In medically refractory cases, an attempt should be made to intensify treatment with high-dose glucocorticoid monotherapy (60 mg daily) or combination glucocorticoid (30 mg daily) plus high-dose azathioprine (150 mg daily) therapy. After a month, doses of prednisone can be reduced by 10 mg a month, and doses of azathioprine can be reduced by 50 mg a month toward ultimate, conventional maintenance doses. Patients refractory to this regimen may be treated with cyclosporine, tacrolimus, or mycophenolate mofetil; however, to date, only limited anecdotal reports support these approaches. If medical therapy fails, or when chronic hepatitis progresses to cirrhosis and is associated with life-threatening complications of liver decompensation, liver transplantation is the only recourse (Chap. 368); failure of the bilirubin to improve after 2 weeks of therapy should prompt early consideration of the patient for liver transplantation. Recurrence of autoimmune hepatitis in the new liver occurs rarely in most experiences but in as many as 35–40% of cases in others.

Like all patients with chronic liver disease, patients with autoimmune hepatitis should be vaccinated against hepatitis A and B, ideally before immunosuppressive therapy is begun, if practical.

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363 Alcoholic Liver Disease

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Chronic and excessive alcohol ingestion is one of the major causes of liver disease. 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 2.5 million deaths each year. Most of the mortality attributed to alcohol is secondary to cirrhosis. Mortality from cirrhosis is declining in most Western countries, concurrent with a reduction in alcohol consumption, with the exceptions of the United Kingdom, Russia, Romania, and Hungary. These increases in cirrhosis and its complications are closely correlated with increased 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 363-1). 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. 467), 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, while women are at increased risk for developing similar degrees of liver injury by consuming significantly less. 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.

TABLE 363-1 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.

Chronic infection with hepatitis C virus (HCV) (Chap. 362) is an important comorbidity in the progression of alcoholic liver disease to cirrhosis in chronic and excessive drinkers. Even moderate alcohol intake of 20–50 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 abuse and HCV infection. In addition, alcohol intake of >50 g/d by HCV-infected patients decreases the efficacy of interferon-based antiviral therapy.

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 to acetaldehyde, 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 production of toxic protein-aldehyde adducts, generation of reducing equivalents, and oxidative stress also contribute to the liver injury. Hepatocyte injury and impaired regeneration following chronic alcohol ingestion are ultimately associated with stellate cell activation and collagen production, which are key events in fibrogenesis. The resulting fibrosis from