86 Alcohol-Associated Liver Disease

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CHAPTER OUTLINE

Alcohol-associated liver disease (ALD) remains a challenging enigma for basic scientists and clinicians. Despite extensive research and clinical trials since the 1940s, many important facets of this disease have yet to be resolved.[1] Paramount among these important questions are the following: (1) Why does cirrhosis develop in only a small fraction of heavy alcohol abusers? (2) What is the pathogenesis of severe ALD? (3) What are the most effective treatments for patients with severe ALD?

EPIDEMIOLOGY

A systematic analysis of the global burden of disease in 2016 evaluated 195 locations around the world and showed that alcohol use was the seventh leading risk factor for both deaths and disability-adjusted life years.[2] Globally, 32.5% of people between 15 and 95 years of age were current drinkers. Another study found that between 1999 and 2016, annual deaths from cirrhosis in the USA increased by 65%, and rates of HCC doubled.[3] Alcohol was a major contributing factor to these events. Moreover, mortality trends from chronic liver disease from 2007 to 2016 in the USA showed that HCV-related mortality had begun to decline due to the use of DAAs, whereas that for ALD continued to increase.[4]

Alcohol abuse is the most common etiology of cirrhosis in the developed world (see Chapter 74). It is the underlying cause of 44% of liver disease deaths in the USA (approximately 13,000 deaths annually), exceeding those for hepatitis C, the second most common fatal liver disease in this country.[5-7] In Europe and the USA combined, ALD and its complications account for approximately 50,000 deaths each year.[8] Unfortunately, although addiction and mental disorders have increasingly gained support from medical care and social support systems, it is remarkable that alcohol addiction has remained severely stigmatized.[9]

Numerous studies have shown that ALD develops in women after a shorter duration of drinking and with a lower daily alcohol intake than in men.[10,11] Population-based surveys have documented that men must usually drink 40 to 80 g of alcohol daily and women 20 to 40 g daily for 10 to 12 years to achieve a significant risk of liver disease.[10-12] Fig. 86.1 illustrates the alcohol content of various beverages sold in the USA, their typical serving sizes, and the definition of a "standard drink."[13] A useful website for drinking information is https://www.rethinkingdrinking.niaaa.nih.gov/. The standard drink in the USA is 14 g of alcohol, and this standardization provides a common definition for reporting alcohol intake. Data from the USA and Europe indicate that subjects diagnosed with alcohol-associated hepatitis or cirrhosis are often drinking about 15 standard drinks/day.

SPECTRUM OF DISEASE

Chronic alcohol abuse can result in a spectrum of liver injury that ranges from mild fatty infiltration to steatohepatitis, steatohepatitis with fibrosis, cirrhosis, and HCC (Fig. 86.2).[14-17] Fat accumulation in liver cells, the earliest and most predictable response to alcohol ingestion, is seen in 90% to 100% of heavy drinkers.[17,18] Although fatty liver is considered to be a benign condition that reverses quickly with abstinence, cirrhosis can develop within 5 years in 10% of patients who continue to drink heavily.[19] Much more important than steatosis is the development of necroinflammation and fibrosis (alcohol-associated hepatitis) that occurs in approximately 10% to 35% of heavy drinkers. On liver histology, steatosis, steatohepatitis with or without fibrosis, and alcohol-associated cirrhosis represent the spectrum of ALD. It is unclear, however, whether the histologic findings always correlate with the clinical presentation.[20] For example, alcohol-associated steatohepatitis on a liver biopsy specimen can be present in patients with minimal symptoms (moderate alcohol-associated hepatitis) or with severe clinical manifestations of the disease (severe alcohol-associated hepatitis). Moderate alcohol-associated hepatitis is diagnosed less often than severe alcohol-associated hepatitis because these patients may not seek medical care or visit emergency departments with only nonspecific symptoms of nausea, diarrhea, or fatigue.[21]

Alcohol-associated hepatitis is an important clinical entity for several reasons: (1) patients with severe alcohol-associated hepatitis have extremely high short-term mortality rates; (2) patients with severe alcohol-associated hepatitis can develop portal hypertension in the absence of cirrhosis; and (3) alcohol-associated hepatitis is a well-documented precursor of cirrhosis, with an elevated long-term

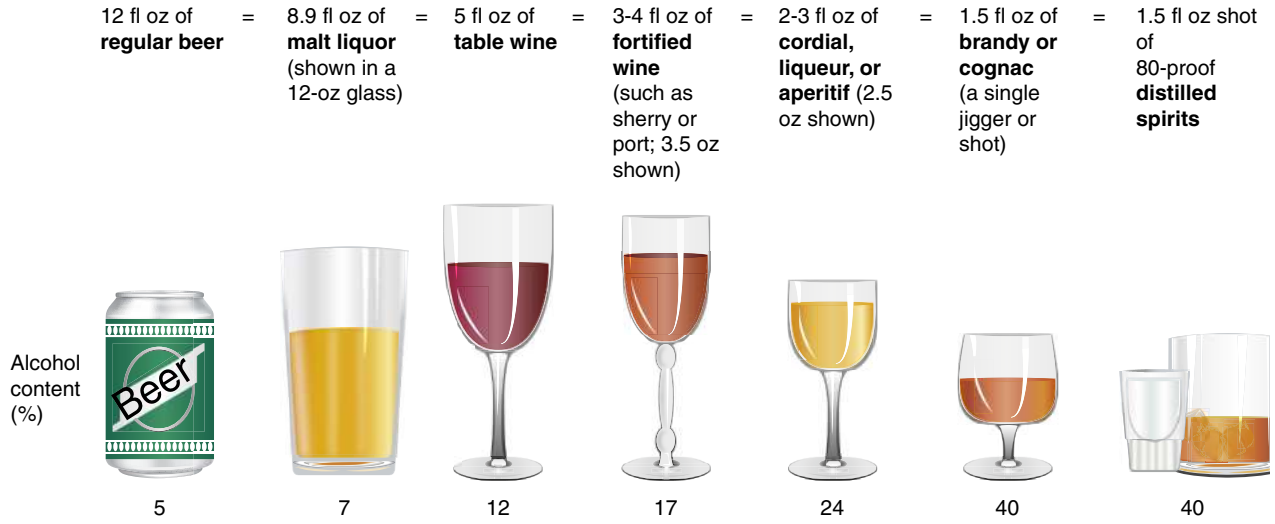


Fig. 86.1 The typical serving size and alcohol content of standard American drinks. (From http://www.rethinkingdrinking.niaaa.nih.gov.)

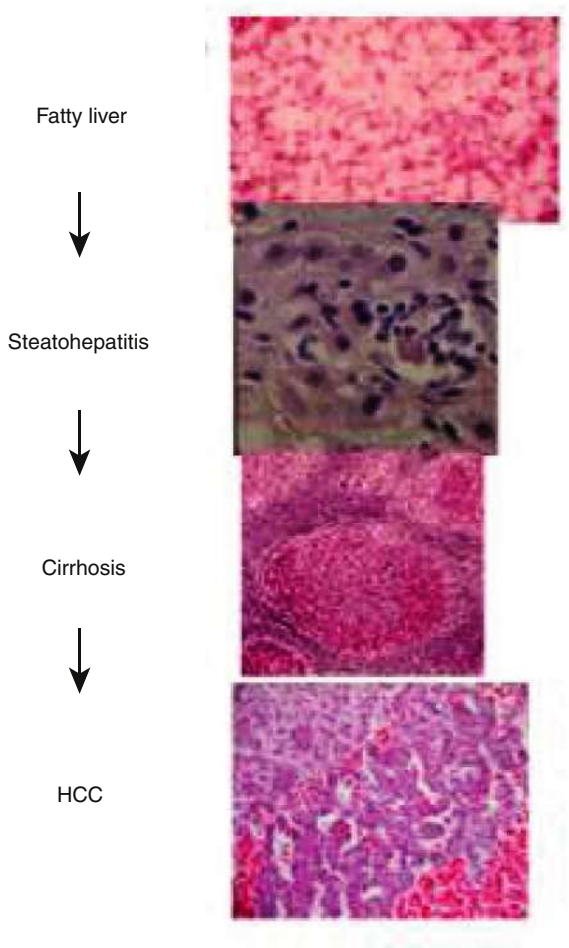


Fig. 86.2 Histologic spectrum of alcohol-associated liver disease.

mortality rate 9 times higher than that for patients with fatty liver alone.[19,22] With continued alcohol abuse, a fine mesh-like pattern of fibrosis (micronodular cirrhosis) develops in 8% to 20% of heavy drinkers. Over time this lesion can evolve to include broad bands of fibrosis that separate large nodules of liver tissue (macronodular cirrhosis).[16] HCC typically develops in this setting.[23]

PATHOGENESIS

Ethanol Metabolism and Toxic Metabolites

The liver is the main organ responsible for ethanol metabolism; other organs such as the stomach contribute to much lesser degrees. Ethanol is metabolized by 3 major systems in the liver: alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and, of least importance, catalase.[24] ADH is the primary enzyme system responsible for metabolism of ethanol at low concentrations, whereas CYP2E1 contributes to ethanol metabolism at higher tissue concentrations of ethanol (>10 mM). Furthermore, CYP2E1 activity is up-regulated by exposure to ethanol, thereby leading to faster metabolism with chronic excessive alcohol use. Both ADH and CYP2E1 convert ethanol to acetaldehyde, which is then converted by aldehyde dehydrogenase (ALDH) to acetate. Acetaldehyde is a highly reactive and potentially toxic compound that is responsible for many of the systemic toxic effects of alcohol, such as nausea, headaches, and flushing.

Acetaldehyde is also postulated to play an etiologic role in ALD by forming adducts with reactive residues on proteins or small molecules (e.g., cysteines). These chemical modifications can alter or interfere with normal biologic processes, exert cellular toxicity, and stimulate the host's immune response and cause autoimmune-like manifestations. Antibodies against such oxidatively modified proteins have been found in both human and animal models of ALD.[25] An example is the hybrid adduct of malondialdehyde and acetaldehyde, unique to alcohol exposure, which induces an immune reaction in human alcoholics and in animal models.[25] Acetaldehyde has also been shown to impair mitochondrial glutathione transport and to sensitize hepatocytes to TNF-α–mediated killing.[26] Lastly, acetaldehyde disrupts intestinal barrier function, contributing to endotoxemia and pro-inflammatory cytokine production.

In addition to forming cytotoxic metabolites such as acetaldehyde, ethanol metabolism can alter the cellular oxidation-reduction

(redox) state, thereby modulating liver injury. Specifically, the oxidation of ethanol uses nicotinamide-adenine dinucleotide (NAD^+) as an electron acceptor and thereby causes a shift in the ratio of reduced NAD (NADH) to NAD^+ to a more reduced state.[24] This change in the redox state can impair normal carbohydrate and lipid metabolism; multiple effects ensue, including a decrease in the supply of ATP to the cell and an increase in hepatic steatosis.

Other Metabolic Mechanisms

Oxidative Stress

Oxidative stress is an imbalance between pro-oxidants and antioxidants. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are products of normal metabolism and can be beneficial to the host (e.g., by contributing to bacterial killing).[27] Overproduction of ROS and RNS or inadequate antioxidant defenses (e.g., low levels of vitamins, selenium, mitochondrial glutathione), or both, can lead to liver injury. Oxidative stress in ALD is usually documented by detection of one of several indirect markers: (1) protein oxidation (e.g., protein thiol or carbonyl products); (2) lipid oxidation (e.g., isoprostanes, malondialdehyde); (3) DNA oxidation (e.g., oxodeoxyguanosine); or (4) depletion or induction of antioxidant defenses (e.g., vitamin E, glutathione, thioredoxin).[28]

The stimulus for oxidative stress in the liver comes from multiple sources. In hepatocytes, CYP2E1 activity increases after alcohol consumption—in part because of stabilization of messenger RNA. The CYP2E1 system leaks electrons to initiate oxidative stress.[27] CYP2E1 is localized in the hepatic lobule in areas of alcohol-induced liver injury. Moreover, overexpression of CYP2E1 in mice and in HepG2 cells (a human hepatoma cell line) in vitro leads to enhanced alcohol hepatotoxicity.[29,30] Nonparenchymal cells and infiltrating inflammatory cells (e.g., polymorphonuclear leukocytes [neutrophils]) are another major source of pro-oxidants that are used for normal cellular processes, such as killing invading organisms. Major enzyme systems for pro-oxidant production in Kupffer cells and infiltrating macrophages in the liver include NAD phosphate (NADPH) and inducible nitric oxide synthase.[31] Mice deficient in NADPH oxidase or mice treated with the drug diphenyleneiodonium sulfate, which blocks NADPH oxidase, are resistant to ethanol-induced liver injury.[32] A critical subunit of the NADPH oxidase complex, p47phox, has been shown to play a role in liver parenchymal cells in producing ALD in mice.[33] Infiltrating neutrophils use enzyme systems such as myeloperoxidase to generate hypochlorous acid ($HOCl^-$, a halide species that causes oxidative stress) and RNS. One study found that in neutrophils the p47phox oxidative pathway is regulated by microRNA-223.[34] Oxidative stress can mediate liver injury through at least 2 major pathways: direct cell injury and cell signaling. Direct cell injury is indicated by markers such as lipid peroxidation and DNA damage. An even more important role is played by signaling pathways; for example, activation of transcription factors such as nuclear factor kappa B (NF-κB) plays a critical role in the production of pro-inflammatory cytokines such as TNF.

Mitochondrial Dysfunction

Mitochondria are the major consumers of molecular oxygen and major generators of ROS in the liver. Mitochondrial dysfunction is well documented in ALD and contributes to oxidative stress.[35] Mitochondrial abnormalities in ALD include megamitochondria observed on light and electron microscopy and functional mitochondrial abnormalities as documented by an abnormal ^{13}C ketoacid breath test result (ketoacids are metabolized by mitochondria). Short-term administration of alcohol enhances hepatic superoxide generation in liver mitochondria, thereby increasing the flow of electrons along the respiratory electron transport chain. The increased NADH/NAD^+ ratio caused by ethanol intake favors superoxide generation.[27] Because hepatic mitochondria lack catalase, glutathione plays a critical role in protecting mitochondria against oxidative stress. Mitochondria do not make glutathione but instead import it from the cytosol. In ALD, the transport of glutathione into mitochondria is impaired, and selective mitochondrial glutathione depletion is observed. Glutathione depletion also sensitizes the liver to the toxic effects of TNF, which also impairs mitochondrial function.

Normal mitochondrial function requires continuous exchange of substrate between the cytosol and the mitochondrial matrix, and this is catalyzed by specific exchangers within the inner mitochondrial membrane. By contrast, exchange of most water-soluble metabolites between the cytosol and the intermembrane space occurs through the voltage-dependent anion channel in the mitochondrial outer membrane. Alcohol-mediated closure of the voltage-dependent anion channel limits free diffusion of metabolites into the intermembrane space and causes mitochondrial dysfunction.[36] This process is likely a cause of global alterations in mitochondrial function related to alcohol abuse and ALD.

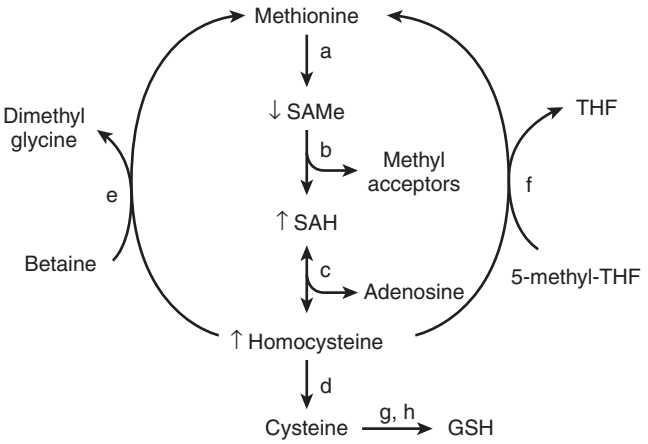


Fig. 86.3 Hepatic methionine metabolism. Chronic alcohol consumption causes S-adenosylmethionine (*SAMe*) deficiency and an increase in homocysteine and S-adenosylhomocysteine (*SAH*) levels. *a,* methionine adenosyltransferase. *b,* enzymes involved in transmethylation reactions, including phosphatidylethanolamine N-methyltransferase. *c,* SAH hydrolase. *d,* cystathionine B-synthase. *e,* Betaine-homocysteine methyltransfe rase. *f,* Methionine synthetase. *g,* Glutamate-cysteine synthetase. *h,* Glutathione *(GSH)* synthetase. *THF,* tetrahydrofolate; ↑↓, effects of alcohol.

Abnormal Metabolism of Methionine, S-Adenosylmethionine, and Folate

In mammals, the liver plays a central role in methionine metabolism; nearly half of the daily intake of methionine is metabolized in the liver (Fig. 86.3). The first step in methionine metabolism is the formation of S-adenosylmethionine (SAMe) in a reaction catalyzed by methionine adenosyltransferase. Activity of this enzyme is depressed in ALD.[37-39] SAMe is the principal biological methyl donor through the transmethylation pathway, the precursor of aminopropyl groups used in polyamine biosynthesis, and a precursor of glutathione through its conversion to cysteine along the transsulfuration pathway.

Deficiency of SAMe in patients with ALD was first noted in the early 1980s, when it was observed that alcoholic subjects had delayed clearance of an oral bolus of methionine (presumably because of blocked conversion of methionine to SAMe).[38,39] Functional methionine adenosyltransferase activity was subsequently

shown to be subnormal in liver biopsy specimens from alcoholic subjects. Exogenous administration of SAMe corrects the deficiency and attenuates the severity of many experimental forms of liver injury.

In models of alcohol-induced hepatotoxicity, SAMe has been shown to maintain mitochondrial glutathione levels. Depletion of mitochondrial glutathione is thought to be one pathogenic factor in the development of ALD, and SAMe, but not other glutathione prodrugs, prevents mitochondrial glutathione depletion in experimental ALD (possibly by protecting mitochondrial glutathione transport systems).[40] The antioxidant response element (ARE) is an essential component of upstream regulatory sequences present on many genes that provide hepatoprotection, including most phase II detoxification enzymes (see Chapter 88). NF-E2-related factor 2 (Nrf2) is a critical transcription factor that binds to the ARE and plays a key role in cellular responses to stress via the Keap1-Nrf2-ARE pathway. In experimental cholestatic liver disease, Nrf2 binding decreases, and this is partially prevented with SAMe therapy. Therefore, SAMe therapy may help maintain GSH levels as well as induce other antioxidant pathways through maintenance of appropriate Nrf2 binding.[41,42] SAMe also decreases lipopolysaccharide (LPS)-stimulated TNF release and increases interleukin (IL)-10 release in a monocyte cell line.[37] Similarly, in rats fed a diet to induce SAMe deficiency, serum TNF levels increase and sensitivity to endotoxin-induced hepatotoxicity, which can be blocked by injection of SAMe, increases markedly. These data support the concept that SAMe may have direct hepatoprotective functions and may modify LPS-stimulated cytokine production.

