

Alcoholic Liver Disease

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Alcoholic liver disease (ALD) is a major health problem in the western world. In the United States, ALD affects at least 2 million people, or approximately 1% of the population.¹ The true incidence of ALD, especially in its milder forms, may be substantially greater because many patients are asymptomatic and may never seek medical attention. ALD alone accounts for approximately 21% of cases of cirrhosis of the liver, and ALD in combination with hepatitis C is responsible for an additional 15% of cirrhosis in the United States.¹

This article reviews the clinical features of 3 distinct clinicopathologic syndromes of ALD: alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. The mechanisms of liver injury associated with alcohol are discussed. Finally, the diagnostic evaluation and clinical management of ALD are reviewed.

CLINICOPATHOLOGIC PATTERNS OF ALCOHOLIC LIVER DISEASE

Alcoholic Fatty Liver

Alcoholic fatty liver, or steatosis, is the accumulation of macrovesicular fat in the cytosol of hepatocytes. Steatosis is the mildest and earliest form of liver injury caused by alcohol. It develops in nearly all individuals who consume more than 60 g of alcohol per day even for a short period of time.² Fatty liver often is undetected because it is usually asymptomatic. Severe fatty infiltration of the liver can sometimes cause constitutional and nonspecific symptoms (eg, fatigue, weakness, malaise, anorexia, nausea, abdominal discomfort). Right upper quadrant abdominal pain or fullness rarely may occur as a result of distension of the liver capsule. Fatty liver may be present in the absence of any abnormalities on physical examination. However, hepatomegaly is quite common, occurring in more than 70% of persons with biopsy-proven steatosis.³

Steatosis develops within days following onset of heavy alcohol use. With complete abstinence, histologic changes return to normal within 2 to 4 weeks.² Liver function typically is unaffected. Although traditionally

considered to be a benign condition, persistent alcoholic steatosis may be associated with insidious fibrosis leading to cirrhosis.⁴

Alcoholic Hepatitis

Alcoholic hepatitis is a subacute inflammatory condition. It is characterized histologically by centrilobular polymorphonuclear infiltrates, ballooning degeneration of hepatocytes, megamitochondria, and Mallory's hyaline (cytosolic inclusions composed of precipitates of cytoskeletal intermediate filaments).⁵ Centrilobular and perisinusoidal fibrosis are characteristic. The persistence of alcoholic hepatitis is associated with relentless progression to cirrhosis over months to years.⁶

Alcoholic hepatitis, unlike simple alcoholic steatosis, is associated with inflammation, liver cell necrosis, impaired liver function, and progression to cirrhosis. Symptoms vary greatly with the severity of the disease. In severe cases, patients complain of weakness, anorexia, weight loss, nausea, vomiting, and right upper quadrant abdominal pain. Patients may be febrile, tachycardic, or tachypneic. Jaundice is sometimes apparent. The liver usually is enlarged and tender.^{7,8}

Complications of alcoholic hepatitis are identical to those of cirrhosis and result from impaired hepatocellular function and acute development of portal hypertension. They include variceal hemorrhage, hepatic encephalopathy, coagulopathy, ascites, and spontaneous bacterial peritonitis. The development of encephalopathy in

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patients with alcoholic hepatitis is associated with a grave prognosis. Other poor prognostic signs are advanced age, jaundice, azotemia, and coagulopathy.^{9,10}

Alcoholic hepatitis is reversible with prolonged abstinence. Characteristically, the inflammatory process persists for several months after cessation of alcohol use and may even worsen during the first few weeks of abstinence.

Alcoholic Cirrhosis

Alcoholic cirrhosis, the end stage of ALD, is characterized by extensive liver fibrosis, micronodular regeneration, impaired liver function, portal hypertension, and predisposition to hepatocellular carcinoma. Although usually insidious in onset, cirrhosis may develop rapidly following florid alcoholic hepatitis. Most deaths from ALD are attributable to complications of cirrhosis, such as ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, encephalopathy, and variceal hemorrhage.¹¹

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE

Although the association between alcohol abuse and liver disease has been known since antiquity, the mechanisms of ALD remain incompletely understood.¹² Individual susceptibility appears to vary widely, and it is estimated that only 10% to 20% of persons with alcoholism develop cirrhosis. For a given level of alcohol intake, women are more likely than men to develop alcoholic hepatitis and cirrhosis. Disease develops in women over a shorter period of time and with smaller amounts of alcohol intake, and liver injury progresses more rapidly.¹³ The reason for this increased susceptibility is unknown. Racial differences in prevalence of ALD, including increased frequency among nonwhites and native Americans, appear to reflect social patterns of alcohol use rather than genetic variation in susceptibility. Although genetics appear to play a role in alcoholism, to date no specific genetic polymorphism has been shown to influence the severity of liver injury in response to alcohol.^{14,15}

