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 (Chap. 367e), 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. 467). 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 363-2). 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.

TABLE 363-2 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.

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. 368) ≥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.

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. 363-1). Exclusion criteria include active gastrointestinal bleeding, renal failure, or pancreatitis. 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 patients unresponsive to therapy.

The role of TNF-α expression and receptor activity in alcoholic liver injury has led to an examination of TNF inhibition as an alternative to glucocorticoids for severe alcoholic hepatitis. The nonspecific TNF inhibitor, pentoxifylline, demonstrated improved survival in the therapy of severe alcoholic hepatitis, primarily due to a decrease in hepatorenal syndrome (Fig. 363-2). Monoclonal antibodies that neutralize serum TNF-α should not be used in alcoholic hepatitis because of studies reporting increased deaths secondary to infection and renal failure.

Liver transplantation is an accepted indication for treatment in selected and motivated patients with end-stage cirrhosis. Outcomes are equal or superior to other indications for transplantation. In general, transplant candidacy should be reevaluated after a defined