Although serum SAMe levels are decreased in patients with ALD, levels of the downstream products S-adenosylhomocysteine (SAH) and homocysteine are elevated.[38,39,43] Elevated SAH levels have been shown to sensitize hepatocytes to TNF-mediated destruction, and SAH may be a critical physiologic sensitizer of TNF-mediated killing in liver injury.[43] Homocysteine and SAH can be removed by giving betaine, which facilitates regeneration of methionine from homocysteine. Folic acid also can play a critical role in the regeneration of homocysteine to methionine by means of 5-methyltetrahydrofolate (5-MTHF).[44] Folic acid deficiency enhances the development of alcohol-induced liver injury in micropigs, and alcohol feeding interferes with normal folic acid metabolism in several different pathways—from impaired intestinal uptake to increased renal excretion.[44] Collectively, the data support a role for altered methionine-transmethylation-transsulfuration metabolism in ALD and link these pathways to TNF hepatotoxicity.[39]

Hypoxia

The centrilobular area of the hepatic lobule (the functional unit of the liver) has the lowest oxygen tension and greatest susceptibility to hypoxia (see Chapter 71). Chronic alcohol intake increases oxygen uptake by the liver and increases the lobular oxygen gradient. A chronic intragastric feeding model in rats has been used to define the mechanisms underlying hepatic hypoxia and the association of these mechanisms with cycling of urinary alcohol levels (UALs).[45] At high UALs, hepatic hypoxia is observed, along with reduced ATP levels; the NADH/NAD^+ ratio is shifted to the reduced state; and, hypoxia-inducible factor (HIF) genes are up-regulated. When UALs fall, reperfusion injury occurs, with free radical formation and peak liver enzyme release from hepatocytes. Hepatocyte-specific HIF-1α has been shown to be up-regulated in alcohol-fed mice and to play a role in hepatic lipid accumulation.[46] One study has shown that the increase in HIF-1α in ALD is regulated by microRNA-122, a negative regulator of HIF-1α.[47] Levels of microRNA-122, the most abundant microRNA in hepatocytes, are increased in the circulation but significantly decreased in the liver in ALD in mice and in humans. The low miR-122 levels in ALD are due to a direct inhibitory effect of alcohol on the transcription of this microRNA.[47] Whereas HIF and HIF-regulated proteins appear to be up-regulated in the liver during alcohol feeding, intestinal HIF is markedly down-regulated. This down-regulation appears to contribute to increased intestinal permeability with subsequent endotoxemia and liver injury. Indeed, one mechanism of the beneficial action of the probiotic *Lactobacillus* GG in experimental ALD appears to be maintenance of intestinal HIF.[48,49]

Endoplasmic Reticulum Stress, Impaired Proteasome Function, and Autophagy

The endoplasmic reticulum (ER) stress response is induced by the accumulation of unfolded or misfolded proteins. To deal with the ER stress response, cells activate a series of signaling pathways termed the unfolded protein response, which can either be protective (usually in the short term) or detrimental (usually in the long term). One of the effects of a prolonged unfolded protein response can be increased production of TG and cholesterol, which can lead to fatty liver. Some potential inducers of ER stress in ALD include elevated homocysteine levels, acetaldehyde and acrolein adducts, and oxidative stress.[50-52] Moreover, the cascade of ER stress and activation of the ER-associated molecule, STING, that triggers phosphorylation of the interferon regulatory factor 3 has been identified as an important mechanism for alcohol-induced hepatocyte damage. Phosphorylated interferon regulatory factor 3 interacts with mitochondrial apoptotic proteins to result in hepatocyte damage, apoptosis, and the release of damage-associated molecular patterns (DAMPs), such as ATP and uric acid, that then contribute to inflammasome activation (see Chapter 88).[53]

Both of the major pathways that degrade most cellular proteins in eukaryotic cells, the ubiquitin-proteasome system and autophagy, are affected in ALD.[54] The ubiquitin-proteasome pathway is the primary proteolytic pathway of eukaryotic cells (see Chapter 72). It controls the levels of numerous proteins involved in gene regulation, cell division, and surface receptor expression, as well as the stress response and inflammation. The proteasome system is now considered a cellular defense mechanism because it also removes irregular and damaged proteins generated by mutations, translational errors, or oxidative stress.[55]

Animal studies have demonstrated that chronic ethanol feeding results in a significant decrease in proteolytic activity of the proteasome. This decreased activity can lead to abnormal protein accumulation, including accumulation of oxidized proteins.[56] The decrease in proteasome function correlates significantly with the level of hepatic oxidative stress. Hepatocytes from alcoholics contain large amounts of ubiquitin in the form of cellular inclusions, or Mallory (or Mallory-Denk) bodies, which accumulate because they are not degraded efficiently by the proteasome.[57] When hepatocytes die as a result of proteasome inhibition, they inappropriately release cytokines such as IL-8 and IL-18. IL-8 recruits neutrophils and probably plays a role in neutrophil infiltration in alcohol-associated hepatitis, whereas IL-18 sustains inflammation in the liver.[58]

Evidence for the effects of alcohol on autophagy, a process responsible for degradation of long-lived or aggregated proteins and cellular organelles, is emerging (see Chapter 72). Studies in rats have shown that alcohol consumption inhibits multiple key steps in autophagy.[59]

Immune and Inflammatory Mechanisms

Gut-Liver Axis and Pathogen-Associated Molecular Patterns (PAMPs)

It is now generally accepted that the gut flora and gut-derived toxins play a critical role in the development of ALD and its complications (Fig. 86.4).[60] Indeed, in the 1960s, it was shown that germ-free rodents or rodents treated with antibiotics to "sterilize the gut" were resistant to nutritional and toxin-induced liver

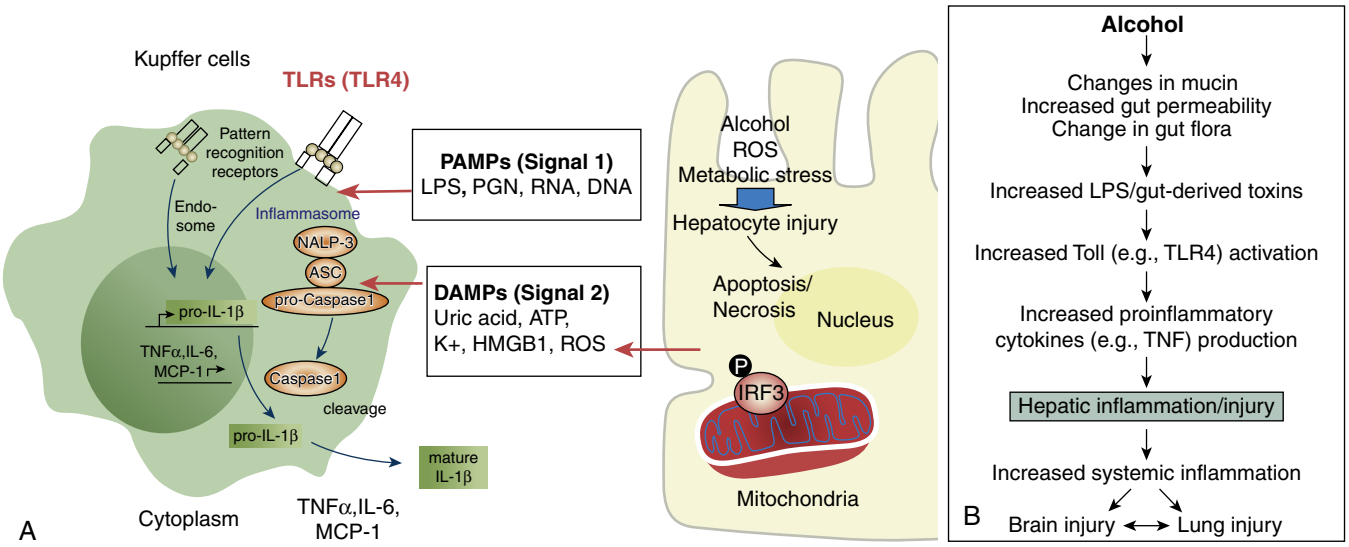


Fig. 86.4 The gut-liver axis. *A,* Under certain circumstances, gut-derived pathogen-associated molecular patterns (*PAMPs*), including lipopolysaccharide (*LPS*), lipopeptides, unmethylated DNA, double-stranded RNA, and others, translocate from the gut into the portal vein and to the liver, where they are recognized by specific recognition receptors, the Toll-like receptors (*TLRs*), resulting in initiation of the innate immune response, production of inflammatory mediators, activation of inflammasomes, and subsequent liver injury. Alcohol-injured hepatocytes also release damage-associated molecular patterns (DAMPs), such as uric acid, ATP, K+, HMGB1, and ROS, and represent a second signal that further activates inflammasomes. *B,* Alcohol alters gut-barrier function, thereby promoting bacteria and LPS translocation, TLR activation, cytokine production, liver injury, and potentially other organ injury, including brain inflammation, which may stimulate further alcohol consumption. See text for further details. *ASC,* apoptosis-associated speck-like protein; *HMGB1,* high mobility group box 1; *IL,* interleukin; *IRF3,* interferon regulatory factor 3; *MCP-1*, monocyte chemoattractant protein-1; *NALP-3,* NACHT, LRR, and PYD domains-containing protein; *PGN,* peptidoglycans; *ROS,* reactive oxygen species. (From Iracheta-Vellve A, Petrasek J, Satishchandran A, et al. Inhibition of sterile danger signals, uric acid and ATP, prevents inflammasome activation and protects from alcoholic steatohepatitis in mice. J Hepatol 2015;63:1147–55.)

injury. Early studies showed that rats fed a choline-deficient diet developed cirrhosis, which could be prevented by oral neomycin.[61] When endotoxin was added to the water supply, however, neomycin no longer prevented the development of liver injury and fibrosis.[61] Subsequently, antibiotics, prebiotics, and probiotics have all been used to prevent experimental alcohol-induced liver injury.[62] Numerous clinical studies also have demonstrated that plasma endotoxin levels are significantly elevated in patients with different stages of ALD—fatty liver, hepatitis, and cirrhosis—when compared with healthy control subjects. Ethanol-induced endotoxemia observed in experimental rodent models of ALD has also provided support for the essential role of LPS in the development of liver injury. Drastic reduction in gut microbiota with antibiotics in mice has been shown to result in significant attenuation of alcohol-induced inflammation not only in the liver, but also in the intestine and in the brain.[63] Despite prevention of an alcohol-induced increase in LPS in the circulation and elimination of liver inflammation, however, alcohol still induced serum ALT elevations in mice, thereby suggesting a direct effect of alcohol on hepatocyte damage.[63]

LPS is a prototype PAMP that represents a strong inflammatory signal for the host through recognition by Toll-like receptor 4, a pattern recognition receptor expressed on immune cells and many other cell types in the liver.[64] With increased gut leakiness, many different PAMPs can translocate to the liver via the portal circulation and contribute to inflammatory cell activation.[65] Alcohol-induced gut barrier dysfunction and endotoxemia are multifactorial events, with altered microflora and impaired intestinal integrity among the causal factors (see Fig. 86.4). Alcohol promotes the overgrowth of Gram-negative bacteria in the intestines of patients with chronic alcohol abuse. Studies on gut flora from alcoholics in an inpatient treatment program have demonstrated altered microflora composition, with decreased numbers of *Bifidobacteria* spp. and *Lactobacilli* spp.[66] One human study found depletion of *Akkermansia muciniphila* in humans with ALD and showed that replacement of *Akkermansia* spp. can ameliorate alcohol-induced liver disease in mice.[67] Another study found that after a 10-day alcohol feeding binge, a decrease in intestinal *A. muciniphila* was an early change in the gut microbiota related to alcohol.[68] Multiple animal studies have documented altered gut flora with chronic alcohol feeding. Intestinal bacterial overgrowth of both aerobic and anaerobic bacteria after 3 weeks of intragastric alcohol feeding has been demonstrated in an animal model of ALD.[69] Hepatic steatosis and steatohepatitis occurred at the same time as translocation of live bacteria into the systemic circulation. Importantly, prebiotic therapy attenuated liver injury. In another study, mice were fed alcohol for 8 weeks,[70] and major changes in gut flora occurred relatively late in the disease process, whereas changes in gut barrier function and endotoxemia occurred much earlier. Fecal pH increased in association with altered gut flora, and probiotic therapy for the final 2 weeks effectively treated the liver disease (with a decrease in serum liver enzyme levels, reduction in endotoxemia, and correction of intestinal trefoil factor and tight-junction proteins). In these studies, alcohol intake decreased the levels of critical gut antimicrobial peptides.

Alcohol and its metabolite, acetaldehyde, induce intestinal permeability to various macromolecules, including LPS, in both human subjects and animal models of ALD.[39] Translocation of LPS across the gut epithelial barrier has been attributed to the disruption of the intestinal barrier integrity. Indeed, decreased tight-junction (ZO-1) protein levels were observed in sigmoid colonic biopsies of human alcoholics compared with healthy controls. The decrease was attributed to an increase in miRNA-212 expression observed in alcoholic subjects compared with controls.[71]

Alcohol-induced oxidative stress and generation of nitric oxide in the intestines of experimental animals leading to loss of tight junction integrity, gut leakiness, endotoxemia, hepatic inflammation, and liver injury have also been reported.[72] A number of laboratories have also reported increased intestinal permeability in experimental animal models of ALD due to redistribution and decreased expression of intestinal tight-junction proteins.[39] Increased intestinal production of proinflammatory cytokines, such as TNF and IL-6, can also contribute to alcohol-associated endotoxemia by altering tight-junction morphology and distribution, thereby creating a self-perpetuating vicious cycle that can amplify bacterial translocation.[73] Finally, emerging evidence suggests that intestinal fungi also contribute to ALD. Alcohol-dependent patients have been shown to display reduced intestinal fungal diversity and overgrowth of *Candida* spp.[74] Consistent with this finding, antifungal therapy reduced the alcohol-related intestinal fungal overgrowth and increased serum β-glucan levels.[74]

Inflammasome Activation and DAMPs

Inflammasomes are intracellular multiprotein complexes that sense danger signals from damaged cells and pathogens and assemble to mediate the caspase-1 activation that results in piroteolytic cleavage of pro-IL-1β and IL-18 into bioactive forms.[75] Inflammasome activation is present in the liver in ALD, and the NLRP3 inflammasome seems to play a central role (see Fig. 86.4). The levels of DAMPs, including uric acid and ATP, are increased in ALD, and inhibition of these sterile danger signals can prevent inflammasome activation in mice.[76] Metabolic DAMPs have been shown to mediate inflammation and crosstalk between damaged hepatocytes and to mediate immune-cell activation in ALD.[77] Inflammasome activation in chronic alcohol use is not limited to the liver, and NLRP3 inflammasome activation and increased IL-1β levels have also been found in the brains of alcohol-fed mice.[78] Inflammasome activation requires 2 signals; the first, usually a TLR-mediated signal, induces pro-IL-1β production, and the second, usually a DAMP-induced signal, results in inflammasome and capase-1 activation that releases bioactive IL-1β.[79] Secreted IL-1β quickly binds to its receptor, thereby amplifying inflammation, increasing hepatocyte damage, and promoting liver fibrosis.[79] Inhibition of the actions of IL-1β with a recombinant IL-1 receptor antagonist has been shown to improve ALD in mice and accelerate liver regeneration after chronic alcohol exposure.[80,81]

Inflammasome activation can also lead to *pyroptosis*, a form of cell injury and death.[82] Pyroptosis has been reported in alcohol-associated hepatitis in mice. Caspase-11 is up-regulated in hepatocytes in alcohol-associated hepatitis, and gasdermin D, which is downstream of caspase 11, contributes to pyroptosis.[83]

In addition to ATP and uric acid, experimental evidence suggests a role for other DAMPs in ALD. For example, high mobility group box-1 (HMGB-1) is highly induced in ALD in the liver, where hepatocytes have been shown to secrete this normally intracellular and intranuclear protein.[84] Other DAMPs—IL-33 and its decoy receptor soluble ST2 (IL-1 receptor like 1)—have been shown to play different roles in early and late stages of ALD in mice.[85]

Dysregulated Cytokine Production

Increased plasma and hepatic concentrations of proinflammatory cytokines (e.g., TNF) are consistently observed in rodent models of ALD and are stimulated in large part by gut-derived toxins (see Fig. 86.4). TLR-4 activation by endotoxin results in recruitment of the adaptor molecules, MyD88, and Toll/IL-1 receptor domain-containing adapter inducing interferon-β (TRIF), which each activate separate downstream signaling cascades. Data suggest that the MyD88-independent pathway TRIF is more important in the development of experimental ALD, whereas NASH appears to signal through the MyD88-dependent pathway.[86]

Dysregulated cytokine metabolism in human ALD has been recognized since the 1980s, with the initial observation that peripheral blood monocytes from patients with alcohol-associated hepatitis significantly increases basal and LPS-stimulated TNF production.[87,88] Serum concentrations of TNF-inducible cytokines and chemokines, such as IL-6, IL-8, IL-18, monocyte chemoattractant protein 1, and others, are elevated in patients with alcohol-associated hepatitis or cirrhosis, and the levels often correlate with markers of an acute-phase response, reduced liver function, and poor clinical outcomes.[87]

This enhanced cytokine response to a physiologic stimulus such as LPS is termed *priming*. Increased serum or urinary levels of neopterin and other markers indicate that monocytes and Kupffer cells are primed in ALD. This priming for LPS-stimulated TNF production has been reproduced in vitro by culturing monocyte cell lines with relevant concentrations of alcohol. This response appears to be mediated, at least in part, by induction of CYP2E1 and oxidative stress.[89] Not only are levels of proinflammatory cytotoxic cytokines increased in ALD, but also monocyte and Kupffer cell production of protective anti-inflammatory cytokines, such as IL-10, is decreased.[90]

Several strategies have been devised to decrease cytokine production or activity in an attempt to block or attenuate liver injury. Examples include antibiotics to modulate intestinal flora and LPS, gadolinium chloride to destroy Kupffer cells, and antioxidants such as glutathione prodrugs to inhibit cytokine production. Each of these strategies has been successful in attenuating alcohol-induced liver injury in rats.[87] Prebiotics, such as oat bran, and probiotics have also been shown to decrease endotoxemia in experimentally induced alcohol-associated liver injury. Moreover, anti-TNF antibody has been used to prevent liver injury in alcohol-fed rats,[91] and alcohol-associated liver injury does not develop in mice that lack the TNF type I receptor.[92]

Hepatocytes normally are resistant to TNF killing. Hepatocytes from rats fed alcohol or hepatocytes incubated in alcohol are sensitized to TNF killing, however.[29,93] Some potentially relevant mechanisms for such *sensitization* include mitochondrial depletion of glutathione, accumulation of SAH, and proteasome inhibition, among others. Therefore, in ALD, monocytes and Kupffer cells are primed to increase production of TNF, and hepatocytes are sensitized to TNF killing. These processes are closely intertwined with previously described mechanisms such as oxidative stress, mitochondrial dysfunction, abnormal metabolism of methionine, and dysfunction of proteasomes.