Ethanol Metabolism

The major site of ethanol metabolism is the liver, where ethanol is oxidized by 3 enzymatic pathways: the cytosolic alcohol dehydrogenase (ADH) pathway, the microsomal ethanol oxidizing system, and the peroxisomal catalase pathway.¹⁶ Variations in ADH isoforms may account for significant individual differences in ethanol elimination rates. The central enzyme in the microsomal ethanol oxidizing system is cytochrome P-450 2E1 (CYP2E1), which also is responsible for the

biotransformation of other drugs, including acetaminophen, haloalkanes, and nitrosamines.¹⁷ CYP2E1 is induced by alcohol, and the proportion of alcohol metabolized via this pathway increases with the severity and duration of alcohol use. The peroxisomal catalase pathway is the least used pathway in alcohol metabolism and it takes place in the peroxisomes and mitochondria. The product of all three of these reactions is acetaldehyde, which is then metabolized to acetate by acetaldehyde dehydrogenase (ALDH).¹⁶

Acetaldehyde, a reactive molecule that can oxidize and covalently bind to a variety of functional groups, is thought to be a major cause of alcoholic liver injury. Acetaldehyde causes depletion of mitochondrial glutathione, impairs mitochondrial β -oxidation of fatty acids, and promotes formation of oxygen-free radicals that cause peroxidation of membrane lipids.¹⁸ Along with ethanol, acetaldehyde may damage liver cell membranes, especially those of mitochondria, by altering membrane fluidity and modifying membrane-bound enzymes and transport proteins.^{18,19}

Acetate generated from alcohol metabolism is employed in synthesis of fatty acids and ketone bodies or oxidized via the Krebs cycle and electron transport chain. Alcohol, thus, is a major energy source, and this has 2 consequences. First, alcoholics often have inadequate diets and develop nutritional deficiencies, which may play a role in liver injury.²⁰ Second, alcohol may impede metabolism of other energy substrates, such as fat. Oxidation of ethanol converts nicotinamide adenine dinucleotide (NAD) into its reduced form, NADH. Because NAD is required for the oxidation of fatty acids, its depletion inhibits fatty acid oxidation and leads to the accumulation of fat within the hepatocytes (ie, steatosis).²¹

Immunologic mechanisms play a role in the pathogenesis of ALD, especially in alcoholic hepatitis. Acetaldehyde may bind covalently with hepatic macromolecules (such as the amines and thiols found in cell membranes, enzymes, and microtubules) and form acetaldehyde adducts, which may serve as "neoantigens" and trigger an immune response.²² The proinflammatory cytokine tumor necrosis factor- α (TNF) is thought to be a key factor in this process.²³ The production of TNF is one of the earliest events in alcoholic liver injury, triggering the production of other cytokines. Together, they recruit inflammatory cells, kill hepatocytes, and initiate a healing response that induces fibrogenesis. High levels of TNF and several TNF-inducible cytokines (interleukin [IL]-1, IL-6, and IL-8) have been demonstrated in the sera of patients with alcoholic hepatitis. It is believed that the inflammatory cytokines (ie, TNF, IL-1, IL-8) and the hepatic acute phase cytokine IL-6 play a

significant role in producing liver injury of alcoholic hepatitis and cirrhosis.^{24–26}

DIAGNOSTIC LABORATORY EVALUATION

Key elements in evaluation of ALD are establishing the presence of alcohol abuse, excluding other contributing causes, determining the pattern and severity of liver disease, and identifying the presence of complications.

Establishing the Presence of Alcohol Abuse

Alcoholism often is readily apparent, but in some patients alcohol abuse is surreptitious and may be difficult to detect. Elevated serum levels of γ -glutamyl transpeptidase (GGTP) occur in 85% to 90% of persons who ingest more than 50 g of ethanol daily and may be a useful clue to the presence of ongoing alcohol use.²⁷ GGTP also is elevated by a variety of liver diseases, by biliary obstruction, and by many drugs that induce hepatic metabolism (eg, barbiturates, phenytoin, rifampin); therefore, abnormal levels must be interpreted with caution. Macrocytosis with an elevated erythrocyte mean corpuscular volume occurs in a majority of patients with alcohol abuse,²⁷ which is a direct effect of alcohol on developing erythroblasts and may occur in the absence of folate deficiency.

