TABLE 335-1 Risk Factors for Alcoholic Liver Disease

RISK FACTOR	COMMENT
Quantity	In men, 40–80 g/d of ethanol produces fatty liver; 160 g/d for 10–20 years causes hepatitis or cirrhosis. Only 15% of alcoholics develop alcoholic liver disease.
Gender	Women exhibit increased susceptibility to alcoholic liver disease at amounts >20 g/d; two drinks per day is probably safe.
Hepatitis C	HCV infection concurrent with alcoholic liver disease is associated with younger age for severity, more advanced histology, and decreased survival.
Genetics	Patatin-like phospholipase domain-containing protein 3 (PNPLA3) has been associated with alcoholic cirrhosis.
Fatty liver	Alcohol injury does not require malnutrition, but obesity and nonalcoholic fatty liver are risk factors. Patients should receive vigorous attention to nutritional support.

335 Alcoholic Liver Disease

Mark E. Mailliard, Michael F. Sorrell

Chronic and excessive alcohol ingestion is a major cause of liver disease and is responsible for nearly 50% of the mortality from all cirrhosis. The pathology of alcoholic liver disease consists of three major lesions, with the progressive injury rarely existing in a pure form: (1) fatty liver, (2) alcoholic hepatitis, and (3) cirrhosis. Fatty liver is present in >90% of daily as well as binge drinkers. A much smaller percentage of heavy drinkers will progress to alcoholic hepatitis, thought to be a precursor to cirrhosis. The prognosis of severe alcoholic liver disease is dismal; the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years. Although alcohol is considered a direct hepatotoxin, only between 10 and 20% of alcoholics will develop alcoholic hepatitis. The explanation for this apparent paradox is unclear but involves the complex interaction of facilitating factors such as drinking patterns, diet, obesity, and gender. There are no diagnostic tools that can predict individual susceptibility to alcoholic liver disease.

GLOBAL CONSIDERATIONS

Alcohol is the world's third largest risk factor for disease burden. The harmful use of alcohol results in about 3.5 million deaths worldwide each year. Most of the mortality attributed to alcohol is secondary to cirrhosis. Mortality from cirrhosis is directly related to alcohol consumption, with the Eastern European countries the most significantly burdened. Cirrhosis and its complications are closely correlated with volume of alcohol consumed per capita population and are regardless of gender.

ETIOLOGY AND PATHOGENESIS

Quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease **(Table 335-1)**. The roles of beverage type(s), i.e., wine, beer, or spirits, and pattern of drinking (daily versus binge drinking) are less clear. Progress beyond the fatty liver stage seems to require additional risk factors that remain incompletely defined. Although there are genetic predispositions for alcoholism **(Chap. 445)**, gender is a strong determinant for alcoholic liver disease. Women are more susceptible to alcoholic liver injury when compared to men. They develop advanced liver disease with substantially less alcohol intake. In general, the time it takes to develop liver disease is directly related to the amount of alcohol consumed. It is useful in estimating alcohol consumption to understand that one beer, four ounces of wine, or one ounce of 80% spirits all contain ~12 g of alcohol. The threshold for developing alcoholic liver disease is higher in men (>14 drinks per week), while women are at increased risk for liver injury by consuming >7 drinks per week. Gender-dependent differences result from poorly understood effects of estrogen, proportion of body fat, and the gastric metabolism of alcohol. Obesity, a high-fat diet, and the protective effect of coffee have been postulated to play a part in the development of the pathogenic process.

Chronic infection with hepatitis C virus (HCV) **(Chap. 334)** is an important comorbidity in the progression of alcoholic liver disease to cirrhosis in chronic drinkers. Even light to moderate alcohol intake of 15–30 g/d increases the risk of cirrhosis and hepatocellular cancer in HCV-infected individuals. Patients with both alcoholic liver injury and HCV infection develop decompensated liver disease at a younger age and have poorer overall survival. Increased liver iron stores and, rarely, porphyria cutanea tarda can occur as a consequence of the overlapping injurious processes secondary to alcohol and HCV infection.

The pathogenesis of alcoholic liver injury is unclear. The present conceptual foundation is that alcohol acts as a direct hepatotoxin and that malnutrition does not have a major role. Ingestion of alcohol initiates an inflammatory cascade by its metabolism, resulting in a variety of metabolic responses. Steatosis from lipogenesis, fatty acid synthesis, and depression of fatty acid oxidation appears secondary to effects on sterol regulatory transcription factor and peroxisome proliferator-activated receptor α (PPAR-α). Intestinal-derived endotoxin initiates a pathogenic process through toll-like receptor 4 and tumor necrosis factor α (TNF-α) that facilitates hepatocyte apoptosis and necrosis. The cell injury and endotoxin release initiated by ethanol and its metabolites also activate innate and adaptive immunity pathways releasing proinflammatory cytokines (e.g., TNF-α), chemokines, and proliferation of T and B cells. The effect of chronic ethanol ingestion on intestinal permeability influences liposaccharide hepatic influx as well as microbiome dysbiosis, further contributing to the pathogenic process. The production of toxic protein-aldehyde adducts, generation of reducing equivalents, and oxidative stress also play a role. Hepatocyte injury and impaired regeneration following chronic alcohol ingestion are ultimately associated with stellate cell activation and collagen production; key events in fibrogenesis. The resulting fibrosis from continuing alcohol use determines the architectural derangement of the liver and associated pathophysiology.