Immune Responses to Altered Hepatocellular Proteins

Alcohol-associated hepatitis may persist histologically for many months after exposure to ethanol has ceased, suggesting an ongoing immune or autoimmune response. Autoimmune reactions are well documented in patients with ALD, with autoantibodies directed against phospholipids, ADH, heat shock protein, and other potential antigens. Patients with ALD are at increased risk for the development of immune responses directed at neoantigens generated from the interactions of metabolites of alcohol (e.g., acetaldehyde or hydroxyethyl radicals) with liver proteins. Some studies also have linked genetic susceptibility and autoimmunity in ALD.[94]

Genetics and Epigenetic Factors

Genetic polymorphisms in alcohol-metabolizing systems such as CYP2E1 and ADH likely play a role in susceptibility to ALD. People with nucleotide substitution from glutamine to lysine in ALDH have significantly low or absent ALDH activity, leading

to acetaldehyde accumulation.[95-99] CYP2E1 is inducible, with the activity increased by 20-fold after alcohol consumption. The C2 variant has higher activity than that of C1, leading to the assumption that it will lead to high levels of acetaldehyde, oxidative stress, and liver injury[100-104]; however, none of these polymorphisms explains the spectrum of ALD among different patients.

Polymorphisms in the promoter regions of the genes for the cytokines TNF and IL-10 have also been reported to predispose affected persons to the development of ALD and are under active study.[105] A sequence variation within the gene coding for patatin-like phospholipase encoding 3 (PNPLA3, rs738409) has been found to modulate steatosis, necroinflammation, and fibrosis in NAFLD (see Chapter 87). This same variant has also been shown to be a robust genetic risk factor for progressive ALD.[105] A large genome-wide association study has also identified the variants of 2 genes on chromosome 19—*TM6SF2* and *MBOAT* 7—that are significantly associated with alcohol-associated cirrhosis.[106,107]

Epigenetic mechanisms that regulate gene expression primarily involve alterations to the chromatin structure via DNA methylation and post-translational histone modifications without changes to the underlying DNA sequence.[108-110] Histone acetylation is a key component in the regulation of gene expression and is associated with enhanced transcriptional activity, whereas deacetylation is typically associated with transcriptional repression. Steady-state levels of acetylation of the core histones result from the balance between the opposing activities of histone acetyltransferases and histone deacetylases (HDACs). Binge alcohol exposure significantly alters messenger RNA expression of liver class I, II, and IV HDACs.[111] These data strongly support a major pathogenic role for binge alcohol-induced alterations in HDAC alterations that regulate the expression of genes that are relevant for hepatic steatosis.

Another type of epigenetic effect is microRNA (miRNA, small noncoding RNA molecules that regulate gene expression post-transcriptionally). Several miRNAs have been linked to both ALD and HCC as either biomarkers or molecular mediators. For example, miRNA 155 (miR-155) has been shown to modulate LPS-induced TNF-α production in Kupffer cells and TNF production in macrophages from patients with ALD.[112] Furthermore, deficiency in miR-155 in a mouse model attenuated alcohol-induced liver steatosis through peroxisome proliferator-activated receptor-α and inflammation involving peroxisome proliferator-activated receptor-γ regulation. Fibrogenic gene expression is also attenuated in alcohol-fed miR-155 knockout mice compared with controls.[113]

Emerging Mechanisms

Endogenous cannabinoids, which are ubiquitous lipid signaling molecules that mediate their effects through specific cannabinoid receptors, CB1 and CB2, appear to have a role in ALD. Studies have demonstrated that inhibition of CB1 receptors can cause weight loss and attenuate fatty liver and hyperlipidemia in animal models of obesity and steatohepatitis. Moreover, CB1 blockade reduces hepatic fibrosis in a variety of animal models of cirrhosis.[114]

Malnutrition has re-emerged as another mechanism of interest. Alterations in micronutrients, such as vitamins A, D, and zinc, as well as macronutrients, such as dietary fat, are increasingly recognized to play a role in the development and progression of ALD.[112] Decreased serum zinc levels, inadequate dietary zinc intake, and altered zinc metabolism are well documented in ALD.[115] Zinc plays a critical role in a host of metabolic pathways, including functioning of zinc-finger proteins. Oxidative stress can cause zinc to be released from the zinc-finger proteins and cause loss of functional activity. Therefore, nutrient modulation may be a way of protecting against or treating ALD.

Fibrosis

The development of hepatic fibrosis, leading to cirrhosis, indicates major progression of ALD and represents a maladaptive wound healing response (see Chapter 74). The development of fibrosis is a dynamic state, with constant remodeling of scar tissue; fibrosis may regress with discontinuation of exposure to alcohol. The activated stellate cell (myofibroblast) is the major source of collagen production in the liver. It normally exists in a quiescent state and serves as a major storehouse for vitamin A. With activation, the stellate cell assumes a myofibroblast-like contractile phenotype and produces collagen. The cytokine TGF-β is a major stimulus for stellate cell activation and collagen production. Selected other cytokines implicated in the activation of stellate cells include platelet-derived growth factor and connective tissue growth factor (see Chapters 72 and 92). Whereas the hepatic stellate cell is considered the major origin of myofibroblasts, other resident cells (portal fibroblasts), bone-marrow derived mesenchymal cells, and cells undergoing epithelial-to-mesenchymal transition have been postulated to be sources of myofibroblasts.[116] Importantly, Toll-like receptor 4 signaling in hepatic stellate cells plays a major role in stellate cell activation, myofibroblast chemokine secretion, interactions between myofibroblasts and Kupffer cells, and sensitization of myofibroblasts to TGF-β signaling.[117]

Oxidative stress also plays a major role in stellate cell activation, and a variety of antioxidants can block both stellate cell activation and collagen production in vitro. Serum levels of 4-hydroxy-nonenal, a specific product of lipid peroxidation, are elevated in patients with ALD and up-regulate both procollagen type I and tissue inhibitor of metalloproteinase-1 gene expression. Matrix metalloproteinase-1 plays a major role in degrading type I collagen. Tissue inhibitor of metalloproteinase-1 levels are also elevated in ALD. The result appears to be an increase in stellate cell activation and collagen production on the one hand and a decrease in matrix degradation on the other hand.[118-120]

The main extracellular matrix (ECM) protein associated with fibrosis is collagen type I, but other ECM proteins also accumulate, including fibrin. The liver is the major organ regulating the fibrin coagulation system. Fibrin metabolism is regulated via 2 pathways, coagulation and fibrinolysis.[24] Inhibition of fibrinolysis by plasminogen activator inhibitor-1 can cause fibrin ECM to accumulate, even in the absence of enhanced fibrin deposition by the thrombin cascade. Hepatic injury in models of liver disease often involves dysregulation of the coagulation cascade and fibrinolysis, resulting in the formation of fibrin clots in the hepatic sinusoids.[24] Fibrin clots block the blood flow within the hepatic parenchyma, thereby causing microregional hypoxia and subsequent hepatocellular death.[24] In summary, important cross-talk between cell types (e.g., stellate and Kupffer cells) and major metabolic pathways (e.g., wound healing, clotting, innate immunity) plays a critical role in both early and late stages of fibrosis.

DIAGNOSIS OF ALCOHOL ABUSE

Alcohol abuse should be suspected if there is a history of heavy alcohol intake, other organ system damage is present, or there is a history of an excessive frequency of falls, lacerations, or fractures. Only 10% of patients with drinking problems are identified by primary care providers.[121] Owing to delays in diagnosis and treatment, many patients have cirrhosis by the time they are referred to a gastroenterologist or hepatologist.[122] Underdiagnosis is common in teenagers and older patients and is of particular concern in women of childbearing age.[123,124] The first step to ensure more timely diagnosis of alcohol abuse is the uniform application of screening tools in various practice settings. Three such tools are in common use: the 10-item AUDIT (**A**lcohol **U**se **D**isorders **I**dentification **T**est), the 3-item AUDIT-C (AUDIT-concise) consumption

questions, and the 4-item CAGE (*C*ut, *A*nnoyed, *G*uilty, *Eye*-opener) questionnaire.[125,126] An alternative approach is the use of a single question: "How many times in the past year have you had *x* or more drinks a day?" (where *x* = 5 for men and 4 for women) to identify individuals with risky drinking.[125] Specific tools also have been developed for use in pregnant women.[124] Regardless of which instrument is chosen, it is important that physicians incorporate systematic screening into their practices.[127] An excellent guide to various screening strategies is available at http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005.pdf.

There is ongoing interest in developing laboratory tests that can reliably identify patients with problem drinking. Although not as sensitive as screening questions, they are particularly useful in patients suspected of drinking who deny alcohol use. Blood or breath alcohol measurements are the most sensitive and specific indicators of recent alcohol use, particularly among binge drinkers.[128] The major limitation of these tests is the short half-life of ethanol in blood, urine, and breath. As a result, efforts have focused on developing biomarkers of alcohol abuse that are detectable over longer periods of time. Possibly the most widely used of these biomarkers thus far is carbohydrate-deficient transferrin.[129] Even higher sensitivity and specificity for alcohol abuse has been reported by combining carbohydrate-deficient transferrin with mean corpuscular erythrocyte volume and serum GGTP levels.[130] Measurement of 2 alcohol metabolites, phosphatidylethanol and ethyl glucuronide, also shows promise in detecting recent alcohol use.[131,132] Phosphatidylethanol has been used in a variety of situations ranging from the ICU to the post-transplantation setting to diagnose recent alcohol abuse.[133] An innovative new approach is the development of transdermal sensors and wearable devices to monitor alcohol use continuously.[134]

DIAGNOSIS OF ALCOHOL-ASSOCIATED LIVER DISEASE

The clinical diagnosis of ALD and alcohol-associated hepatitis can be accurate; however, the diagnostic accuracy is increased by the use of liver biopsy.[20] A consensus report from the National Institute on Alcoholism and Alcohol Abuse defined the clinical diagnosis of acute alcohol-associated hepatitis.[135] This working definition of alcohol-associated hepatitis includes the onset of jaundice within 60 days of heavy consumption (>50 g/day) of alcohol for a minimum of 6 months, a serum bilirubin level greater than 3 mg/dL, an elevated serum AST level (50 to 400 U/L), a serum AST:ALT ratio greater than 1.5, and no other obvious cause for hepatitis.[135] This consensus statement proposed classifying patients with alcohol-associated hepatitis as definite when a liver biopsy was used to establish the diagnosis, probable when the clinical and laboratory features were present without potential confounding problems, and possible when confounding problems were present.

History

Most patients with fatty liver are asymptomatic. Although patients with alcohol-associated hepatitis and cirrhosis may be asymptomatic, many present with a variety of complaints including anorexia, nausea and vomiting, weakness, jaundice, weight loss, abdominal pain, fever, and diarrhea.

Physical Examination

The most detailed clinical information on ALD in the USA comes from studies of hospitalized patients who were assigned the diagnosis on the basis of classical histologic features.[136,137] The most common physical finding in patients with fatty liver and alcohol-associated hepatitis is hepatomegaly, which is detectable in more than 75% of patients, regardless of disease severity. Patients with alcohol-associated hepatitis and cirrhosis also may have hepatic tenderness, an audible bruit over the liver, spider angiomata, splenomegaly, and peripheral edema. Jaundice and ascites, which are found in approximately 60% of patients, are more frequent in patients with severe disease (Table 86.1). Various degrees of hepatic encephalopathy can be seen, usually in the most severely ill patients. Some patients with alcohol-associated hepatitis have a fever, with temperatures as high as 104°F, that can persist for weeks (likely mediated by proinflammatory cytokines such as IL-1 and TNF).

TABLE 86.1 Symptoms and Signs in Hospitalized Patients with Alcohol-Associated Liver Disease*

	Patients Affected (%)			
	Disease Severity			
Symptom or Sign	Mild (*n* = 89)	Moderate* (*n* = 58)	Severe† (*n* = 37)	Overall
Hepatomegaly	84.3	94.7	79.4	86.7
Jaundice	17.4	100	100	60.1
Ascites	30.3	79.3	86.5	57.1
Hepatic encephalopathy	27.3	55.2	70.3	44.6
Splenomegaly	18.0	30.9	39.4	26.0
Fever	18.0	31.0	21.6	22.8

*Moderate disease was defined by a serum bilirubin level >5 mg/dL.
†Severe disease was defined by a serum bilirubin level >5 mg/dL and a prolonged prothrombin time >4 sec.
Data from Mendenhall CL. Alcoholic hepatitis. Clin Gastroenterol 1981; 10:417–41.

In patients with well-compensated cirrhosis, the physical examination can be normal; however, most patients have obvious hepatomegaly and splenomegaly. As the disease progresses, the liver decreases in size and has a hard and nodular consistency. Patients with decompensated cirrhosis typically have muscle wasting, ascites, spider telangiectasias, palmar erythema, and Dupuytren contractures. Enlarged parotid and lacrimal glands are often seen, and severely ill patients may have Muehrcke lines or white nails. Patients with hepatopulmonary syndrome often have digital clubbing (see Chapter 92).

Laboratory Features

Only one third of hospitalized patients with fatty liver have laboratory abnormalities, which usually consist of mild increases in serum AST and ALT levels. As illustrated in Table 86.2, surprisingly modest elevations of serum aminotransferase levels are seen in patients with alcohol-associated hepatitis and cirrhosis, even when the disease is severe.[136,137] Serum AST levels are almost always less than 400 U/L and typically are associated with trivial elevation of serum ALT levels, resulting in an AST/ALT ratio greater than 2. A ratio greater than 2 is characteristic of ALD, in part because of deficiency of pyridoxal 5′ phosphate (a cofactor disproportionately affecting serum ALT activity) in alcoholic patients (see Chapter 73). Serum alkaline phosphatase levels can range from normal to values greater than 1000 U/L. Serum bilirubin levels range from normal to 20 to 40 mg/dL, and serum albumin levels may be normal or depressed to a value as low as 1.0 to 1.5 g/dL. Most patients with ALD are anemic and have some degree of thrombocytopenia. By contrast, the white blood cell count usually is normal or elevated, occasionally to levels consistent with a leukemoid state. Severely ill patients usually have marked prolongation of the prothrombin time—often expressed as the INR—and often have an elevated serum creatinine value.

TABLE 86.2 Typical Laboratory Values in Hospitalized Patients with Alcohol-Associated Liver Disease*

Laboratory Test	Disease Severity		
	Mild (*n* = 89)	Moderate* (*n* = 58)	Severe† (*n* = 37)
Hematocrit value (%)	38	36	33
MCV (μm³)	100	102	105
WBC count (per mm³)	8000	11,000	12,000
Serum AST level (U/L)	84	124	99
Serum ALT level (U/L)	56	56	57
Serum alkaline phosphatase level (U/L)	166	276	225
Serum bilirubin level (mg/dL)	1.6	8.7	13.5
Prolongation of prothrombin time (sec)	0.9	2.4	6.4
Serum albumin level (g/dL)	3.7	2.7	2.4

*Moderate disease was defined by a serum bilirubin level >5 mg/dL.
†Severe disease was defined by a serum bilirubin level >5 mg/dL and a prolonged prothrombin time >4 sec.
MCV, mean corpuscular volume.
Data from Mendenhall CL. Alcoholic hepatitis. Clin Gastroenterol 1981; 10:417-41.

Histopathology

The clinical diagnosis of ALD is quite sensitive and specific; therefore, liver biopsy is usually not needed to establish the diagnosis. A liver biopsy is useful, however, in selecting patients for clinical trials, determining the severity of hepatic injury, and clarifying the diagnosis in atypical cases (see Fig. 86.2). Centrilobular and perivenular fatty infiltration is seen in most persons who drink more than 60 g of alcohol daily. Classic histologic features of alcohol-associated hepatitis include ballooning degeneration of hepatocytes, alcoholic hyaline (Mallory, or Mallory-Denk, bodies) within damaged hepatocytes, and a surrounding infiltrate composed of neutrophils.[14,15,17] Most patients have moderate to severe fatty infiltration. Varying degrees of fibrosis may be present, and many patients exhibit an unusual perisinusoidal distribution of fibrosis, at times with partial or complete obliteration of the terminal hepatic venules (sclerosing hyaline necrosis).[17,22] Cirrhosis can be identified by the presence of nodules of hepatic tissue that are completely surrounded by fibrous tissue.

Alcohol-associated cirrhosis typically is micronodular or mixed micro- and macronodular. In patients with coexisting alcohol-associated hepatitis, alcoholic hyaline is almost universal, and sclerosing hyaline necrosis and moderate-to-severe fatty infiltration are common. In patients with alcohol-associated cirrhosis who abstain from alcohol for long periods, a frequent finding is a gradual transformation to macronodular cirrhosis, which is indistinguishable from cirrhosis caused by other forms of liver disease (see Chapter 74).[16,17,22]

Conditions That May Resemble ALD

Although the clinical diagnosis of ALD usually is quite straightforward, the similarity of clinical and histologic features of other disorders to those of ALD sometimes causes diagnostic confusion. The most commonly encountered conditions that have clinical or histologic features in common with ALD are NAFLD, hereditary hemochromatosis, and Budd-Chiari syndrome.

NAFLD

NAFLD is the most difficult condition to differentiate from ALD (see Chapter 87). There is considerable overlap between the histologic features of NAFLD and ALD.[17,138] As a consequence, the differentiation between the 2 conditions requires careful clinicopathologic correlation. Patients with ALD typically manifest clinical features of more advanced liver disease. Patients with NAFLD are more likely to have features of the metabolic syndrome including peripheral insulin resistance, obesity, hypertension, and dyslipidemia, although these features are not invariably present.[139,140] They also should have weekly alcohol intake of fewer than 21 drinks for men and 14 for women.[141] When a patient's alcohol intake is questionable, differentiating the 2 conditions can be difficult, if not impossible. The use of structured questionnaires to assess alcohol intake is recommended in this situation.[141]

Hereditary Hemochromatosis

On occasion, distinguishing patients with ALD and secondary iron overload from those with liver disease caused by hereditary hemochromatosis can be difficult (see Chapter 75). Patients with end-stage liver disease from alcohol-associated cirrhosis can have elevated serum iron and ferritin levels and increased hepatic iron levels suggestive of hereditary hemochromatosis.[142] To complicate matters further, 15% to 40% of patients with hereditary hemochromatosis consume more than 80 g of alcohol daily.[143]

The overlapping clinical features of hereditary hemochromatosis and ALD include hepatomegaly, testicular atrophy, cardiomyopathy, and glucose intolerance. Testing for mutations in the gene for hereditary hemochromatosis (*HFE*) and measuring the hepatic iron index are the best methods for differentiating the 2 conditions. Few patients with alcohol-associated cirrhosis and iron overload are homozygous for C282Y or heterozygous for the C282Y and H63D HFE mutations, and few have hepatic iron index values greater than 1.9.[142,144]

DILI

DILI can occur in the setting of chronic alcohol consumption and ALD (see Chapters 88 and 89). The interaction between heavy alcohol consumption and acetaminophen toxicity has been well documented for almost 40 years[145] (see later). Other interactions with drugs such as methotrexate, isoniazid, and certain antiretroviral agents have also been reported.[146] Moreover, patients with ALD often consume drugs that frequently cause DILI, such as certain antibiotics. A meta-analysis of data from the Drug-Induced Liver Injury Network showed that anabolic steroids were the most common cause of DILI in individuals who were heavy alcohol consumers.[146] When heavy drinkers were compared with nondrinkers, however, DILI was not associated with an overall greater proportion of liver-related deaths or LT. Because DILI can present in a variety of different ways, it is important to have a high index of suspicion in patients with alcohol use disorder or ALD who have abnormal liver biochemical test levels.

