepatorenal syndrome should be treated with albumin and vasoconstrictors (e.g., terlipressin, midodrine and octreotide, or norepinephrine).[82-84]

ABSTINENCE FROM ALCOHOL

Immediate and lifetime abstinence from alcohol use is essential to prevent the progression of alcoholic hepatitis. We consult our addiction specialists to tailor a program of psychological and social support for abstinence for each patient with alcoholic hepatitis.[65] There have been no studies that assess the efficacy of medications intended to reduce the craving for alcohol in patients with alcoholic hepatitis, although baclofen, a γ-aminobutyric acid (GABA) B-receptor agonist, has recently been reported to promote short-term abstinence in a group of actively drinking patients with alcoholic cirrhosis.[85] It also has an acceptable safety profile, whereas the safety of naltrexone or acamprosate in the treatment of patients with alcohol-related liver failure has not been established.

CORTICOSTEROIDS

Corticosteroid therapy abrogates the inflammatory process, in part, by inhibiting the action of transcription factors such as activator protein 1 (AP-1) and NF-κB.[86] In alcoholic hepatitis, this effect is manifested as reductions of circulating levels of the proinflammatory cytokines interleukin-8 and TNF-α, of soluble intracellular adhesion molecule 1 in hepatic venous blood, and of the expression of intracellular adhesion molecule 1 on hepatocyte membranes.[87,88]

The use of corticosteroids to treat alcoholic hepatitis has been controversial, owing to the divergent findings of individual studies and meta-analyses.[66-69] A recent meta-analysis did not favor corticosteroid use, although the authors concluded that the evidence base is compromised by heterogeneous clinical trials with a high risk of bias.[69] Nevertheless, the same meta-analysis showed that corticosteroids significantly reduced mortality in the subgroup of trials that enrolled patients with a Maddrey's discriminant function of at least 32 or hepatic encephalopathy and that had a study design with a low risk of bias. Similarly, a reanalysis of the combined individual data from the three most recent studies in which corticosteroids were administered to subjects for 28 days indicated that the 1-month survival rate for

Table 2. Therapies for Alcoholic Hepatitis.*

Treatment	Clinical Purpose	Dose	Evidence
Psychotherapy	Maintain abstinence	Optimum approach and frequency not determined	No clear evidence of benefit in patients with alcoholic liver disease; has not been studied in patients with alcoholic hepatitis[65]
Corticosteroids	Reduce inflammation	40 mg of prednisolone orally, once a day for up to 28 days	Reduces short-term mortality in selected patients with severe alcoholic hepatitis[17,18,66-70]
Pentoxifylline	Ablate TNF-α, help maintain kidney function, and many other actions	400 mg orally, three times daily	Improves in-hospital survival in patients with severe alcoholic hepatitis; fewer instances of the hepatorenal syndrome in group receiving pentoxifylline[71]
Infliximab	Ablate TNF-α	Most effective dose has not been determined	May increase risks of infection and death[72]
Etanercept	Ablate TNF-α	Most effective dose has not been determined	May increase risks of infection and death[73]
Nutritional support	Reverse malnutrition	35–40 kcal/kg of body weight per day, including 1.2–1.5 g protein/kg/day	Improves nutritional status but does not improve short-term survival in patients with severe alcoholic hepatitis[74-76]
Oxandrolone	Increase muscle mass	Most effective dose has not been determined	Does not improve short-term survival in patients with severe alcoholic hepatitis[77]
Vitamin E	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis[78]
Silymarin (milk thistle extract)	Ablate oxidant-mediated liver injury	Most effective dose has not been determined	Does not improve survival in patients with severe alcoholic hepatitis[79]

* TNF-α denotes tumor necrosis factor α.

patients with severe alcoholic hepatitis (Maddrey's discriminant function, ≥32) who were treated with corticosteroids was 85%, as compared with 65% for those who received placebo (P=0.001).[18] The most common corticosteroid therapy for alcoholic hepatitis is prednisolone at a dose of 40 mg per day for 28 days. At the end of the course of treatment, the prednisolone can be stopped all at once,[17] or the dose can be gradually tapered over a period of 3 weeks.[66] Indications for treatment include a Maddrey's discriminant function of 32 or more (or a MELD score of ≥21) in the absence of sepsis, the hepatorenal syndrome, chronic hepatitis B virus infection, and gastrointestinal bleeding. Five patients need to be treated with corticosteroids to prevent one death.[70]

Some data suggest that the decision to stop prednisolone because of lack of efficacy can be determined by calculating the Lille score after 7 days of treatment (www.lillemodel.com). A Lille score greater than 0.45 indicates a lack of response to corticosteroids and predicts a 6-month survival rate of less than 25%.

Unfortunately, alcoholic hepatitis is unresponsive to corticosteroid treatment in approximately 40% of patients. No other treatment, including pentoxifylline (see below), has been identified as effective in this subgroup.[89]

Corticosteroids should not be given to patients with a Maddrey's discriminant function of less than 32 or a MELD score of less than 21 until data are available that will permit identification of patients with a high short-term risk of death.