PATHOLOGY

The liver has a limited repertoire in response to injury. Fatty liver is the initial and most common histologic response to hepatotoxic stimuli, including excessive alcohol ingestion. The accumulation of fat within the perivenular hepatocytes coincides with the location of alcohol dehydrogenase, the major enzyme responsible for alcohol metabolism. Continuing alcohol ingestion results in fat accumulation throughout the entire hepatic lobule. Despite extensive fatty change and distortion of the hepatocytes with macrovesicular fat, the cessation of drinking results in normalization of hepatic architecture and fat content. Alcoholic fatty liver has traditionally been regarded as entirely benign, but similar to the spectrum of nonalcoholic fatty liver disease, the appearance of steatohepatitis and certain

pathologic features such as giant mitochondria, perivenular fibrosis, and macrovesicular fat may be associated with progressive liver injury.

The transition between fatty liver and the development of alcoholic hepatitis is blurred. The hallmark of alcoholic hepatitis is hepatocyte injury characterized by ballooning degeneration, spotty necrosis, polymorphonuclear infiltrate, and fibrosis in the perivenular and perisinusoidal space of Disse. Mallory-Denk bodies are often present in florid cases but are neither specific nor necessary to establish the diagnosis. Alcoholic hepatitis is thought to be a precursor to the development of cirrhosis. However, like fatty liver, it is potentially reversible with cessation of drinking. Cirrhosis is present in up to 50% of patients with biopsy-proven alcoholic hepatitis, and its regression is uncertain, even with abstention.

CLINICAL FEATURES

The clinical manifestations of alcoholic fatty liver are subtle and characteristically detected as a consequence of the patient's visit for a seemingly unrelated matter. Previously unsuspected hepatomegaly is often the only clinical finding. Occasionally, patients with fatty liver will present with right upper quadrant discomfort, nausea, and, rarely, jaundice. Differentiation of alcoholic fatty liver from nonalcoholic fatty liver is difficult unless an accurate drinking history is ascertained. In every instance where liver disease is present, a thoughtful and sensitive drinking history should be obtained. Standard, validated questions accurately detect alcohol-related problems **(Chap. 445)**. Alcoholic hepatitis is associated with a wide gamut of clinical features. Fever, spider nevi, jaundice, and abdominal pain simulating an acute abdomen represent the extreme end of the spectrum, while many patients will be entirely asymptomatic. Portal hypertension, ascites, or variceal bleeding can occur in the absence of cirrhosis. Recognition of the clinical features of alcoholic hepatitis is central to the initiation of an effective and appropriate diagnostic and therapeutic strategy. It is important to recognize that patients with alcoholic cirrhosis often exhibit clinical features identical to other causes of cirrhosis.

LABORATORY FEATURES

Patients with alcoholic liver disease are often identified through routine screening tests. The typical laboratory abnormalities seen in fatty liver are nonspecific and include modest elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGTP), often accompanied by hypertriglyceridemia and hyperbilirubinemia. In alcoholic hepatitis and in contrast to other causes of fatty liver, AST and ALT are usually elevated two- to sevenfold. They are rarely >400 IU, and the AST/ALT ratio is >1 **(Table 335-2)**. Hyperbilirubinemia is accompanied by modest increases in the alkaline phosphatase level. Derangement in hepatocyte synthetic function indicates more serious disease. Hypoalbuminemia and coagulopathy are common in advanced liver injury. Ultrasonography is useful in detecting fatty infiltration of the liver and determining liver size. The demonstration by ultrasound of portal vein flow reversal, ascites, and intraabdominal venous collaterals indicates serious liver injury with less potential for complete reversal.

PROGNOSIS

Critically ill patients with alcoholic hepatitis have short-term (30-day) mortality rates >50%. Severe alcoholic hepatitis is heralded by coagulopathy (prothrombin time increased >5 s), anemia, serum albumin concentrations <25 g/L (2.5 mg/dL), serum bilirubin levels >137 μmol/L (8 mg/dL), renal failure, and ascites. A discriminant function calculated as 4.6 X (the prolongation of the prothrombin time above control [seconds]) + serum bilirubin (mg/dL) can identify patients with a poor prognosis (discriminant function >32). A Model for End-Stage Liver Disease (MELD) score **(Chap. 338)** ≥21 also is associated with significant mortality in alcoholic hepatitis. The presence of ascites, variceal hemorrhage, deep encephalopathy, or hepatorenal syndrome predicts a dismal prognosis. The pathologic stage of the injury can be helpful in predicting prognosis. Liver biopsy should be performed whenever possible to establish the diagnosis and to guide the therapeutic decisions.