COFACTORS THAT MAY INFLUENCE PROGRESSION OF ALCOHOL-ASSOCIATED LIVER DISEASE

Many people drink heavily, yet only a limited number (~35%) develop more advanced diseases such as alcohol-associated hepatitis or cirrhosis. Therefore, there must be modifying factors that act to prevent or to facilitate disease activity and progression. These modifiers can either be fixed (e.g., genetics) or can be amenable to intervention (e.g., smoking, diet). Eleven disease modifiers of particular importance to ALD are shown in Box 86.1, and selected

BOX 86.1 Disease Modifiers in Alcohol-Associated Liver Disease

- Age
- Continued drinking
- Diet/nutrition
- Genetics/epigenetics/family history
- Medications and drugs of abuse
- Obesity
- Occupational and environmental exposure
- Other liver diseases
- Race
- Sex
- Smoking

modifiers are reviewed in this section. Some, such as continued drinking (the most important modifier) and genetics, are covered elsewhere in this chapter.

Obesity and smoking are highly associated with ALD. Obesity is also an independent risk factor for disease progression in alcohol-associated hepatitis and cirrhosis.[125,127,147,148] Patients with alcohol-associated cirrhosis who are overweight also appear to be at increased risk for developing HCC.[149] Cigarette smoking has also been shown to accelerate the progression of fibrosis and risk of HCC.[125,150,151]

Diet and nutrition play a major role in ALD, and patients with ALD show various degrees of nutritional deficiency.[152] Studies conducted by the Veterans Health Administration Cooperative Studies Program in patients with alcohol-associated hepatitis[153-156] showed that almost every patient with alcohol-associated hepatitis showed some degree of malnutrition.[154] Approximately 50% of patients' energy intake came from alcohol. Although caloric intake was frequently not inadequate, the intake of protein and critical micronutrients was often deficient. Dietary fat represents a macronutrient dietary modifier for ALD. Dietary unsaturated fat, enriched in linoleic acid in particular, promotes alcohol-induced liver damage.[157-159] Linoleic acid is enzymatically converted to bioactive oxidation products oxidized linoleic acid metabolites that are highly inflammatory and hepatotoxic. Deficiency of the micronutrient zinc also appears to occur early and to play a role in the development and progression of alcohol-associated liver injury.[160]

Alcohol and drugs (including prescription medications, over-the-counter agents, and illicit drugs) may interact to cause hepatotoxicity. For example, chronic alcoholics are more susceptible to acetaminophen hepatotoxicity for multiple reasons (see Chapter 88). Alcohol abuse can occur in HIV-infected patients, and alcohol abuse can enhance hepatotoxicity of certain antiretroviral regimens.[161] Alcohol may also interact with illicit drugs such as 3,4-methylenedioxymethamphetamine (ecstasy), which is commonly used with alcohol.[162]

Exposure to potential toxins in the workplace or environment can cause hepatotoxicity, which can be exacerbated by alcohol. Vinyl chloride (VC) represents a potential industrial exposure the toxicity of which may be exacerbated by alcohol (see Chapter 89). VC-induced histologic steatohepatitis may be indistinguishable from alcohol-induced steatohepatitis and has been termed toxicant-associated steatohepatitis.[163] VC is metabolized in a fashion similar to ethanol, which may account for the observed similarities between toxicant-associated steatohepatitis and alcohol-associated hepatitis. With environmental exposures, there are usually multiple contaminants rather than just one compound. Use of a cocktail of 22 clinically relevant contaminants (Northern Contaminant Mixture) showed that both a high-fat diet and alcohol intake increased the frequency of fatty liver and liver injury in exposed mice.[164]

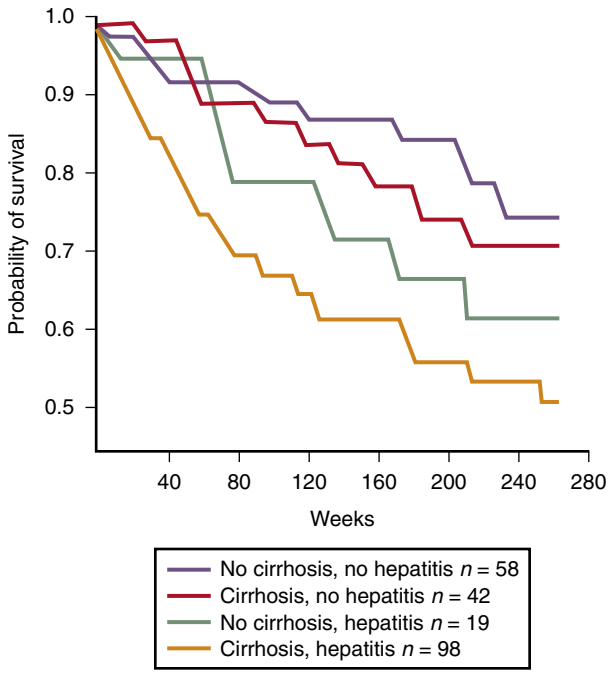


Fig. 86.5 Survival of patients with alcohol-associated liver disease stratified by histologic severity of disease. (From Orrego H, Black JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence or absence of alcoholic hepatitis. Gastroenterology 1987;92:208–14, with permission.)

Female gender is a well-accepted risk factor for the development and rapid progression of ALD.[10,11,165] Studies in rats or mice chronically fed alcohol have also demonstrated that females are more susceptible to liver injury than males. Risk factors for the development of liver disease in females appear to include sex hormone levels, endotoxemia, lipid peroxidation, chemokines, and NF-κB activation. Decreased gastric ADH activity and first-pass metabolism may also contribute to higher blood alcohol levels in women than men. These risk factors are critical for determining "safe" levels of alcohol consumption in women. Indeed, many authorities consider any amount of alcohol above 20 g a day to be a risk factor for the development of liver disease in women.

Race can influence susceptibility to ALD. Research from large multicenter Veterans Affairs studies has shown that alcohol-associated cirrhosis is more frequent in Hispanics (73%) than in non-Hispanic Whites (52%) and African Americans (44%). Moreover, African Americans have been consistently shown to be more likely to have hepatitis B or hepatitis C as confounders.[166]

Between one fourth and one third of patients with ALD also have hepatitis C.[167] Liver disease is more severe, advanced disease develops at a younger age, and survival is shorter in patients with both ALD and HCV infection.[7,125,127,167] In addition, alcohol and HCV act synergistically in the development of HCC (see Chapters 80 and 96).[149,168,169]

PROGNOSIS

The prognosis for individual patients with ALD depends on the degree of pathologic injury, the patient's nutritional status, the occurrence of complications of advanced liver disease, the presence of other comorbid conditions such as obesity and HCV infection, and the patient's ability to discontinue destructive patterns of drinking. Patients with fatty liver have the best outcome, those with alcohol-associated hepatitis or cirrhosis have an intermediate outcome, and those with cirrhosis combined with alcohol-associated hepatitis have the worst outcome (Fig. 86.5).[170] Estimating the prognosis of

TABLE 86.3 Correlation of the Maddrey Discriminant Function (DF)* with Prognosis in Alcohol-Associated Hepatitis

	Non-Severe Disease	Severe Disease
Score	<32	≥32
Short-term mortality rate (%)	10	30-60
Glucocorticoid therapy indicated	No	Yes

*DF = {4.6 × [prothrombin time (sec) – control prothrombin time (sec)]} + (serum bilirubin [mg/dL]).

TABLE 86.4 Correlation of the MELD Score* with 3-month Mortality Rate in Alcohol-Associated Hepatitis

Score	3-Mo Mortality (%)
22	10
29	30
33	50
38	80

*MELD = (0.957 × log [creatinine] + 0.378 × log[bilirubin] + 1.12 × log[INR] + 0.643) × 10.

TABLE 86.5 Correlation of the ABIC Score* and the 90-day Mortality Rate in Alcohol-Associated Hepatitis

Severity	90-Day Mortality (%)
Low (<6.71)	0
Intermediate (6.71-8.99)	30
High (≥9.0)	75

*ABIC score = (age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8).

TABLE 86.6 The Glasgow Alcohol-Associated Hepatitis Score

Parameters	Points		
	1	2	3
Age (yr)	<50	≥50	–
WBC count (10^9/L)	<15	≥15	–
Blood urea nitrogen (mmol/L)	<5	≥5	–
Serum bilirubin level (μmol/L)	<125	125-250	>250
INR	<1.5	1.5-2.0	>2.0

The total score ranges from 5 to 12. A score ≥ 9 indicates a poor prognosis.

patients with ALD is particularly important to determine the need for specific therapy in patients with severe alcohol-associated hepatitis and for LT in those with alcohol-associated cirrhosis.

Alcohol-associated Hepatitis

Patients with alcohol-associated hepatitis account for almost 1% of hospital admissions in the USA. Almost 7% during their initial hospitalization and 40% of those with severe disease die within 6 months of clinical presentation.[171,172] Clinical features associated with severe disease include hepatic encephalopathy, marked prolongation of the prothrombin time, elevation of the serum bilirubin level above 25 mg/dL, and development of renal insufficiency.

A number of models have been shown to predict short-term prognosis in these often critically ill patients.[173] Maddrey and Boitniott developed a simple formula called the discriminant function (DF), which proved useful in identifying patients with poor short-term survival rates.[174] A modification of the original DF (mDF) calculated as {[4.6 × prothrombin time – control value (seconds)] + serum bilirubin (mg/dL)} has proved useful in identifying patients with a poor prognosis who should be considered for specific therapy.[175] Three prospective studies demonstrated that patients with mDF values of 32 or greater have a poor prognosis, with 1-month mortality rates of 35% to 50% (Table 86.3).[175-177] As a result, the mDF has been incorporated into the selection criteria for most therapeutic trials of patients with alcohol-associated hepatitis. The prognosis of patients with mDF values greater than or equal to 32 can be further stratified by the presence of encephalopathy and development of acute kidney injury.[175,178]

Three other prognostic models, the MELD score (see Chapter 97), the Glasgow alcohol-associated hepatitis score, and the ABIC score, have been shown to predict survival in patients with severe alcohol-associated hepatitis (Tables 86.4 to 86.6).[179,180] Although none is perfect, each of these models appears to be effective in selecting patients for medical therapy.[125,127,181] The short-term survival of patients with mDF values less than 32 have ranged from 83% to 100% in various studies.[181] To determine the prognosis of all patients with alcohol-associated hepatitis more accurately, a scoring system (ABIC) has been proposed that separates patients into 3 groups with predicted 3-month survival rates of 25%, 70%, and 100% based on the patient's age, bilirubin, INR, and creatinine (see Table 86.5).[182]

Alcohol-associated Cirrhosis

The 5-year mortality rate of patients with alcohol-associated cirrhosis ranges from 60% to 85%.[183] Within 15 years, 90% of patients can be expected to die if they do not undergo LT.[184] The prognosis of individual patients is dependent on the development of various complications. The 1-year mortality rate is 15% to 20% in patients with no complications, 20% following variceal bleeding, 30% after the onset of ascites, 50% in those with variceal bleeding and ascites, and 65% following the development of hepatic encephalopathy.[183] The clinical tool used most widely to determine prognosis in patients with alcohol-associated cirrhosis is the Child-Turcotte-Pugh (CTP) score (see Chapter 97). Although it has limitations, the CTP score been adopted widely for risk-stratifying patients with cirrhosis because of its simplicity and ease of use. Five-year survival rates for patients with alcohol-associated cirrhosis vary dramatically based on the CTP score at the time of clinical presentation (Fig. 86.6).[185,186] The other model that has been used to predict prognosis in patients with alcohol-associated cirrhosis is the MELD score. The MELD model, which is useful for predicting short-term survival in groups of patients with various liver diseases, is the system used for allocation of donor organs in the USA (see Chapter 97).

Acute-on-Chronic Liver Failure

Patients with stable, compensated cirrhosis can gradually develop complications or suddenly develop jaundice and coagulopathy with the rapid onset of ascites or encephalopathy, a syndrome referred to as acute-on-chronic liver failure (see Chapter 74).[183,187,188] The 3 most common precipitating factors are superimposed alcohol-associated hepatitis due to an increase in alcohol intake, a viral infection, and drug toxicity.[189]

Patients hospitalized with decompensated cirrhosis or acute-on-chronic liver failure are inordinately predisposed to infection and the subsequent development of hepatic encephalopathy, sepsis, acute kidney injury, and multiorgan failure.[190,191] The 90-day mortality rate of patients who require ICU management for 3 or more failing organ systems due to these complications exceeds 90%.[192] The prognosis of patients hospitalized in the ICU is more accurately reflected by Sequential Organ Failure

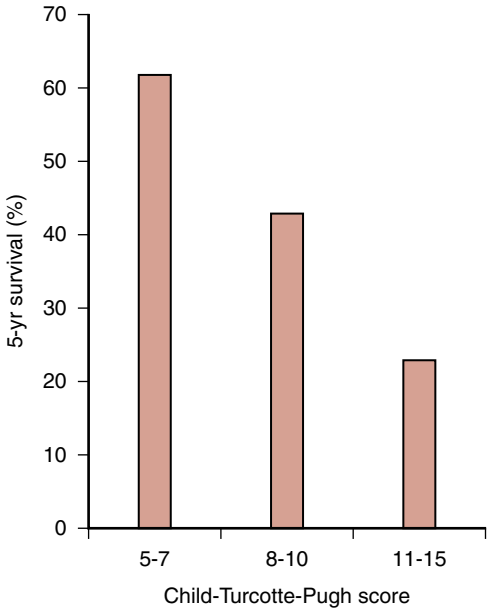


Fig. 86.6 Five-year survival rates in patients with alcohol-associated cirrhosis according to their Child-Turcotte-Pugh scores. (Data from Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005–23; and Gleeson D, Evans S, Bradley M, et al. HFE genotypes in decompensated alcoholic liver disease: phenotypic expression and comparison with heavy drinking and with normal controls. Am J Gastroenterol 2006;101:304–10.)

Assessment score than by the CPT or other liver-related scores (Chapter 74).[125,192,193]

Acute Viral Illness

Patients with alcohol-associated cirrhosis are vulnerable to sudden decompensation from infection with hepatotropic viruses including HAV, HBV, HEV, and nonhepatotropic viruses such as influenza A.[187] The potential for sudden deterioration from these infections underscores the importance of routine immunizations in all persons with ALD.[194]

Hepatotoxic Drugs

Sudden and unexplained clinical deterioration in patients with alcohol-associated cirrhosis can also result from ingestion of hepatotoxic medications and herbal remedies. The morbidity and mortality associated with these conditions are considerable. Because of induction of CYP2E1, drinkers are uniquely susceptible to acetaminophen hepatotoxicity (see Chapter 88). Chronic alcoholics who take excessive doses of this drug over a period of days to weeks for relief of a headache, toothache, or other minor pain can experience sudden deterioration of their clinical condition.[195] The clinical features in these patients are indistinguishable from those of ALD, with one obvious exception: AST values are frequently more than 1000 U/L, much higher than expected in patients with ALD. Because liver injury has already occurred by the time of hospitalization, acetaminophen levels are usually not helpful for diagnosis or management. Recognition of the cause of the unusually elevated serum aminotransferase levels comes from careful questioning of the patient and family about acetaminophen ingestion in the days to weeks before hospitalization. Sudden clinical deterioration in a patient with alcohol-associated cirrhosis also can result from an idiosyncratic hepatotoxic reaction to a number of other drugs and herbal and dietary supplements (see Chapters 88 and 89).[196,197]

HCC

Although the incidence of many other cancers is decreasing in the USA, HCC has approximately doubled in incidence since 2000, and alcohol has been postulated to play a major etiologic role (see Chapter 96). Some of the potential mechanisms for the initiation and promotion of HCC by alcohol include acetaldehyde-DNA adduct formation, generation of ROS, chronic inflammation, glutathione depletion, hypomethylation of oncogenes, retinoic acid depletion in hepatocytes, liver fibrosis, and decreased natural killer cell function and number.[198] Alcohol has also been shown to potentiate liver cancer in animal models. The true frequency of HCC in patients with alcohol-associated cirrhosis is still somewhat unclear.[199] Although ALD has been long considered to be the leading cause of HCC in the USA and Europe, many affected patients were also infected with HCV. Studies suggest that the incidence of HCC is 2 to 3 times higher in HCV coinfected patients than in the normal population without evidence of HCV infection.[23] The risk of HCC shows a strong correlation with alcohol intake and is roughly doubled in persons with concurrent HCV infection.[169] The risk of HCC is higher in men than women and increases with age.[149] Given the ongoing risk for HCC, lifetime surveillance with imaging every 6 months is recommended for all patients with alcohol-associated cirrhosis (see Chapter 96).[199]

TREATMENT

Therapy for ALD can be viewed as an inverted pyramid, with all patients receiving lifestyle modification, most receiving nutritional intervention, some receiving drug therapy, and only a few considered for LT. Importantly, therapy should be directed, in part, by disease severity.

Abstinence and Lifestyle Modification

Abstinence from continued excessive drinking is the most important predictor of survival in patients with alcohol-associated cirrhosis.[125,127,184,186,200] The 3-year survival rate is 70% to 80% among patients who abstain or dramatically reduce their excessive drinking, compared with only 20% to 30% in those who continue to drink heavily.[200] Reducing, but not completely stopping, alcohol consumption also has been shown to improve survival (Fig. 86.7).[184] The question is how best to achieve these goals effectively.