Serum levels of the liver aminotransferases aspartate transaminase (AST) and alanine transaminase (ALT) increase in patients with all types of liver disease. Whereas ALT in the hepatocyte is purely a cytosolic enzyme, AST is present in 2 immunologically distinct isoenzymes: cytoplasmic (cAST) and mitochondrial (mAST). Most causes of liver injury are associated with higher serum levels of ALT than AST. In contrast, in ALD, especially alcoholic hepatitis, selective mitochondrial injury leads to release of mAST.²⁸ An elevated serum AST/ALT ratio (to a level > 2), thus, is suggestive of alcoholic hepatitis.²⁹ However an AST/ALT ratio of greater than 1 may accompany cirrhosis of any cause; therefore, this ratio is not a specific marker for alcohol as the cause of liver injury in the setting of cirrhosis.³⁰

Alcoholic hepatitis is accompanied by systemic evidence of inflammation. Neutrophilic leukocytosis with a left shift on differential is common and can range in severity from minimal to severe. Other manifestations of systemic inflammation may include elevated erythrocyte sedimentation rate, mild anemia, and thrombocytosis.^{8,31}

Assessing the Severity of Alcoholic Liver Disease

In both alcoholic hepatitis and cirrhosis, laboratory abnormalities can reflect deterioration of hepatic synthetic function and portal hypertension. Myelosuppression and portal hypertension with splenic sequestration

may produce thrombocytopenia. Hypoalbuminemia occurs because of decreased hepatic synthetic function and coexisting protein-calorie malnutrition.

Hyperbilirubinemia results from portosystemic shunting of blood and reduced hepatocellular function, which leads to impaired bilirubin uptake, conjugation and secretion. Typically, the hyperbilirubinemia associated with ALD is a mixture of unconjugated and conjugated forms, with the latter predominating.

Coagulopathy results from decreased hepatic synthesis of clotting factors, particularly factors V and VII; it predominantly affects the extrinsic pathway of coagulation and usually is unresponsive to vitamin K administration. The severity of jaundice and coagulopathy reflect the severity of the alcoholic hepatitis and thus are of prognostic value.

The nausea and vomiting, dehydration, and malnutrition that often accompany moderate-to-severe liver disease may lead to electrolyte derangements. In severe cases of ALD, systemic vasodilatation and hypotension leading to renal hypoperfusion and oliguria are associated with increases in serum creatinine and blood urea nitrogen, an ominous finding known as hepatorenal syndrome.^{7,12}

Excluding Other Causes of Liver Disease

An important use of the diagnostic laboratory is to exclude other causes of liver disease. Patients with a history of alcoholism and liver disease often are infected with the hepatitis C virus. Alcohol abuse and hepatitis C are synergistic in causing cirrhosis,³² and hepatitis C can be eradicated in some cases by treatment with interferon and ribavirin.

Other concurrent causes of liver disease that need to be excluded include hepatitis B, hemochromatosis, Wilson's disease, α_1 -antitrypsin deficiency, autoimmune hepatitis, sarcoidosis, primary biliary cirrhosis, and primary sclerosing cholangitis.

DIAGNOSTIC IMAGING

Ultrasonography

Ultrasonography is very useful in the initial evaluation of ALD as it is inexpensive, noninvasive, widely available, and informative. Fatty liver appears diffusely echogenic on ultrasound images ("bright liver"), with attenuation of echogenicity in deep regions, blurring of the hepatic vein, and increased liver-kidney contrast.³³ Ultrasonography detects steatosis only when there is a substantial fat accumulation and is not sensitive for detecting mild degrees of steatosis. In alcoholic hepatitis, the liver appears enlarged and diffusely hyperechoic. In cirrhosis, features such as nodularity, varices, splenomegaly, and

Table 1. Treatment of Alcoholic Liver Disease

Fatty liver

- Abstinence from alcohol
- Nutritional support
- ? Insulin-receptor “sensitizers” (experimental)

Alcoholic hepatitis

- Conventional/accepted therapies
 - Adequate nutrition
 - Withdrawal from alcohol
 - Avoidance of hepatotoxic drugs (especially acetaminophen)
 - Glucocorticoids*
 - Pentoxifylline
- Controversial/experimental therapies
 - Anabolic steroids
 - Antioxidants
 - Colchicine
 - Insulin/glucagon/glucose
 - Penicillamine
 - Propylthiouracil

Alcoholic cirrhosis

- Alcohol withdrawal
- Prompt treatment of complications
- Antifibrotic agent (experimental)
- Orthotopic liver transplantation

*In patients with a Maddrey’s discriminant function value of > 32.