TABLE 335-2 Laboratory Diagnosis of Alcoholic Fatty Liver and Alcoholic Hepatitis

TEST	COMMENT
AST	Increased two- to sevenfold, <400 IU/L, greater than ALT
ALT	Increased two- to sevenfold, <400 IU/L
AST/ALT	Usually >1
GGTP	Not specific to alcohol, easily inducible, elevated in all forms of fatty liver
Bilirubin	May be markedly increased in alcoholic hepatitis despite modest elevation in alkaline phosphatase

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGTP, γ-glutamyl transpeptidase.

TREATMENT

Alcoholic Liver Disease

Complete abstinence from alcohol is the cornerstone in the treatment of alcoholic liver disease. Improved survival and the potential for reversal of histologic injury regardless of the initial clinical presentation are associated with total avoidance of alcohol ingestion. Referral of patients to experienced alcohol counselors and/or alcohol treatment programs should be routine in the management of patients with alcoholic liver disease. Attention should be directed to the nutritional and psychosocial states during the evaluation and treatment periods. Because of data suggesting that the pathogenic mechanisms in alcoholic hepatitis involve cytokine release and the perpetuation of injury by immunologic processes, glucocorticoids have been extensively evaluated in the treatment of alcoholic hepatitis. Patients with severe alcoholic hepatitis, defined as a discriminant function >32 or MELD >20, should be given prednisone, 40 mg/d, or prednisolone, 32 mg/d, for 4 weeks, followed by a steroid taper **(Fig. 335-1)**. Exclusion criteria include active gastrointestinal bleeding, renal failure, or pancreatitis. Patients with infection can be concurrently treated with antibiotics and steroids. Women with encephalopathy from severe alcoholic hepatitis may be particularly good candidates for glucocorticoids. A Lille score >0.45, at *http://www.lillemodel.com*, uses pretreatment variables plus the change in total bilirubin at day 7 of glucocorticoids to identify those patients unresponsive to therapy.

The role of TNF-α expression and receptor activity in alcoholic liver injury has led to an examination of pentoxifylline, the nonspecific TNF inhibitor, either by itself, or with glucocorticoids for severe alcoholic hepatitis. In one study, pentoxifylline demonstrated an improved survival in the therapy of severe alcoholic hepatitis, primarily due to a decrease in hepatorenal syndrome. Subsequent clinical trials failed to find an increased benefit from pentoxifylline, either by itself or in combination with prednisolone **(Fig. 335-2)**.

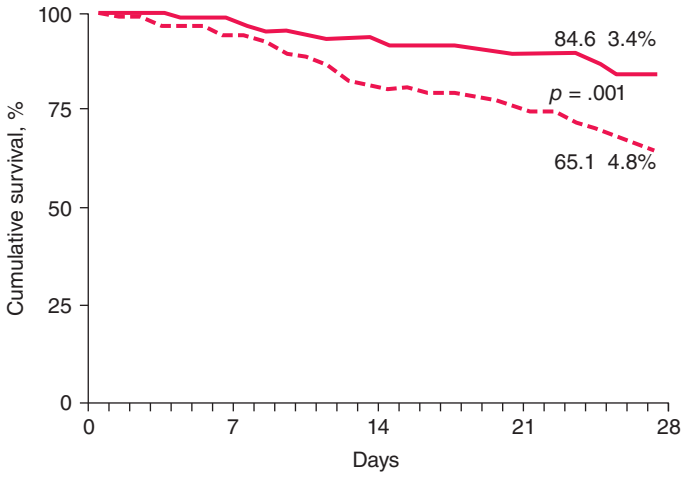

FIGURE 335-1 Effect of glucocorticoid therapy of severe alcoholic hepatitis on short-term survival: the result of a meta-analysis of individual data from three studies. Prednisolone, solid line; placebo, dotted line. *(Adapted from P Mathurin et al: J Hepatol 36:480, 2002, with permission from Elsevier Science.)*

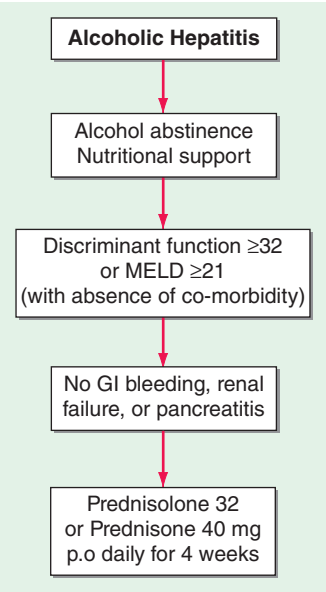

FIGURE 335-2 Treatment algorithm for alcoholic hepatitis. As identified by a calculated discriminant function >32 or MELD >20 (see text), patients with severe alcoholic hepatitis, without the presence of gastrointestinal bleeding, renal failure or pancreatitis would be candidates for glucocorticoids.