The first steps are to identify excessive drinking, determine the severity of the drinking problem, and assess the patient's motivation for change. Patients may experience risky drinking, alcohol abuse, or dependence.[201] Patients with risky drinking without dependence respond well in primary care settings to brief interventions that result in reduced consumption and reductions in alcohol-related injury and mortality.[125,202] Brief interventions have also been effective in reducing alcohol intake in pregnant women, with a subsequent reduction in fetal mortality.[124] Most patients seen in acute care settings by a gastroenterologist have alcohol abuse or dependence. Although brief interventions may be very effective in individual patients, the majority need a referral to a qualified alcohol and substance abuse counselor for assessment and specialty treatment if they are to have the best opportunity to achieve long-term remission. From 20% to 30% of patients remain abstinent for a year after a single course of treatment, and another 10% reduce their intake to the point that they no longer experience adverse consequences from their drinking.[201]

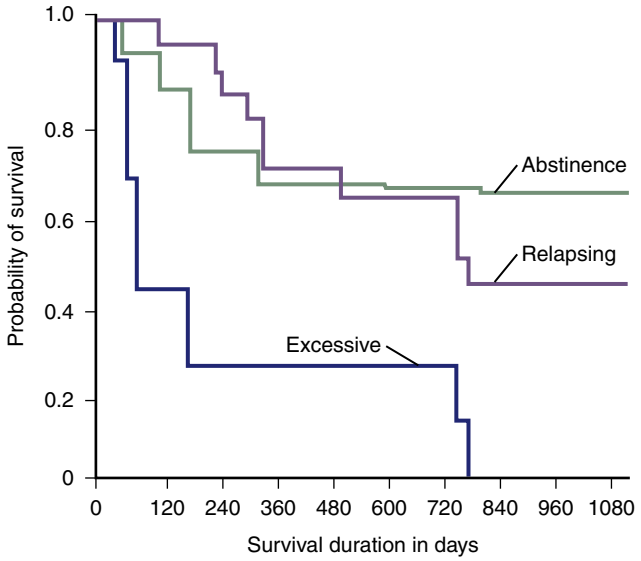


Fig. 86.7 Survival curves during the 3 years following hospital discharge for alcohol-associated cirrhosis according to alcohol consumption: *abstinence*: patients who were abstinent; *relapsing*: patients with one or more periods of abstinence alternating with one or more periods of excessive consumption; *excessive*: patients with excessive consumption of alcohol at the first follow-up point. Survival differed significantly between abstinent and excessively drinking patients ($P < 0.001$). (Modified with permission of Veldt BJ, Laine F, Guillygomarc'h A, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: qualitative evaluation and optimal timing. J Hepatol 2002;36:93–8.)

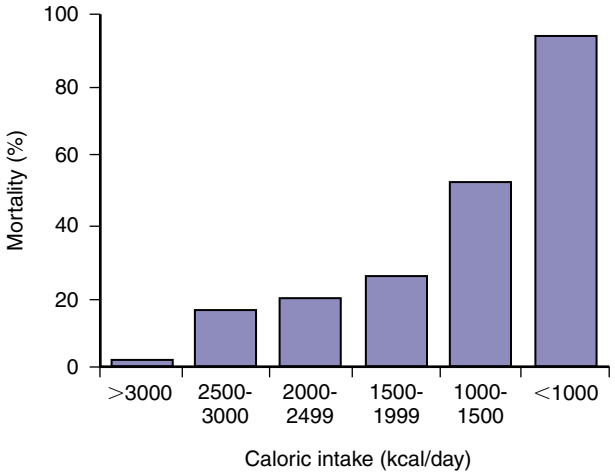


Fig. 86.8 Relationship between voluntary dietary intake and survival in patients with severe alcoholic hepatitis. (From McClain CJ, Barve SS, Barve A, Marsano L. Alcoholic liver disease and malnutrition. Alcohol Clin Exp Res 2011;35:815–20, with permission.)

Three oral medications (disulfiram, acamprosate, and naltrexone) and an extended-release injectable form of naltrexone have been approved by the FDA to treat alcohol dependence. Pharmacotherapy with these agents is only modestly effective; however, all have side effects and are underused.[125,127,201] *Baclofen*, a gamma aminobutyric acid B-receptor agonist, shows promise in decreasing craving and improving abstinence and thus decreasing the likelihood of relapse in patients with alcohol-associated cirrhosis.[125,203] Baclofen (studied in alcohol-associated cirrhosis) and acamprosate are the only 2 agents that should be considered in persons with ALD. Given the limited efficacy of the currently available medications to prevent relapse, a number of new approaches are under active investigation.[204] These include therapy to decrease neuroinflammation, which may be a factor in continued alcohol intake. Involvement in mutual support groups, such as Alcoholics Anonymous, can reduce the risk of relapse, primarily by building social support for sobriety.[201] An excellent guide to various treatment strategies is available at: https://www.niaaa.nih.gov/research/major-initiatives/medications-development-program. The National Institute on Alcoholism and Alcohol Abuse Alcohol Treatment Navigator also has a website that provides information on local treatment programs (https://alcoholtreatment.niaaa.nih.gov).

The goal of intervention should be sustained abstinence, which improves the histologic features of alcohol-associated liver injury, reduces portal pressure, and slows progression to cirrhosis.[125,127] In two thirds of patients, significant clinical improvement can be seen within 3 months.[127] Within 2 years, many patients achieve complete clinical and biochemical recovery, regain lost muscle mass, and can safely stop diuretics and other liver-related medicines.[205] Although reducing alcohol intake to "safe" levels does reduce mortality and morbidity, only 10% of individuals are able to maintain safe levels of drinking over extended periods of time.[201] Three quarters of patients have a relapse within 1 year. Longitudinal care by the treatment program is important. Clinicians can also be helpful by providing regular visits in a nonjudgmental manner and providing ongoing counseling and support of the longer-term treatment goals.[201] It is also important to address obesity and smoking, the 2 comorbidities associated with progression of ALD.

Nutritional Support

Malnutrition is a widespread clinical problem among patients with ALD. Every patient with moderate to severe alcohol-associated hepatitis or cirrhosis shows some signs of malnutrition, which is associated with higher rates of liver-related complications and mortality. Malnutrition has also been associated with longer ICU stays, longer durations of hospitalization, and higher mortality rates after LT.[206] Provision of adequate nutritional support is the most frequently overlooked aspect of the management of patients with ALD.

Accurate assessment of the nutritional status of patients with liver disease can be quite difficult. Many of the tests typically used for this purpose are influenced by either the liver disease or alcohol consumption. Visceral proteins such as albumin and prealbumin are produced in the liver, and serum levels correlate better with the severity of liver disease than nutritional status. Anthropometric measurements such as BMI and the creatinine-height index are unreliable in patients with altered renal function and fluid retention.[205,206] The subjective global assessment of protein-energy malnutrition, a simple bedside tool, often reveals obvious malnutrition, particularly in patients with muscle wasting and ascites.[205-207] Measurement of handgrip strength and middle arm muscle mass can also be helpful in assessing the nutritional status of these patients.[206,207]

Adequate nutritional support is critical to the management of patients with severe alcohol-associated hepatitis. In 2 large Veterans Administration studies, 6-month mortality correlated in a dose-responsive fashion with voluntary dietary intake (Fig. 86.8).[205] Despite this knowledge and expert care by nutritionists and hepatologists, two thirds of patients failed to consume the recommended caloric intake of 2500 kcal/day.[205] It is typical for patients with severe alcohol-associated hepatitis to spend extended periods of time in the hospital with inadequate nutritional intake. These patients often have little or no appetite for prolonged periods and are deprived of adequate nutrition by their caregivers because of dietary restrictions of salt, water, and protein as well as intermittent interruption of all nutritional support for various procedures. Patients with severe alcohol-associated hepatitis often develop

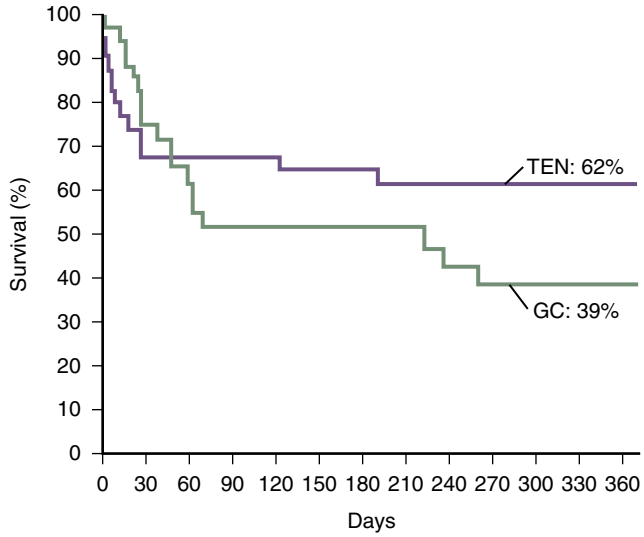


Fig. 86.9 Probability of survival for one year after randomization of 72 patients with severe alcohol-associated hepatitis to total enteral nutrition (*TEN*) or to glucocorticoid therapy (*GC*). (From Cabre E, Rodriguez-Iglesias P, Caballeria J, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology 2000;32:36–42, with permission.)

a hypermetabolic state with higher than normal resting energy expenditure. Because of the vital need for adequate nutrition in these often critically ill patients, we do not hesitate to place an NG feeding tube if the patient cannot voluntarily ingest at least 2500 kcal/day, even when esophageal varices are present.[205,208] Glucocorticoid therapy can increase voluntary dietary intake, but providing adequate calories through enteral feeding provides the same 1-month survival benefit with significantly lower mortality at 1 year (Fig. 86.9).[136,209]

Patients with stable cirrhosis have nutritional deficiencies almost as severe as those found in patients with alcohol-associated hepatitis.[205] The frequency of malnutrition increases with the severity of disease. For example, the risk of profound malnutrition increases from 45% in patients with Child-Pugh class A to 95% in those with Child-Pugh class C cirrhosis.[205,206] Patients with cirrhosis who require hospitalization have a substantially higher prevalence of malnutrition compared with general medical inpatients and have significantly longer hospital stays and a 2-fold higher risk of in-hospital mortality.[210] Even in patients with stable, compensated cirrhosis, malnutrition is associated with higher 1-year mortality (20% vs. 0%) and complication rates (65% vs. 13%).[206,207]

Hepatic glycogen stores are depleted in patients with cirrhosis. As a result, these patients go into an early starvation mode after only 12 hours of fasting compared with 48 hours in normal persons. Therefore, even short periods of inadequate nutrition can result in peripheral muscle proteolysis, which contributes to protein malnutrition. Patients with decompensated cirrhosis also can be hypermetabolic. Not surprisingly, the protein intake recommended for patients with cirrhosis is higher than that for healthy adults.[207,208] The positive impact of judicious nutritional supplements in patients with cirrhosis is illustrated by a randomized trial showing that a nighttime snack of 700 kcal each evening resulted in an accrual of 2 kg of lean tissue over 12 months.[211] Therefore, patients with severe alcohol-associated hepatitis or cirrhosis should be given nighttime (9 PM) snacks to prevent "starvation" overnight; this is especially important in the outpatient setting.

Protein restriction has no beneficial effect on encephalopathy and can be nutritionally catastrophic.[205,207,212] If, despite appropriate medical therapy, standard enteral formulas lead to encephalopathy, a branched-chain amino acid-enriched formula can be given as a supplement to meet nitrogen needs (see Chapter 94).[205,208]

Patients with ALD also can have a plethora of vitamin and mineral deficiencies.[205,206] In addition to the commonly recognized deficiencies in folate and B vitamins, deficiencies in fat-soluble vitamins (A, D, and E) and minerals (magnesium, selenium, and zinc) are common causes of symptoms and physical findings in these patients.[206] Zinc deficiency, for example, may contribute to the skin lesions, night blindness, mental irritability, confusion and hepatic encephalopathy, anorexia, altered taste and smell, hypogonadism, and altered wound healing so commonly seen in patients with ALD.[213] Assessment and judicious corrections of each of these deficiencies is an important aspect of the care of these patients.

The nutritional status of patients at the time of LT is also important. Morbid obesity and severe malnutrition are each predictors of a poor outcome.[214] Among those transplanted in the USA since the late 1990s, extremes of BMI (<18.5 and >40) were more common in patients with ALD than in patients transplanted for other conditions. Severely malnourished patients had longer lengths of stay, a higher retransplantation rate, and diminished survival.[214] A reduced cross-sectional area of the psoas muscle measured by CT has shown a strong correlation with poor survival following transplantation, confirms the importance of malnutrition in these patients, and may offer a means of more systematic and objective detection of this condition in future transplant candidates.[215]

Specific Therapy for Alcohol-Associated Hepatitis

Glucocorticoids and Pentoxifylline (PTX)

Glucocorticoid therapy was first demonstrated to provide a short-term survival benefit for patients with severe alcohol-associated hepatitis in a small USA prospective randomized multicenter trial in the late 1980s.[175] Each of the patients enrolled had a clinical diagnosis of alcohol-associated hepatitis and either an mDF greater than 32, spontaneous hepatic encephalopathy, or both. Treatment consisted of 32 mg of methylprednisolone daily for 28 days followed by a 2-week taper. The 28-day mortality rate among patients who received prednisolone was only 6%, compared with 35% among the placebo-treated controls. It is now generally accepted that glucocorticoid therapy has a beneficial effect on one-month survival, as confirmed by many studies over the ensuing years, although this effect is now documented to be relatively modest. Unfortunately, there is no benefit in survival at 3 or 6 months. These data are supported by a meta-analysis of studies of glucocorticoid therapy in severe alcohol-associated hepatitis.[216]

Glucocorticoids work by binding to glucocorticoid receptors (GRs) in the cytoplasm. GRs then translocate to the nucleus and bind to the GR elements in the promoter regions of glucocorticoid responsive genes to switch on expression of certain anti-inflammatory genes and reduce inflammation.[217] Unfortunately, many patients are "glucocorticoid resistant" through multiple mechanisms and do not respond to glucocorticoid therapy. Early identification of the subset of resistant patients (25% to 30%) is important for implementing alternative treatment strategies. One simple and clinically used definition of glucocorticoid resistance in severe alcohol-associated hepatitis patients is the lack of an early improvement in serum bilirubin levels at 7 days.[218] The subsequently developed Lille model score allows patients to receive a 7-day course of glucocorticoids and then assesses the responsiveness based on an algorithm that combines age, serum albumin, serum creatinine, prothrombin time, serum bilirubin, and change in bilirubin level at day 7 (Box 86.2). Patients with a score greater than or equal to 0.45 had a 6-month survival rate of 25%, and glucocorticoids could be discontinued in them. Those patients

BOX 86.2 The Lille Model Score*

PARAMETERS

Age
Albumin
Bilirubin (initial)
Bilirubin level (day 7)
Creatinine
Prothrombin time

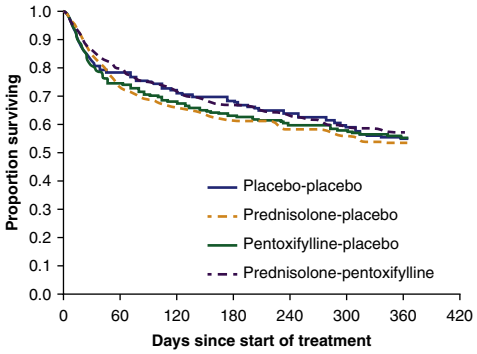
*The Lille score = 3.19 – 0.101 (age [yrs]) + 0.147 (serum albumin [g/L]) + 0.0165 (change in serum bilirubin at day 7) – 0.206 (serum creatinine [mg/dL]) – 0.0065 (baseline serum bilirubin [mg/dL]) – 0.0096 (prothrombin time [sec]).
The score at 7 days determines response to treatment. A score of < 0.45 is associated with a 15% mortality rate at 6 months. A score of ≥ 0.45 is associated with a 75% mortality rate at 6 months.

with scores less than 0.45 had an 85% survival rate and benefited from continued glucocorticoid treatment. This scoring system allows discontinuation of glucocorticoids early in patients in whom there is no benefit to continuing them.[219]

PTX is a nonselective phosphodiesterase (PDE) inhibitor that was shown to lead to a survival benefit in initial studies and that has been used by many hepatologists as an alternative to glucocorticoids.[220,221] It appeared to be especially effective in preventing and treating early hepatorenal syndrome (see Chapter 94). Treatment with PTX increases intracellular concentrations of cyclic adenosine monophosphate and cyclic guanosine monophosphate. Increased cyclic adenosine monophosphate concentrations positively modulates the cytokine inflammatory response, with a decrease in the proinflammatory cytokine TNF and an increase in the anti-inflammatory cytokine IL-10. Unfortunately, later studies did not confirm beneficial survival effects of PTX in patients with severe alcohol-associated hepatitis, due in part to the advent of new and better modalities to treat hepatorenal syndrome and better medical management of severe alcohol-associated hepatitis, as well as the need for PTX to be taken 3 times a day and associated GI distress, thus limiting adherence. PTX is also a weak PDE inhibitor, and much more robust and specific PDE inhibitors are now available.

The pivotal study involving current therapy for severe alcohol-associated hepatitis was the STOPAH trial, which evaluated prednisolone, PTX, the combination, or placebo in severe alcohol-associated hepatitis.[222] This large, multicenter trial of more than 1000 patients showed a modest beneficial effect of prednisolone at 28 days, but no later beneficial effect on mortality. For all groups, 28-day and 90-day mortality rates were excellent at less than 20% and less than 30%, respectively (Fig. 86.10). Unfortunately, the overall one-year mortality rate was 56%, and only about 37% of people remained abstinent at one year. Therefore, return to drinking was a major health problem. The study confirmed the beneficial effects of glucocorticoids on one-month survival and suggested that PTX has no impact on survival. Moreover, the combination of PTX and glucocorticoids showed no significant benefit. Other studies have shown that switching glucocorticoid-resistant patients to PTX does not improve survival.

Therefore, at the current time, one can use glucocorticoids in selected patients with severe alcohol-associated hepatitis.[223] Early stopping rules should be applied at one week, or even earlier (4 days), to ensure that glucocorticoids are used only in those patients who will benefit (Fig. 86.11). Some hepatologists may continue to use PTX in selected patients because it has a good safety profile. Clearly, new drugs are needed. New approaches are also needed in which new drugs are given based on the severity of disease and for varying durations of time. Multiple drug therapies that attack multiple targets is also an attractive approach.



No. at risk							
Placebo-placebo	272	199	159	142	121	104	89
Prednisolone-placebo	274	182	139	116	102	91	84
Pentoxifylline-placebo	271	178	133	119	104	95	83
Prednisolone-pentoxifylline	272	201	157	137	115	101	84

Fig. 86.10 Results of the STOPAH Trial. Survival curves for all 4 study groups up to 1 yr are shown. A nonsignificant survival advantage during the first 28 days was seen in patients with severe alcohol-associated hepatitis who received prednisolone as compared with those who did not receive prednisolone (odds ratio, 0.72; 95% confidence interval [CI], 0.52 to 1.01; $P = 0.06$). No significant survival advantage was seen for patients who received pentoxifylline as compared with those who did not receive pentoxifylline (odds ratio, 1.07; 95% CI, 0.77 to 1.49; $P = 0.69$). (From Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619–28.)

Drugs of Unlikely Benefit and Promising New Agents Under Investigation

A number of other therapeutic agents have been studied in patients with alcohol-associated hepatitis. These include androgenic steroids, propylthiouracil, antioxidants, and specific anti-TNF therapy. None has been shown to improve survival.[5,125-127,171,181] The National Institutes of Health have supported several studies to evaluate novel mechanisms and new therapies for alcohol-associated hepatitis. One program used an IL-1-receptor antagonist, based in part on very high IL-1 levels in the serum of patients with alcohol-associated hepatitis and the fact that IL-1-receptor blockade attenuates experimental alcohol-associated hepatitis.[224] This study in patients with severe alcohol-associated hepatitis combined IL-1 inhibitor therapy with PTX and zinc. For moderate alcohol-associated hepatitis, a probiotic (*Lactobacillus* GG) was used in one study as was an oral agent that inhibits intestinal absorption of endotoxin in another trial (the results have not yet been analyzed). Trials of granulocyte colony-stimulating factor (G-CSF) have shown promise in patients with severe alcohol-associated hepatitis.[225] G-CSF is thought to stimulate liver regeneration and improve granulocyte function. Based on the aforementioned data, the National Institutes of Health has funded a multicenter study evaluating prednisone versus anakinra (an IL-1 receptor antagonist) plus zinc versus G-CSF. The primary end point is mortality at 90 days. A nondrug therapy that has received much recent attention in severe alcohol-associated hepatitis is fecal transplantation, which has shown positive results in pilot studies.[226,227] Table 86.7 lists multiple drugs under clinical investigation for alcohol-associated hepatitis or cirrhosis.