PENTOXIFYLLINE

One randomized, controlled trial showed that pentoxifylline, a phosphodiesterase inhibitor with many effects, including modulation of *TNF-α* transcription, reduced short-term mortality among patients with alcoholic hepatitis. In this study, 101 patients with a Maddrey's discriminant function of 32 or more were given either placebo or 400 mg of pentoxifylline three times a day for 28 days.[71] None of the patients received corticosteroids. Twelve of the 49 patients in the pentoxifylline group (24%) and 24 of the 52 patients in the pla-

cebo group (46%) died during the initial hospitalization (P<0.01). The hepatorenal syndrome was the cause of death in 6 of 12 deaths (50%) in the pentoxifylline group and in 22 of 24 deaths (92%) in the placebo group. Curiously, serial TNF-α levels did not differ significantly between the two groups during the course of the study, which suggests that the efficacy of pentoxifylline in alcoholic hepatitis may be independent of TNF-α. We speculate that whereas corticosteroids influence hepatic inflammation, the benefit of pentoxifylline therapy may be related to prevention of the hepatorenal syndrome. Despite the absence of confirmatory studies, pentoxifylline is an agent worth considering for some patients.

ANTI–TNF-α THERAPY

Two anti–TNF-α agents have been studied as therapy for alcoholic hepatitis: infliximab and etanercept. Three small, preliminary studies of infliximab (two nonrandomized and one randomized) had encouraging results that led to the conduct of a larger study to assess its efficacy.[90-92] The resulting randomized, controlled clinical trial compared the effects of intravenous infusions of infliximab plus prednisolone with placebo plus prednisolone in patients with severe alcoholic hepatitis (Maddrey's discriminant function, ≥32).[72] However, the trial was stopped early by the independent data and safety monitoring board because of a significant excess of severe infections and a nonsignificant increase in deaths in the infliximab cohort. The dose of infliximab (intravenous infusion of 10 mg per kilogram of body weight three times per day on days 1, 14, and 28) has been criticized as excessively high as compared with the single dose of 5 mg per kilogram used in the other studies.

Etanercept appeared to increase short-term survival of patients with alcoholic hepatitis in a small pilot study,[93] although a subsequent randomized, placebo-controlled trial conducted by the same investigators showed a worse 6-month survival rate in the group treated with etanercept than in the placebo group.[73] Our opinion is that anti–TNF-α agents should not be used outside clinical trials to treat alcoholic hepatitis.

NUTRITIONAL SUPPORT

All patients with alcoholic hepatitis are malnourished,[74] and the risk of death is closely correlated with the degree of malnutrition.[75] Parenteral and enteral feeding improves nutritional status but does not improve short-term survival.[76] A randomized, controlled clinical trial compared enteral tube feeding (2000 kcal per day) with prednisolone therapy (40 mg of prednisolone per day) for 28 days in 71 patients with severe alcoholic hepatitis. The survival rate in the two groups was similar at 28 days and at 1 year, suggesting that nutritional support may be as effective as corticosteroids in some patients.[94]

OTHER PHARMACOLOGIC TREATMENTS

Anabolic–androgenic steroids, which increase muscle mass in healthy subjects, do not improve survival in patients with alcoholic hepatitis.[77] Although alcoholic liver disease is associated with enhanced oxidative stress, studies of treatment with antioxidants, including vitamin E, and silymarin, the active ingredient in milk thistle, have not shown any survival benefit in either patients with alcoholic hepatitis or those with alcoholic cirrhosis.[78,79] Neither oral administration of colchicine or propylthiouracil, nor a combined intravenous regimen of insulin and glucagon, is effective in patients with alcoholic hepatitis.

LIVER TRANSPLANTATION

Alcoholic hepatitis has been considered an absolute contraindication to liver transplantation,[95,96] on the grounds that patients with this disorder have been drinking recently and that a period of abstinence will allow many to recover. Most U.S. transplantation programs now require 6 months of abstinence before a patient with alcoholic hepatitis can become eligible for transplantation.[97] Unfortunately, many patients die during this interval, and the patients who have a recovery with maximal medical treatment will be recognizable well before 6 months have elapsed. Veldt et al. suggested that patients with liver failure resulting from alcoholic liver disease who do not recover within the first 3 months of abstinence are unlikely to survive.[98] Consequently, liver transplantation centers face a dilemma when caring for a patient with alcoholism who has severe alcoholic hepatitis and whose condition deteriorates despite adherence to abstinence, nutritional support, corticosteroids, and other elements of medical management. A return to alcohol use after transplantation also remains a concern.

CONCLUSIONS

The diagnosis of alcoholic hepatitis is based on a history of heavy alcohol use, jaundice, and the absence of other possible causes of hepatitis. Liver biopsy is a valuable diagnostic aid but is not required either to determine the prognosis or to establish the timeline of previous drinking or abstinence. Abstinence from alcohol is the cornerstone of recovery. Malnourished subjects should be given adequate caloric and protein support. Patients with severe alcoholic hepatitis (Maddrey's discriminant function, ≥32; or MELD score, ≥21) who do not have sepsis should be given a trial of prednisolone at a dose of 40 mg per day for 28 days. After 7 days of corticosteroid treatment, patients with a Lille score of more than 0.45 may have disease that will not respond to continued treatment with corticosteroids or to an early switch to pentoxifylline. When the clinical situation is such that clinicians are reluctant to prescribe corticosteroids, pentoxifylline appears to be useful in preventing the hepatorenal syndrome, which can lead to death. The efficacy of combined treatment with pentoxifylline and corticosteroids has not been studied and warrants a randomized, controlled trial. Patients with less severe alcoholic hepatitis, whose short-term survival approaches a rate of 90%, should not be treated with corticosteroids, since the risks of complications such as systemic infections outweigh the benefits.[18] Finally, there is a need for well-conducted studies of liver transplantation in carefully selected patients with severe alcoholic hepatitis that is not responding to medical management.

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