Liver transplantation is an accepted indication for treatment in select patients with complications of cirrhosis secondary to alcohol abuse. Outcomes are equal or superior to other indications for transplantation. In general, transplant candidacy should be reevaluated after a defined period of sobriety. Patients presenting with alcoholic hepatitis have been largely excluded from transplant candidacy because of the perceived risk of increased surgical mortality and high rates of recidivism following transplantation. A European multidisciplinary group has reported excellent long-term transplant outcomes in highly selected patients with florid alcoholic hepatitis. General application of transplantation in such patients must await confirmatory outcomes.

FURTHER READING

Mathurin P et al: Corticosteroids improves short-term survival in patients with severe alcoholic hepatitis (AH): Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. J Hepatol 36:480, 2002.

Sanyal AJ et al: Alcoholic and nonalcoholic fatty liver disease. Gastroenterology 150:8 (suppl), 2016.

Thurz MR et al: Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 372:1619, 2015.

336 Nonalcoholic Fatty Liver Diseases and Nonalcoholic Steatohepatitis

Manal F. Abdelmalek, Anna Mae Diehl

INCIDENCE, PREVALENCE, AND NATURAL HISTORY

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in many parts of the world, including the United States. Population-based abdominal imaging studies have demonstrated fatty liver in at least 25% of American adults. Because the vast majority of these subjects deny hazardous levels of alcohol consumption (defined as greater than one drink per day in women or two drinks per day in men), they are considered to have NAFLD. NAFLD is strongly associated with overweight/obesity and insulin resistance. However, it can also occur in lean individuals and is particularly common in those with a paucity of adipose depots (i.e., lipodystrophy). Ethnic/racial factors also appear to influence liver fat accumulation; the documented prevalence of NAFLD is lowest in African Americans (~25%), highest in Americans of Hispanic ancestry (~50%), and intermediate in American whites (~33%).

NAFLD encompasses a spectrum of liver pathology with different clinical prognoses. The simple accumulation of triglyceride within hepatocytes (hepatic steatosis) is on the most clinically benign extreme of the spectrum. On the opposite, most clinically ominous extreme, are cirrhosis **(Chap. 337)** and primary liver cancer **(Chap. 78)**. The risk of developing cirrhosis is extremely low in individuals with chronic hepatic steatosis, but increases as steatosis becomes complicated by histologically conspicuous hepatocyte death and inflammation (i.e., nonalcoholic steatohepatitis [NASH]). NASH itself is also a heterogeneous condition; sometimes it improves to steatosis or normal histology, sometimes it remains relatively stable for years, but sometimes it results in progressive accumulation of fibrous scar that eventuates in cirrhosis. Once NAFLD-related cirrhosis develops, the annual incidence of primary liver cancer can be as high as 3%.

Abdominal imaging is not able to determine which individuals with NAFLD have associated liver cell death and inflammation (i.e., NASH), and specific blood tests to diagnose NASH are not yet available. However, population-based studies that have used elevated serum ALT as a marker of liver injury indicate that about 6–8% of American adults have serum ALT elevations that cannot be explained by excessive alcohol consumption, other known causes of fatty liver disease **(Table 336-1)**, viral hepatitis, or drug-induced or congenital liver diseases. Because the prevalence of such "cryptogenic" ALT elevations increases with

TABLE 336-1 Alternative Causes of Hepatic Steatosis

- Alcoholic liver disease
- Hepatitis C (particularly genotype 3)
- Inborn errors of metabolism
  - Abetalipoproteinemia
  - Cholesterol ester storage disease
  - Galactosemia
  - Glycogen storage disease
  - Hereditary fructose intolerance
  - Homocystinuria
  - Systemic carnitine deficiency
  - Tyrosinemia
  - Weber-Christian syndrome
  - Wilson's disease
  - Wolman's disease
- Medications **(see Table 336-2)**
- Miscellaneous
  - Industrial exposure to petrochemical
  - Inflammatory bowel disease
  - Lipodystrophy
  - Bacterial overgrowth
  - Starvation
  - Parenteral nutrition
- Surgical procedures
  - Bilopancreatic diversion
  - Extensive small-bowel resection
  - Gastric bypass
  - Jejunoileal bypass
- Reye's syndrome
- Acute fatty liver of pregnancy
- HELLP syndrome (*h*emolytic anemia, elevated *l*iver enzymes, *l*ow *p*latelet count)