There are several new therapeutic approaches based on preclinical discoveries that may deserve exploration in future clinical trials. Levels of the spleen tyrosine kinase were shown to be increased in animal models of alcohol-associated hepatitis and ALD, and in vivo administration of a chemical spleen tyrosine kinase inhibitor significantly reduced alcohol-induced steatosis, liver damage, inflammation, and fibrosis.[228] Mice treated with allopurinol, which reduces the levels of the endogenous DAMP uric acid, or with probenecid, a drug that promotes uric acid renal excretion

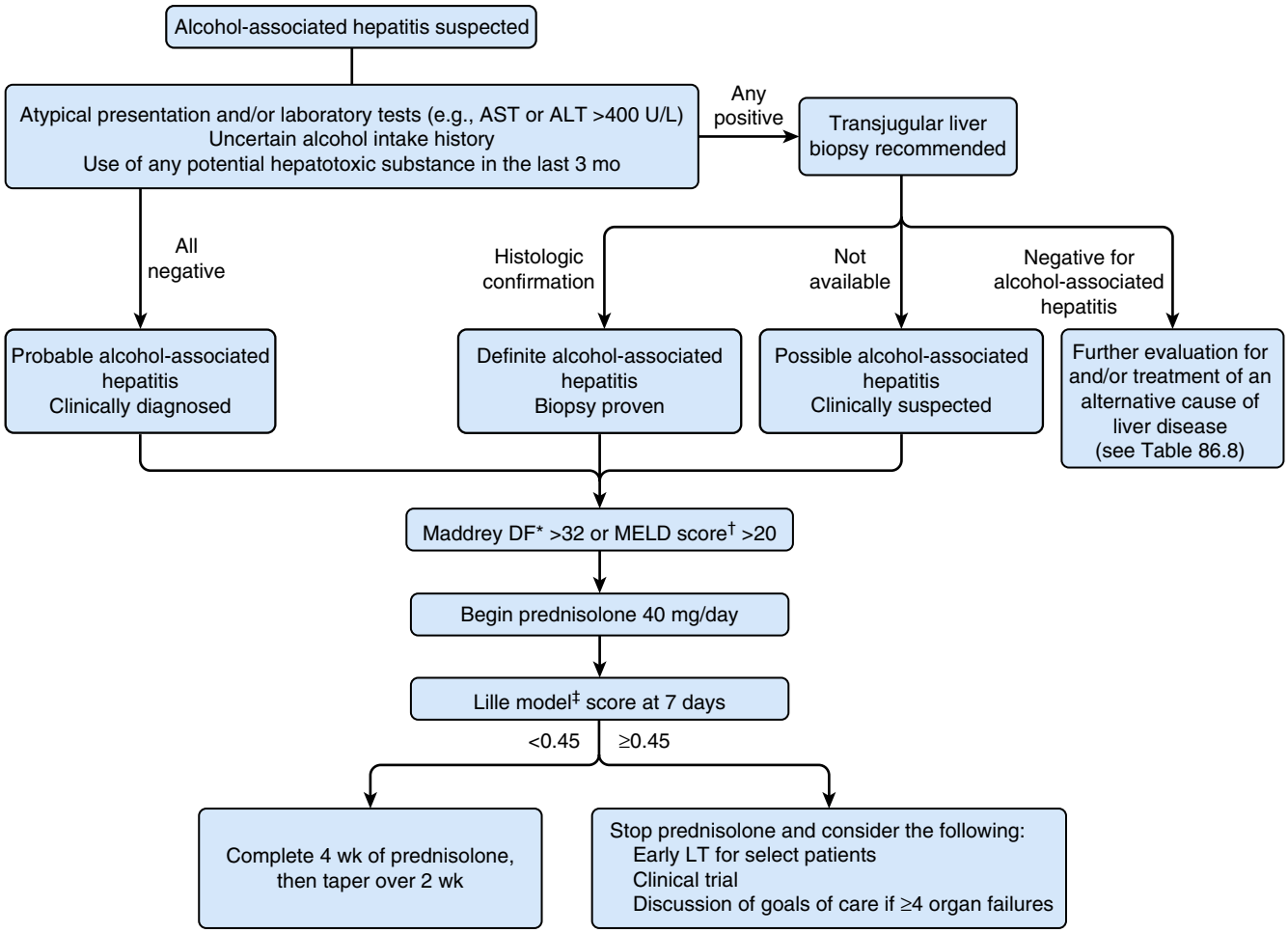


Fig. 86.11 Algorithm for the management of a patient with suspected alcohol-associated hepatitis. *The Maddrey discriminant function (DF) is calculated as follows: 4.6 (prothrombin time of patient – prothrombin time of control) + serum bilirubin level (in mg/dL). †The MELD score is based on the serum bilirubin level, INR, and serum creatinine level (see Chapter 97). ‡The Lille model score is based on the patient's age, serum albumin, serum bilirubin, serum creatinine, and prothrombin time. Online calculators for these various models are available at http://www.lillemodel.com.

TABLE 86.7 Drugs Used or Studied for the Treatment of Alcohol-Associated Hepatitis

Not Effective	Currently Used	Under Investigation
Anabolic steroids	Glucocorticoids	Antibiotics
Antioxidants	Pentoxifylline	Anti-endotoxins
Colchicine		Cytokine inhibitors/ inflammasome inhibitors
Lecithin		FXR agonists/nuclear hormone receptor modulators
Propylthiouracil		Inhibitors of cell death
S-Adenosylmethionine		Prebiotics/probiotics/ nutritional therapies
		Stimulators of regeneration

FXR, farnesoid-X receptor.

and inhibits ATP signaling, have shown significant attenuation of alcohol-induced liver damage, steatosis, and inflammation.[76] The beneficial effects of these drugs are linked to attenuation of NLRP3 inflammasome activation.[76] Another "old" medication, digoxin, was shown to be effective in maintaining cellular homeostasis and suppressing HIF-1α pathway activation in ALD as well as in NASH.[229]

In a murine model of chronic binge ethanol feeding, administration of IL-22 ameliorated alcohol-associated liver injury. The beneficial effects of IL-22 were attributed to antioxidant and antiapoptotic effects, and IL-22 also reduced liver steatosis and had antimicrobial effects.[230] IL-22 administration is being studied in an open-label human clinical trial. Inhibition of CCR2/CCR5 signaling with a small molecule inhibitor showed a remarkable reversal of ALD when administered to mice for the treatment of liver damage (serum ALT increase), steatosis, macrophage and neutrophil infiltration, inflammatory cytokine production, and liver fibrosis.[231] Cenicriviroc, the CCR2/CCR5 inhibitor, is in phase 3 human clinical trials of NASH fibrosis and will be studied in ALD.

Recommendations

Glucocorticoid therapy can result in dramatic improvement in survival in carefully selected patients with severe alcohol-associated hepatitis.[175,176] Three factors limit its usefulness: (1) a number of patients are not candidates for therapy because of obvious contraindications; (2) a significant number of patients fail to respond; and (3) glucocorticoids have limited efficacy in patients with chronic kidney disease or acute kidney injury and

TABLE 86.8 Factors to Consider in the Approach to the Patient with Suspected Severe Alcohol-Associated Hepatitis

INITIAL FINDINGS THAT SUPPORT A DIAGNOSIS OF ALCOHOL-ASSOCIATED HEPATITIS	
Clinical presentation	Prolonged heavy alcohol intake, recent-onset jaundice, malaise, ascites, edema, pruritus, fever, confusion/lethargy/agitation, asterixis, tender hepatomegaly, splenomegaly, pedal edema
Laboratory features	Abrupt rise in serum total bilirubin (>3 mg/dL), AST > ALT (usually > 2X ULN), GGTP > 100 U/mL, albumin < 3.0 g/L, INR > 1.5, leukocyte count > 12,000/mm^3
EXCLUSION OF OTHER CAUSES OF JAUNDICE	
Autoimmune hepatitis	Exclude severe autoimmune hepatitis if first episode and/or clinical suspicion (see Chapter 90)
DILI	Review detailed history of medication, supplements, pharmacy records Consult http://livertox.nih.gov (see Chapter 88)
Ischemic hepatitis	Suspect if hypotension, septic shock, massive bleeding, or recent cocaine use (see Chapter 85)
Mechanical obstruction	Rule out HCC, biliary obstruction, Budd-Chiari syndrome Perform Doppler abdominal US, and, if indicated, MRI
Viral hepatitis	Rule out acute hepatitis A, B, C, or E, especially if first episode or high clinical suspicion (see Chapters 78-82)
TREATMENT OF ALCOHOL ABUSE AND LIVER-RELATED COMPLICATIONS	
Alcoholism	Consult addiction specialist Moderate withdrawal symptoms: baclofen Severe withdrawal symptoms: benzodiazepines, phenobarbital
Hepatic encephalopathy	Assess for precipitant: GI bleed, infection, medication nonadherence Treat underlying precipitant, add lactulose, rifaximin, zinc (see Chapter 94)
Infection	Rule out pneumonia, cellulitis, SBP, urinary tract infection, meningitis Obtain chest film Broad-spectrum antibiotics, if indicated
Renal insufficiency	Early detection and close monitoring Volume expansion with albumin Consider IV albumin plus a vasoconstrictor if progressive hepatorenal syndrome (see Chapter 94)

ULN, upper limit of normal.

do not appear to prevent the development of hepatorenal syndrome. Therefore, in patients who have contraindications to glucocorticoid therapy or any degree of renal disease, aggressive standard medical care with attention to factors such as nutrition, infection, and adequate perfusion should be pursued, and opportunities for clinical trials of LT should be considered (see later). Table 86.8 lists the factors that should be taken into account in the approach to patients with suspected severe alcohol-associated hepatitis.

Specific Therapy for Alcohol-Associated Cirrhosis

Abstinence is the only treatment that clearly improves survival in patients with alcohol-associated cirrhosis. All patients should also receive optimal inpatient and outpatient nutritional support. A variety of treatments for which there is a specific rationale have been investigated over the years, including silymarin, SAMe, betaine, colchicine, androgenic steroids, lecithin, vitamin E, and PTX. None, however, has been shown to improve survival.[5,125]

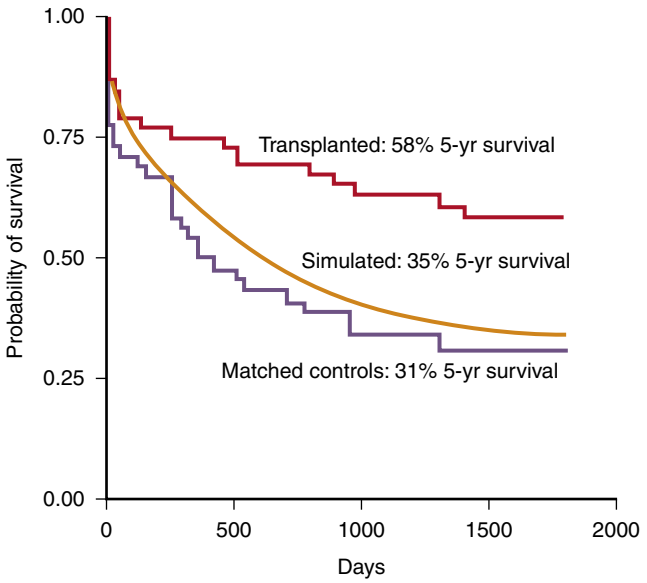


Fig. 86.12 Improved probability of survival over 5 years in patients with Child-Turcotte-Pugh scores of 11 to 15 after 6 months of abstinence from alcohol who underwent LT (*top line*), compared with matched control subjects ($P = 0.008$) and simulated control subjects (i.e., predicted from a model) ($P = 0.001$). (Modified from Poynard T, Naveau S, Doffoel M, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. Multi-centre group. J Hepatol 1999;30:1130-7.)

LT

Alcohol-associated cirrhosis is the second most common indication for LT in the USA and Europe and is likely to become the most common in the USA due to the advent of DAAs for HCV infection (see Chapter 80).[232] The outcome following LT is quite favorable (see also Chapter 97).[233] Important factors that reduce survival after transplantation are concurrent HCV infection, smoking-related cancers, cardiovascular disease, and a return to destructive patterns of drinking.[151,233-236] Although almost half of the transplant recipients drink some alcohol after LT, few return to destructive patterns of alcohol use.[237] A multidisciplinary approach both before and after the operation, including addiction specialists, psychiatrists, and transplant professionals, appears to offer the best opportunity for patients with ALD to achieve long-term high quality of life after LT.[238,239]

Many patients with apparently advanced alcohol-associated cirrhosis can recover to the degree that LT is not required if they can abstain from drinking (Fig. 86.12).[200] Because the benefits of abstinence can be so dramatic, requiring a period of abstinence before proceeding with transplantation is reasonable; however, if patients do not show evidence of significant recovery within 3 months, they are unlikely to survive without transplantation.[232] Referral to a transplant center at that time for further evaluation of their alcoholism and candidacy for transplantation gives patients the best opportunity to be placed on the transplant waiting list after the traditional 6-month abstinence period required by many transplant centers and insurance companies. This "6-month rule" was initiated in 1997 to help ensure maximal hepatic recovery off alcohol and to document sobriety; however, this arbitrary time limit has not been shown to affect long-term survival or sobriety.

It is important to be able to diagnose alcohol consumption accurately as part of the transplant evaluation process and

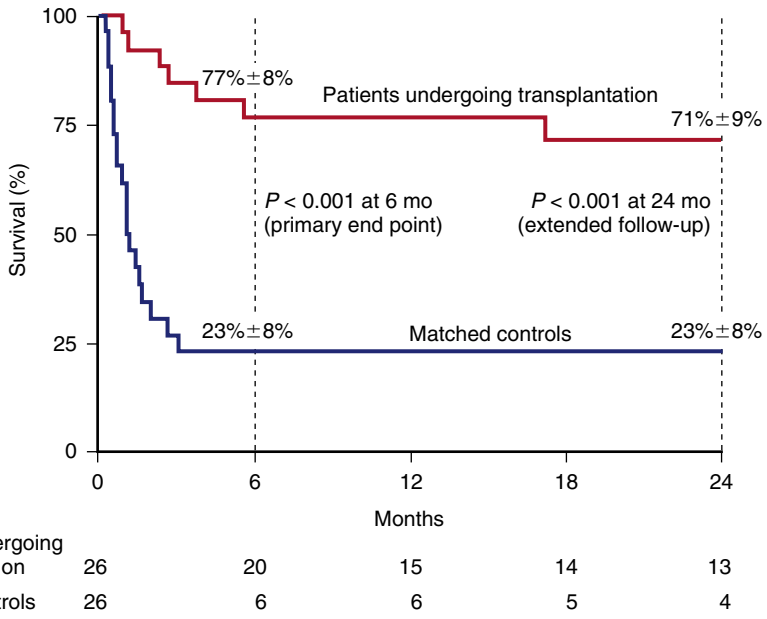


Fig. 86.13 Kaplan-Meier estimates of survival in 26 patients with severe alcohol-associated hepatitis who failed corticosteroid therapy and underwent early LT compared with matched controls who did not undergo LT. (From Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790–800, with permission.)

following transplantation. As noted previously, various methods of history taking, unique biomarkers, and wearable alcohol sensors have been proposed. Studies have suggested that addiction experts may be better than hepatologists at uncovering alcohol intake post-transplantation,[240] supporting a team approach to diagnosis and follow-up. Moreover, the phosphatidyl ethanol level has been reported to be 100% specific, detects more than 90% of moderate-to-heavy drinkers, and has been used to detect clandestine drinking post-transplantation.[241]

Patients with severe alcohol-associated hepatitis traditionally have not been considered to be appropriate candidates for LT because of recent drinking, the fear that they will return to drinking after the transplant, and the assumption that many will recover with abstinence or appropriate medical therapy.[5,127,171] These assumptions were challenged by a multicenter French-Belgian study in which carefully selected patients with severe alcohol-associated hepatitis who failed to respond to glucocorticoid therapy were shown to have a dramatic improvement in survival with early LT compared with matched controls who did not undergo LT (Fig. 86.13).[242] These initial results from Europe have been replicated in a single-center pilot program in the USA (100% survival at 6 months)[243] as well as in the ACCELERATE-AH study from the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis—12 centers in 8 UNOS regions (see Chapter 97).[244] In that study, 1- and 3-year survival rates were excellent (94% and 84%, respectively), and sustained alcohol use was 17% at 3 years. With expanded indications and better multidisciplinary approaches, LT for ALD is likely to increase in frequency.

Optimal Management

Reducing the terrible morbidity and mortality associated with alcohol abuse will occur only if the global medical community makes a major commitment to early diagnosis of alcohol misuse. Systematic application of alcohol questionnaires at all points of entry into medical care will be required to achieve this goal. Government programs that provide frequent monitoring and swift, certain, and modest sanctions for violations also show promise in reducing arrests for driving under the influence of alcohol and domestic violence.[245]

For patients with stable cirrhosis, maintaining abstinence is the most important aspect of management, because no drugs have been shown to improve survival. Nutritional support with evening snacks can be very beneficial. All patients should receive recommended vaccinations. In addition, they should undergo regular surveillance for HCC and screening for esophageal varices as appropriate (see Chapters 92 and 97). Weight control and cessation of smoking are also important.

For hospitalized patients with alcohol-associated hepatitis or cirrhosis, electrolyte disturbances and vitamin deficiencies should be corrected and withdrawal symptoms treated when present. During the first few days of admission, the patient should be offered a nutritious diet if the patient's mental status is adequate. Patients with severe alcohol-associated hepatitis should receive enteral feedings to ensure adequate calorie and protein intake. In patients with severe alcohol-associated hepatitis who do not have a systemic infection or GI bleeding, a short course of glucocorticoid therapy should be considered. Transfer to a liver transplant center for participation in a clinical trial should be considered in selected patients, including those who are not candidates for glucocorticoid therapy. Given the extremely poor prognosis of patients hospitalized with multiple organ failure, palliative care teams should be involved within the first few days after admission to provide appropriate support for both patients and families. LT is effective in providing prolonged survival with an excellent quality of life in carefully selected patients with alcohol-associated cirrhosis and, potentially, in patients with severe alcohol-associated hepatitis who fail to respond to medical therapy.

Full references for this chapter can be found on www.expertconsult.com.

REFERENCES

1. Patek Jr AJ, Post J, et al. Dietary treatment of cirrhosis of the liver; results in 124 patients observed during a 10 year period. J Am Med Assoc 1948;138:543–9.
2. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015–35.
3. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. BMJ 2018;362:k2817.
4. Kim D, Li AA, Gadiparthi C, et al. Changing trends in etiology-based annual mortality from chronic liver disease, from 2007 through 2016. Gastroenterology 2018;155:1154–63.
5. Frazier TH, Stocker AM, Kershner NA, et al. Treatment of alcoholic liver disease. Therap Adv Gastroenterol 2011;4:63–81.
6. Schwartz JM, Reinus JF. Prevalence and natural history of alcoholic liver disease. Clin Liver Dis 2012;16:659–66.
7. Paula H, Asrani SK, Boetticher NC, et al. Alcoholic liver disease-related mortality in the United States: 1980-2003. Am J Gastroenterol 2010;105:1782–7.
8. Bosetti C, Levi F, Lucchini F, et al. Worldwide mortality from cirrhosis: an update to 2002. J Hepatol 2007;46:827–39.
9. Schomerus G, Lucht M, Holzinger A, et al. The stigma of alcohol dependence compared with other mental disorders: a review of population studies. Alcohol Alcohol 2011;46:105–12.
10. Fuchs C, Stampfer M, Colditz G, et al. Alcohol consumption and mortality among women. N Engl J Med 1995;332:1245–50.
11. Becker U, Deis A, Sorensen T, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 1996;23:1025–9.
12. Thun M, Peto R, Lopez A, et al. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. N Engl J Med 1997;337:1705–14.
13. Brick J. Standardization of alcohol calculations in research. Alcohol Clin Exp Res 2006;30:1276–87.
14. Lefkowitch JH. Morphology of alcoholic liver disease. Clin Liver Dis 2005;9:37–53.
15. Yip WW, Burt AD. Alcoholic liver disease. Semin Diagn Pathol 2006;23:149–60.
16. Crawford JM. Histologic findings in alcoholic liver disease. Clin Liver Dis 2012;16:699–716.
17. Brunt EM. Alcoholic and nonalcoholic steatohepatitis. Clin Liver Dis 2002;6:399–420.
18. Rubin E, Lieber CS. Alcohol-induced hepatic injury in nonalcoholic volunteers. N Engl J Med 1968;278:869–76.
19. Mathurin P, Beuzin F, Louvet A, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment Pharmacol Ther 2007;25:1047–54.
20. Roth NC, Saberi B, Macklin J, et al. Prediction of histologic alcoholic hepatitis based on clinical presentation limits the need for liver biopsy. Hepatol Commun 2017;1:1070–84.
21. Crittenden NE, McClain C. Management of patients with moderate alcoholic liver disease. Clin Liver Dis 2013;2:76–9.
22. Ma C, Brunt EM. Histopathologic evaluation of liver biopsy for cirrhosis. Adv Anat Pathol 2012;19:220–30.
23. Kalaitzakis E, Gunnarsdottir SA, Josefsson A, Bjornsson E. Increased risk for malignant neoplasms among patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:168–74.
24. Beier JI, Arteel GE, McClain CJ. Advances in alcoholic liver disease. Curr Gastroenterol Rep 2011;13:56–64.
25. Thiele G, Worrall S, Tuma D, et al. The chemistry and biological effects of malondialdehyde-acetaldehyde adducts. Alcohol Clin Exp Res 2001;25(5 Suppl ISBRA):218S–224S.
26. Lluis J, Colell A, Garcia-Ruiz C, et al. Acetaldehyde impairs mitochondrial glutathione transport in HepG2 cells through endoplasmic reticulum stress. Gastroenterology 2003;124:708–24.
27. Arteel G. Oxidants and antioxidants in alcohol-induced liver disease. Gastroenterology 2003;124:778–90.
28. Meagher E, Barry O, Burke A, et al. Alcohol-induced generation of lipid peroxidation products in humans. J Clin Invest 1999;104:805–13.
29. Wu D, Cederbaum A. Ethanol cytotoxicity to a transfected HepG2 cell line expressing human cytochrome P4502E1. J Biol Chem 1996;271:23914–9.
30. Morgan K, French S, Morgan T. Production of a cytochrome P450 2E1 transgenic mouse and initial evaluation of alcoholic liver damage. Hepatology 2002;36:122–34.
31. Jiang JX, Torok NJ. NADPH oxidases in chronic liver diseases. Adv Hepatol 2014:2014.
32. Kono H, Rusyn I, Uesugi T, et al. Diphenyleneiodonium sulfate, an NADPH oxidase inhibitor, prevents early alcohol-induced liver injury in the rat. Am J Physiol Gastrointest Liver Physiol 2001;280:G1005–12.
33. Levin I, Petrasek J, Szabo G. The presence of p47phox in liver parenchymal cells is a key mediator in the pathogenesis of alcoholic liver steatosis. Alcohol Clin Exp Res 2012;36:1397–406.
34. Li M, He Y, Zhou Z, et al. MicroRNA-223 ameliorates alcoholic liver injury by inhibiting the IL-6-p47(phox)-oxidative stress pathway in neutrophils. Gut 2017;66:705–15.
35. Hoek J, Cahill A, Pastorino J. Alcohol and mitochondria: a dysfunctional relationship. Gastroenterology 2002;122:2049–63.
36. Holmuhamedov E, Lemasters JJ. Ethanol exposure decreases mitochondrial outer membrane permeability in cultured rat hepatocytes. Arch Biochem Biophys 2009;481:226–33.
37. McClain C, Hill D, Song Z, et al. S-adenosylmethionine, cytokines, and alcoholic liver disease. Alcohol 2002;27:185–92.
38. Lu SC, Mato JM. S-adenosylmethionine in liver health, injury, and cancer. Physiol Rev 2012;92:1515–42.
39. Purohit V, Abdelmalek M, Barve S, et al. Role of S-adenosylmethionine, folate, and betaine in the treatment of alcoholic liver disease: summary of a symposium. Am J Clin Nutr 2007;86:14–24.
40. Colell A, Garcia-Ruiz C, Miranda M, et al. Selective glutathione depletion of mitochondria by ethanol sensitizes hepatocytes to tumor necrosis factor. Gastroenterology 1998;115:1541–51.
41. Li M, Chiu JF, Kelsen A, et al. Identification and characterization of an Nrf2-mediated ARE upstream of the rat glutamate cysteine ligase catalytic subunit gene (GCLC). J Cell Biochem 2009;107:944–54.
42. Yang H, Ramani K, Xia M, et al. Dysregulation of glutathione synthesis during cholestasis in mice: molecular mechanisms and therapeutic implications. Hepatology 2009;49:1982–91.
43. Song Z, Zhou Z, Uriarte S, et al. S-adenosylhomocysteine sensitizes to TNF hepatotoxicity in mice and liver cells: a possible etiological factor in alcoholic liver disease. Hepatology 2004;40:989–97.
44. Halsted C, Villanueva J, Devlin A, Chandler C. Metabolic interactions of alcohol and folate. J Nutr 2002;132: 2367S–72.
45. French S. The role of hypoxia in the pathogenesis of alcoholic liver disease. Hepatol Res 2004;29:69–74.
46. Nath B, Levin I, Csak T, et al. Hepatocyte-specific hypoxia-inducible factor-1alpha is a determinant of lipid accumulation and liver injury in alcohol-induced steatosis in mice. Hepatology 2011;53:1526–37.
47. Burroughs SE, Calloway DH. Gastrointestinal response to diets containing pineapple. J Am Diet Assoc 1968;53:336–41.
48. Wang Y, Liu Y, Sidhu A, et al. Lactobacillus rhamnosus GG culture supernatant ameliorates acute alcohol-induced intestinal permeability and liver injury. Am J Physiol Gastroint Liver Physiol 2012;303:G32–41.
49. Shao T, Zhao C, Li F, et al. Intestinal HIF-1alpha deletion exacerbates alcoholic liver disease by inducing intestinal dysbiosis and barrier dysfunction. J Hepatol 2018;69:886–95.
50. Ji C. Dissection of endoplasmic reticulum stress signaling in alcoholic and non-alcoholic liver injury. J Gastroenterol Hepatol 2008;23:S16–24.
51. Chen WY, Zhang J, Ghare S, et al. Acrolein is a pathogenic mediator of alcoholic liver disease and the scavenger hydralazine is protective in mice. Cell Mol Gastroenterol Hepatol 2016;2:685–700.
52. Vatsalya V, Kong M, Gobejishvili L, et al. Urinary acrolein metabolite levels in severe acute alcoholic hepatitis patients. Am J Physiol Gastrointest Liver Physiol 2019;316:G115–22.
53. Petrasek J, Iracheta-Vellve A, Csak T, et al. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. Proc Natl Acad Sci U S A 2013;110:16544–9.
54. Lilienbaum A. Relationship between the proteasomal system and autophagy. Int J Biochem Mol Biol 2013;4:1–26.
55. Yang Y, Yu X. Regulation of apoptosis: the ubiquitous way. FASEB J 2003;17:790–9.
56. Osna NA, Bardag-Gorce F, White RL, et al. Ethanol and hepatitis C virus suppress peptide-MHC class I presentation in hepatocytes by altering proteasome function. Alcohol Clin Exp Res 2012;36:2028–35.

57. Bardag-Gorce F, van Leeuwen F, Nguyen V, et al. The role of the ubiquitin-proteasome pathway in the formation of Mallory bodies. Exp Mol Pathol 2002;73:75–83.
58. Joshi-Barve S, Barve S, Butt W, et al. Inhibition of proteasome function leads to NF-kappaB-independent IL-8 expression in human hepatocytes. Hepatology 2003;38:1178–87.
59. Menk M, Graw JA, Poyraz D, et al. Chronic alcohol consumption inhibits autophagy and promotes apoptosis in the liver. Int J Med Sci 2018;15:682–8.
60. Purohit V, Bode JC, Bode C, et al. Alcohol, intestinal bacterial growth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. Alcohol 2008;42:349–61.
61. Broitman SA, Gottlieb LS, Zamcheck N. Influence of neomycin and ingested endotoxin in the pathogenesis of choline deficiency cirrhosis in the adult rat. J Exp Med 1964;119:633–42.
62. McClain CJ, Song Z, Barve SS, et al. Recent advances in alcoholic liver disease. IV. Dysregulated cytokine metabolism in alcoholic liver disease. Am J Physiol Gastroint Liver Physiol 2004;287:G497–502.
63. Lowe PP, Gyongyosi B, Satishchandran A, et al. Reduced gut microbiome protects from alcohol-induced neuroinflammation and alters intestinal and brain inflammasome expression. J Neuroinflammation 2018;15:298.
64. Szabo G, Dolganiuc A, Mandrekar P. Pattern recognition receptors: a contemporary view on liver diseases. Hepatology 2006;44:287–98.
65. Szabo G, Petrasek J. Gut-liver axis and sterile signals in the development of alcoholic liver disease. Alcohol Alcohol 2017;52:414–24.
66. Kirpich IA, Solovieva NV, Leikhter SN, et al. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. Alcohol 2008;42:675–82.
67. Grander C, Adolph TE, Wieser V, et al. Recovery of ethanol-induced Akkermansiamuciniphila depletion ameliorates alcoholic liver disease. Gut 2018;67:891–901.
68. Lowe PP, Gyongyosi B, Satishchandran A, et al. Alcohol-related changes in the intestinal microbiome influence neutrophil infiltration, inflammation and steatosis in early alcoholic hepatitis in mice. PLoS One 2017;12:e0174544.
69. Yan AW, Fouts DE, Brandl J, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. Hepatology 2011;53:96–105.
70. Wei X, Shi X, Zhong W, et al. Chronic alcohol exposure disturbs lipid homeostasis at the adipose tissue-liver axis in mice: analysis of triacylglycerols using high-resolution mass spectrometry in combination with in vivo metabolite deuterium labeling. PLoS One 2013;8:e55382.
71. Tang Y, Banan A, Forsyth CB, et al. Effect of alcohol on miR-212 expression in intestinal epithelial cells and its potential role in alcoholic liver disease. Alcohol Clin Exp Res 2008;32:355–64.
72. Tang Y, Forsyth CB, Farhadi A, et al. Nitric oxide-mediated intestinal injury is required for alcohol-induced gut leakiness and liver damage. Alcohol Clin Exp Res 2009;33:1220–30.
73. Amin PB, Diebel LN, Liberati DM. Dose-dependent effect of ethanol and E. coli on gut permeability and cytokine production. J Surg Res 2009;157:187–92.
74. Yang AM, Inamine T, Hochrath K, et al. Intestinal fungi contribute to development of alcoholic liver disease. J Clin Invest 2017;127:2829–41.
75. Szabo G, Petrasek J. Inflammasome activation and function in liver disease. Nat Rev Gastroenterol Hepatol 2015;12:387–400.
76. Iracheta-Vellve A, Petrasek J, Satishchandran A, et al. Inhibition of sterile danger signals, uric acid and ATP, prevents inflammasome activation and protects from alcoholic steatohepatitis in mice. J Hepatol 2015;63:1147–55.
77. Delmez JA, Weerts CA, Hasamear PD, Windus DW. Severe dialyzer dysfunction undetectable by standard reprocessing validation tests. Kidney Int 1989;36:478–84.
78. Lippai D, Bala S, Petrasek J, et al. Alcohol-induced IL-1beta in the brain is mediated by NLRP3/ASC inflammasome activation that amplifies neuroinflammation. J Leukoc Biol 2013;94:171–82.
79. Tilg H, Moschen AR, Szabo G. Interleukin-1 and inflammasomes in alcoholic liver disease/acute alcoholic hepatitis and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. Hepatology 2016;64:955–65.
80. Petrasek J, Bala S, Csak T, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. J Clin Invest 2012;122:3476–89.
81. Iracheta-Vellve A, Petrasek J, Gyogyosi B, et al. Interleukin-1 inhibition facilitates recovery from liver injury and promotes regeneration of hepatocytes in alcoholic hepatitis in mice. Liver Int 2017;37:968–73.
82. Liu X, Zhang Z, Ruan J, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature 2016;535:153–8.
83. Khanova E, Wu R, Wang W, et al. Pyroptosis by caspase11/4-gasdermin-D pathway in alcoholic hepatitis in mice and patients. Hepatology 2018;67:1737–53.
84. Ge X, Antoine DJ, Lu Y, et al. High mobility group box-1 (HMGB1) participates in the pathogenesis of alcoholic liver disease (ALD). J Biol Chem 2014;289:22672–91.
85. Wang M, Shen G, Xu L, et al. IL-1 receptor like 1 protects against alcoholic liver injury by limiting NF-kappaB activation in hepatic macrophages. J Hepatol 2017 Sep 21. [Epub ahead of print].
86. Szabo G, Bala S. Alcoholic liver disease and the gut-liver axis. World J Gastroenterol 2010;16:1321–9.
87. McClain C, Song Z, Barve S, et al. Recent advances in alcoholic liver disease. IV. Dysregulated cytokine metabolism in alcoholic liver disease. Am J Physiol Gastrointest Liver Physiol 2004;287:G497–502.
88. McClain C, Cohen D. Increased tumor necrosis factor production by monocytes in alcoholic hepatitis. Hepatology 1989;9:349–51.
89. Zhang Z, Bagby G, Stoltz D, et al. Prolonged ethanol treatment enhances lipopolysaccharide/phorbol myristate acetate-induced tumor necrosis factor-alpha production in human monocytic cells. Alcohol Clin Exp Res 2001;25:444–9.
90. Le Moine O, Marchant A, De Groote D, et al. Role of defective monocyte interleukin-10 release in tumor necrosis factor-alpha overproduction in alcoholic cirrhosis. Hepatology 1995;22:1436–9.
91. Iimuro Y, Gallucci R, Luster M, et al. Antibodies to tumor necrosis factor alpha attenuate hepatic necrosis and inflammation caused by chronic exposure to ethanol in the rat. Hepatology 1997;26:1530–7.
92. Yin M, Wheeler M, Kono H, et al. Essential role of tumor necrosis factor alpha in alcohol-induced liver injury in mice. Gastroenterology 1999;117:942–52.
93. Pastorino J, Hoek J. Ethanol potentiates tumor necrosis factor-alpha cytotoxicity in hepatoma cells and primary rat hepatocytes by promoting induction of the mitochondrial permeability transition. Hepatology 2000;31:1141–52.
94. Vidali M, Stewart S, Rolla R, et al. Genetic and epigenetic factors in autoimmune reactions toward cytochrome P4502E1 in alcoholic liver disease. Hepatology 2003;37:410–9.
95. Manolio TA, Brooks LD, Collins FS. A HapMap harvest of insights into the genetics of common disease. J Clin Invest 2008;118:1590–605.
96. Hardy J, Singleton A. Genomewide association studies and human disease. N Engl J Med 2009;360:1759–68.
97. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. Nat Rev Genet 2005;6:95–108.
98. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747–53.
99. Anstee QM, Seth D, Day CP. Genetic factors that affect risk of alcoholic and nonalcoholic fatty liver disease. Gastroenterology 2016;150:1728–44 e7.
100. Hayashi S, Watanabe J, Kawajiri K. Genetic polymorphisms in the 5'-flanking region change transcriptional regulation of the human cytochrome P450IIE1 gene. J Biochem 1991;110:559–65.
101. Watanabe J, Hayashi S, Kawajiri K. Different regulation and expression of the human CYP2E1 gene due to the RsaI polymorphism in the 5'-flanking region. J Biochem 1994;116:321–6.
102. Grove J, Brown AS, Daly AK, et al. The RsaI polymorphism of CYP2E1 and susceptibility to alcoholic liver disease in Caucasians: effect on age of presentation and dependence on alcohol dehydrogenase genotype. Pharmacogenetics 1998;8:335–42.
103. Okamoto K, Murawaki Y, Yuasa KH. Effect of ALDH2 and CYP2E1 gene polymorphisms on drinking behavior and alcoholic liver disease in Japanese male workers. Alcohol Clin Exp Res 2001;25:19S–23.
104. Lee HC, Lee HS, Jung SH, et al. Association between polymorphisms of ethanol-metabolizing enzymes and susceptibility to alcoholic cirrhosis in a Korean male population. J Korean Med Sci 2001;16:745–50.
105. Stickel F, Hampe J. Genetic determinants of alcoholic liver disease. Gut 2012;61:150–9.

106. Buch S, Stickel F, Trepo E, et al. A genome-wide association study confirms PNPLA3 and identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis. Nat Genet 2015;47:1443–8.
107. Kozlitina J, Smagris E, Stender S, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014;46:352–6.
108. Mandrekar P. Epigenetic regulation in alcoholic liver disease. World J Gastroenterol 2011;17:2456–64.
109. Moghe A, Joshi-Barve S, Ghare S, et al. Histone modifications and alcohol-induced liver disease: are altered nutrients the missing link? World J Gastroenterol 2011;17:2465–72.
110. Shukla SD, Velazquez J, French SW, et al. Emerging role of epigenetics in the actions of alcohol. Alcohol Clin Exp Res 2008;32:1525–34.
111. Kirpich I, Ghare S, Zhang J, et al. Binge alcohol-induced microvesicular liver steatosis and injury are associated with down-regulation of hepatic Hdac 1, 7, 9, 10, 11 and up-regulation of Hdac 3. Alcohol Clin Exp Res 2012;36:1578–86.
112. Bala S, Marcos M, Kodys K, et al. Up-regulation of microRNA-155 in macrophages contributes to increased tumor necrosis factor {alpha} (TNF{alpha}) production via increased mRNA half-life in alcoholic liver disease. J Biol Chem 2011;286:1436–44.
113. Bala S, Csak T, Saha B, et al. The pro-inflammatory effects of miR-155 promote liver fibrosis and alcohol-induced steatohepatitis. J Hepatol 2016;64:1378–87.
114. Kunos G, Osei-Hyiaman D, Batkai S, Gao B. Cannabanoids hurt, heal in cirrhosis. Nat Med 2006;12:608–10.
115. Beier JI, Landes S, Mohammad MK, McClain C. Nutrition in liver disorders and the role of alcohol. In: Ross AC, Caballero B, Cousins RJ, et al., editors. Modern nutrition in health and disease. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2014. pp 1115–25.
116. Iwaisako K, Brenner DA, Kisseleva T. What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. J Gastroenterol Hepatol 2012;27(Suppl. 2):65–8.
117. Seki E, De Minicis S, Osterreicher CH, et al. TLR4 enhances TGF-beta signaling and hepatic fibrosis. Nat Med 2007;13:1324–32.
118. Friedman S. Liver fibrosis-from bench to bedside. J Hepatol 2003;38:S38–53.
119. Zamara E, Novo E, Marra F, et al. 4-Hydroxynonenal as a selective pro-fibrogenic stimulus for activated human hepatic stellate cells. J Hepatol 2004;40:60–8.
120. Reeves H, Friedman S. Activation of hepatic stellate cells—a key issue in liver fibrosis. Front Biosci 2002;7:d808–26.
121. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. N Engl J Med 2003;348:2635–45.
122. Sofair AN, Barry V, Manos MM, et al. The epidemiology and clinical characteristics of patients with newly diagnosed alcohol-related liver disease: results from population-based surveillance. J Clin Gastroenterol 2010;44:301–7.
123. Caputo F, Vignoli T, Leggio L, et al. Alcohol use disorders in the elderly: a brief overview from epidemiology to treatment options. Exp Gerontol 2012;47:411–6.
124. Jones TB, Bailey BA, Sokol RJ. Alcohol use in pregnancy: insights in screening and intervention for the clinician. Clin Obstet Gynecol 2013;56:114–23.
125. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012;57:399–420.
126. Woo GA, O'Brien C. Long-term management of alcoholic liver disease. Clin Liver Dis 2012;16:763–81.
127. O'Shea RS, Dasarathy S, McCullough AJ. Practice guideline Committee of the American Association for the Study of Liver Disease, Practice parameters Committee of the American College of G. Alcoholic liver disease. Hepatology 2010;51:307–28.
128. Savola O, Niemelä O, Hillbom M. Blood alcohol is the best indicator of hazardous alcohol drinking in young adults and working-age patients with trauma. Alcohol Alcohol 2004;39:340–5.
129. Niemelä O. Biomarkers in alcoholism. Clin Chim Acta 2007;377:39–49.
130. Hock B, Schwarz M, Domke I, et al. Validity of carbohydrate-deficient transferrin (%CDT), gamma-glutamyltransferase (gamma-GT) and mean corpuscular erythrocyte volume (MCV) as biomarkers for chronic alcohol abuse: a study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. Addiction 2005;100:1477–86.
131. Maenhout TM, De Buyzere ML, Delanghe JR. Non-oxidative ethanol metabolites as a measure of alcohol intake. Clin Chim Acta 2013;415:322–9.
132. Staufer K, Andresen H, Vettorazzi E, et al. Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. Hepatology 2011;54:1640–9.
133. Afshar M, Burnham EL, Joyce C, et al. Cut-point levels of phosphatidylethanol to identify alcohol misuse in a mixed cohort including critically ill patients. Alcohol Clin Exp Res 2017;41:1745–53.
134. Leffingwell TR, Cooney NJ, Murphy JG, et al. Continuous objective monitoring of alcohol use: twenty-first century measurement using transdermal sensors. Alcohol Clin Exp Res 2013;37:16–22.
135. Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785–90.
136. Helman RA, Temko MH, Nye SW, Fallon HJ. Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74:311–21.
137. Mendenhall CL. Alcoholic hepatitis. Clin Gastroenterol 1981;10:417–41.
138. Joshi-Barve S, Kirpich I, Cave MC, et al. Alcoholic, nonalcoholic, and toxicant-associated steatohepatitis: mechanistic similarities and differences. Cell Mol Gastroenterol Hepatol 2015;1:356–67.
139. Yilmaz Y. NAFLD in the absence of metabolic syndrome: different epidemiology, pathogenetic mechanisms, risk factors for disease progression? Semin Liver Dis 2012;32:14–21.
140. Almeda-Valdes P, Cuevas-Ramos D, Aguilar-Salinas CA. Metabolic syndrome and non-alcoholic fatty liver disease. Ann Hepatol 2009;8(Suppl. 1):S18–24.
141. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American association for the study of liver diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology 2012;55:2005–23.
142. Gleeson D, Evans S, Bradley M, et al. HFE genotypes in decompensated alcoholic liver disease: phenotypic expression and comparison with heavy drinking and with normal controls. Am J Gastroenterol 2006;101:304–10.
143. Fletcher L, Powell L. Hemochromatosis and alcoholic liver disease. Alcohol 2003;30:131–6.
144. Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011;54:328–43.
145. McClain CJ, Kromhout JP, Peterson FJ, Holtzman JL. Potentiation of acetaminophen hepatotoxicity by alcohol. J Am Med Assoc 1980;244:251–3.
146. Dakhoul L, Ghabril M, Gu J, et al. Heavy consumption of alcohol is not associated with worse outcomes in patients with idiosyncratic drug-induced liver injury compared to non-drinkers. Clin Gastroenterol Hepatol 2018;16:722–9.
147. Naveau S, Giraud V, Borotto E, et al. Excess weight risk factor for alcoholic liver disease. Hepatology 1997;25:108–11.
148. Raynard B, Balian A, Fallik D, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology 2002;35:635–8.
149. N'Kontchou G, Paries J, Htar MT, et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. Clin Gastroenterol Hepatol 2006;4:1062–8.
150. Corrao G, Lepore AR, Torchio P, et al. The effect of drinking coffee and smoking cigarettes on the risk of cirrhosis associated with alcohol consumption. A case-control study. Provincial Group for the Study of Chronic Liver Disease. Eur J Epidemiol 1994;10:657–64.
151. Altamirano J, Bataller R. Cigarette smoking and chronic liver diseases. Gut 2010;59:1159–62.
152. Sarin SK, Dhingra N, Bansal A, et al. Dietary and nutritional abnormalities in alcoholic liver disease: a comparison with chronic alcoholics without liver disease. Am J Gastroenterol 1997;92:777–83.
153. Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995;19:635–41.
154. Mendenhall CL, Moritz TE, Roselle GA, et al. Protein energy malnutrition in severe alcoholic hepatitis: diagnosis and response to treatment. The VA Cooperative Study Group #275. JPEN J Parenter Enteral Nutr 1995;19:258–65.

155. Mendenhall CL, Tosch T, Weesner RE, et al. VA cooperative study on alcoholic hepatitis. II: prognostic significance of protein-calorie malnutrition. Am J Clin Nutr 1986;43:213–8.
156. Mendenhall CL, Anderson S, Weesner RE, et al. Protein-calorie malnutrition Cssociated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on alcoholic hepatitis. Am J Med 1984;76:211–22.
157. Nanji AA, French SW. Dietary linoleic acid is required for development of experimentally induced alcoholic liver injury. Life Sci 1989;44:223–7.
158. Kirpich IA, Feng W, Wang Y, et al. Ethanol and dietary unsaturated fat (corn oil/linoleic acid enriched) cause intestinal inflammation and impaired intestinal barrier defense in mice chronically fed alcohol. Alcohol 2013;47:257–64.
159. Kirpich IA, Miller ME, Cave MC, et al. Alcoholic liver disease: update on the role of dietary fat. Biomolecules 2016;6:1.
160. Vatsalya V, Kong M, Cave MC, et al. Association of serum zinc with markers of liver injury in very heavy drinking alcohol-dependent patients. J Nutr Biochem 2018;59:49–55.
161. Kumar S, Rao PS, Earla R, Kumar A. Drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems. Expert Opin Drug MetabToxicol 2015;11:343–55.
162. Pontes H, Duarte JA, de Pinho PG, et al. Chronic exposure to ethanol exacerbates MDMA-induced hyperthermia and exposes liver to severe MDMA-induced toxicity in CD1 mice. Toxicology 2008;252:64–71.
163. Cave M, Falkner KC, Ray M, et al. Toxicant-associated steatohepatitis in vinyl chloride workers. Hepatology 2010;51:474–81.
164. Mailloux RJ, Florian M, Chen Q, et al. Exposure to a northern contaminant mixture (NCM) alters hepatic energy and lipid metabolism exacerbating hepatic steatosis in obese JCR rats. PLoS One 2014;9:e106832.
165. Szabo G, Momen-Heravi F. Extracellular vesicles in liver disease and potential as biomarkers and therapeutic targets. Nat Rev Gastroenterol Hepatol 2017;14:455–66.
166. Levy R, Catana AM, Durbin-Johnson B, et al. Ethnic differences in presentation and severity of alcoholic liver disease. Alcohol Clin Exp Res 2015;39:566–74.
167. Siu L, Foont J, Wands JR. Hepatitis C virus and alcohol. Semin Liver Dis 2009;29:188–99.
168. Mueller S, Millonig G, Seitz HK. Alcoholic liver disease and hepatitis C: a frequently underestimated combination. World J Gastroenterol 2009;15:3462–71.
169. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264–73.
170. Orrego H, Blake J, Blendis L, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. Gastroenterology 1987;92:208–14.
171. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009;360:2758–69.
172. Stuart L, Gobejishvili L, Crittendon N, et al. Alcoholic hepatitis: steroids vs. pentoxifylline. Curr Hepat Rep 2013;12:59–65.
173. Forrest EH, Atkinson SR, Richardson P, et al. Application of prognostic scores in the STOPAH trial: discriminant function is no longer the optimal scoring system in alcoholic hepatitis. J Hepatol 2018;68:511–8.
174. Maddrey W, Boitnott J, Bedine M, et al. Glucocorticoid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193–9.
175. Carithers Jr RL, Herlong HF, Diehl AM, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med 1989;110:685–90.
176. Ramond MJ, Poynard T, Rueff B, et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. N Engl J Med 1992;326:507–12.
177. Phillips M, Curtis H, Portmann B, et al. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis—a randomised clinical trial. J Hepatol 2006;44:784–90.
178. Altamirano J, Fagundes C, Dominguez M, et al. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. Clin Gastroenterol Hepatol 2012;10:65–71.
179. Srikureja W, Kyulo N, Runyon B, et al. MELD score is a better prognostic model that Child-Turcotte-Pugh score or discriminant function score in patients with alcoholic hepatitis. J Hepatol 2005;42:700–6.
180. Forrest E, Evans C, Stewart S, et al. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 2005;54:1174–9.
181. Singal AK, Shah VH. Alcoholic hepatitis: prognostic models and treatment. Gastroenterol Clin North Am 2011;40:611–39.
182. Dominguez M, Rincon D, Abraldes JG, et al. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. Am J Gastroenterol 2008;103:2747–56.
183. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51:1675–82.
184. Bell H, Jahnsen J, Kittang E, et al. Long-term prognosis of patients with alcoholic liver cirrhosis: a 15-year follow-up study of 100 Norwegian patients admitted to one unit. Scand J Gastroenterol 2004;39:858–63.
185. Poynard T, Naveau S, Doffoel M, et al. Evaluation of efficacy of liver transplantation in alcoholic cirrhosis using matched and simulated controls: 5-year survival. Multi-centre group. J Hepatol 1999;30:1130–7.
186. Pessione F, Ramond MJ, Peters L, et al. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int 2003;23:45–53.
187. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL). Hepatol Int 2009;3:269–82.
188. Fleming KM, Aithal GP, Card TR, West J. The rate of decompensation and clinical progression of disease in people with cirrhosis: a cohort study. Aliment Pharmacol Ther 2010;32:1343–50.
189. Szabo G. More than meets the eye: severe alcoholic hepatitis can present as acute-on-chronic liver failure. J Hepatol 2018;69:269–71.
190. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 2008;28:26–42.
191. Belcher JM, Garcia-Tsao G, Sanyal AJ, et al. Association of AKI with mortality and complications in hospitalized patients with cirrhosis. Hepatology 2013;57:753–62.
192. Cholongitas E, Senzolo M, Patch D, et al. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. Aliment Pharmacol Ther 2006;23:883–93.
193. Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. Crit Care Med 2010;38:2108–16.
194. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2013. Ann Intern Med 2013;158:191–9.
195. Seeff LB, Cuccherini BA, Zimmerman HJ, et al. Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. Ann Intern Med 1986;104:399–404.
196. Fontana RJ. Acute liver failure due to drugs. Semin Liver Dis 2008;28:175–87.
197. Stickel F, Kessebohm K, Weimann R, Seitz HK. Review of liver injury associated with dietary supplements. Liver Int 2011;31:595–605.
198. Purohit V, Rapaka R, Kwon OS, Song BJ. Roles of alcohol and tobacco exposure in the development of hepatocellular carcinoma. Life Sci 2013;92:3–9.
199. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
200. Veldt B, Laine F, Guillygomarc'h A, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. J Hepatol 2002;36:93–8.
201. Friedmann PD. Clinical practice. Alcohol use in adults. N Engl J Med 2013;368:365–73.
202. Jonas DE, Garbutt JC, Amick HR, et al. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2012;157:645–54.
203. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomized, double-blind controlled study. Lancet 2007;370:1915–22.
204. Spanagel R, Vengeliene V. New pharmacological treatment strategies for relapse prevention. Curr Top Behav Neurosci 2013;13:583–609.

205. McClain CJ, Barve SS, Barve A, Marsano L. Alcoholic liver disease and malnutrition. Alcohol Clin Exp Res 2011;35:815–20.
206. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. Clin Liver Dis 2012;16:805–26.
207. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol 2012;10:117–25.
208. Plauth M, Cabre E, Riggio O, et al. ESPEN Guidelines on enteral nutrition: liver disease. Clin Nutr 2006;25:285–94.
209. Cabre E, Rodriguez-Iglesias P, Caballeria J, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology 2000;32:36–42.
210. Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. Liver Int 2009;29:1396–402.
211. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008;48:557–66.
212. Schulz GJ, Campos AC, Coelho JC. The role of nutrition in hepatic encephalopathy. Curr Opin Clin Nutr Metab Care 2008;11:275–80.
213. Mohammad MK, Zhou Z, Cave M, et al. Zinc and liver disease. Nutr Clin Pract 2012;27:8–20.
214. Dick AA, Spitzer AL, Seifert CF, et al. Liver transplantation at the extremes of the body mass index. Liver Transpl 2009;15:968–77.
215. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010;211:271–8.
216. Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids reduce risk of death within 28 days for patients with severe alcoholic hepatitis, compared with pentoxifylline or placebo-a meta-analysis of individual data from controlled trials. Gastroenterology 2018;155:458–68.
217. Smart L, Gobejishvili L, Crittenden N, et al. Alcoholic hepatitis: steroids vs. pentoxifylline. Curr Hepat Rep 2013;12:59–65.
218. Mathurin P, Abdelnour M, Ramond MJ, et al. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 2003;38:1363–9.
219. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348–54.
220. Akriviadis E, Botla R, Briggs W, et al. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:1637–48.
221. De BK, Gangopadhyay S, Dutta D, et al. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol 2009;15:1613–9.
222. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619–28.
223. Mitchell MC, Friedman LS, McClain CJ. Medical management of severe alcoholic hepatitis: expert review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol 2017;15:5–12.
224. Szabo G. Clinical trial design for alcoholic hepatitis. Semin Liver Dis 2017;37:332–42.
225. Singh V, Keisham A, Bhalla A, et al. Efficacy of granulocyte colony-stimulating factor and n-acetylcysteine therapies in patients with severe alcoholic hepatitis. Clin Gastroenterol Hepatol 2018;16:1650–6.
226. Philips CA, Phadke N, Ganesan K, Ranade S, Augustine P. Corticosteroids, nutrition, pentoxifylline, or fecal microbiota transplantation for severe alcoholic hepatitis. Indian J Gastroenterol 2018;37:215–25.
227. Philips CA, Phadke N, Ganesan K, Augustine P. Healthy donor faecal transplant for corticosteroid non-responsive severe alcoholic hepatitis. BMJ Case Rep 2017;2017.
228. Bukong TN, Iracheta-Vellve A, Saha B, et al. Inhibition of spleen tyrosine kinase activation ameliorates inflammation, cell death, and steatosis in alcoholic liver disease. Hepatology 2016;64:1057–71.
229. Ouyang X, Han SN, Zhang JY, et al. Digoxin suppresses pyruvate kinase M2-promoted HIF-1alpha transactivation in steatohepatitis. Cell Metab 2018;27:1156.
230. Ki SH, Park O, Zheng M, et al. Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding: role of signal transducer and activator of transcription 3. Hepatology 2010;52:1291–300.
231. Ambade A, Lowe P, Kodys K, et al. Pharmacological inhibition of CCR2/5 signaling prevents and reverses alcohol-induced liver damage, steatosis and inflammation in mice. Hepatology 2019;69:1105–21.
232. Lucey MR. Liver transplantation in patients with alcoholic liver disease. Liver Transpl 2011;17:751–9.
233. Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transpl 2010;10:138–48.
234. Pfitzmann R, Schwenzer J, Rayes N, et al. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007;13:197–205.
235. Cuadrado A, Fabrega E, Casafont F, Pons-Romero F. Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2005;11:420–6.
236. Gallegos-Orozco JF, Charlton MR. Alcoholic liver disease and liver transplantation. Clin Liver Dis 2016;20:521–34.
237. DiMartini A, Dew MA, Day N, et al. Trajectories of alcohol consumption following liver transplantation. Am J Transpl 2010;10:2305–12.
238. Murray KF, Carithers Jr RL. Aasld. AASLD practice guidelines: evaluation of the patient for liver transplantation. Hepatology 2005;41:1407–32.
239. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19:3–26.
240. Donnadieu-Rigole H, Olive L, Nalpas B, et al. Follow-up of alcohol consumption after liver transplantation: interest of an addiction team? Alcohol Clin Exp Res 2017;41:165–70.
241. Fleming MF, Smith MJ, Oslakovic E, et al. Phosphatidylethanol detects moderate-to-heavy alcohol use in liver transplant recipients. Alcohol Clin Exp Res 2017;41:857–62.
242. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790–800.
243. Lee BP, Chen PH, Haugen C, et al. Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. Ann Surg 2017;265:20–9.
244. Lee BP, Mehta N, Platt L, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology 2018;155:422–30.
245. Kilmer B, Nicosia N, Heaton P, Midgette G. Efficacy of frequent monitoring with swift, certain, and modest sanctions for violations: insights from South Dakota's 24/7 Sobriety Project. Am J Public Health 2013;103:e37–43.