ascites may be present. Ultrasonography also may be useful to rule out biliary obstruction (manifested by biliary duct dilatation) or hepatocellular carcinoma. Duplex-Doppler ultrasonography can further assess patency of the hepatic and portal veins.³⁴

Computed Tomography

Computed tomography (CT) is noninvasive but requires intravenous contrast for optimal results and is more expensive than ultrasonography. Fatty liver is low in density compared with the spleen on noncontrast images. Fat distribution may be non-homogeneous, and areas of focal fat accumulation or focal sparing (ie, relatively normal, fat-free parenchyma in an otherwise steatotic liver) may need to be distinguished from focal mass lesions. CT scanning with contrast provides good visualization of vascular structures and can detect portal vein thrombosis and vascular collaterals as well as other features of cirrhosis and portal hypertension, such as hepatic nodularity and splenomegaly. CT scan-

ning is particularly useful in detecting hepatocellular carcinoma.^{35,36}

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), like CT, can provide high resolution images of liver parenchymal, vascular, and biliary anatomy, equal to or better than those provided by CT. In addition, it is possible to generate very good images of the vasculature (MR angiography) and biliary tree (MR cholangiography). At present, high-quality MRI provides the single most accurate and comprehensive technique for noninvasive evaluation of the liver without exposure to ionizing radiation. Availability and quality of MRI are increasing, and it may eventually replace other diagnostic modalities for most liver imaging.³⁷

LIVER BIOPSY

Liver biopsy is useful in ALD to confirm a diagnosis, to exclude other unsuspected causes of liver disease, to assess the extent and severity of liver damage, and to define prognosis. Biopsy is particularly important for identifying mild alcoholic hepatitis or early cirrhosis that may escape detection on purely clinical grounds; conversely, in patients with clearcut advanced cirrhosis or alcoholic hepatitis, biopsy may add little to the diagnostic evaluation. Liver biopsy can be performed safely in patients with suspected alcoholic hepatitis or cirrhosis unless there is a major contraindication (eg, coagulopathy, thrombocytopenia). In some high-risk patients, liver biopsy may be obtained successfully via a transjugular approach.³⁸ Transient normalization of coagulation function to reduce the risk of hemorrhage following biopsy can be achieved through intravenous administration of fresh frozen plasma, platelets, and/or recombinant factor VIIa.³⁹

TREATMENT AND PROGNOSIS

The only treatments of ALD that have been proven to be of value are abstinence from alcohol and supportive care. A variety of pharmacologic interventions have been examined for their ability to reduce inflammation and fibrosis as well as improve outcome in ALD. To date, none are clearly effective, although several trials support the use of glucocorticoids in severe alcoholic hepatitis. Accepted and experimental treatments for fatty liver, alcoholic hepatitis, and alcoholic cirrhosis are listed in **Table 1**.

Abstinence

Abstinence from alcohol improves survival and is the mainstay of long-term management of ALD. Abstinence

should be emphasized early and continuously. Given the addictive nature of alcohol consumption, it is prudent to recommend abrupt cessation of alcohol intake and complete abstinence. Patients should be fully informed regarding the serious potential consequences of continued alcohol use. Supportive care for prevention and management of alcohol withdrawal syndromes (eg, seizures, delirium tremens) may be required during the first 2 weeks of abstinence. Abstinence from alcohol reverses steatosis within a few weeks, but complete resolution of moderate-to-severe alcoholic hepatitis may take more than 6 months. Persistence of alcohol abuse in patients with alcoholic hepatitis will lead to cirrhosis and progressive deterioration of liver function with a dramatically worse prognosis.⁶

Nutritional Support

Protein-calorie malnutrition (PCM) is almost universal in patients with alcoholic hepatitis and cirrhosis. In alcoholic hepatitis, severity of PCM correlates with disease severity and predicts mortality; the mortality rate is 50% in patients with severe PCM as compared to 10% in those with mild PCM.⁴⁰ Some studies have suggested that improved caloric and protein intake via parenteral or enteral feeding may improve survival in patients with severe alcoholic hepatitis.⁴¹ However, complications associated with parenteral hyperalimentation (eg, sepsis, hemothorax) or enteral hyperalimentation (eg, aspiration pneumonia) may outweigh the benefits of these approaches.⁴² Thus, if the patient is able to take food orally, this is the route of choice. Formal nutritional support is reserved for patients who are unable to ingest enough by mouth to meet their nutritional needs.¹

Protein restriction should be avoided because a protein-deficient diet may impair liver regeneration and worsen liver function. Even in the presence of hepatic encephalopathy, it is usually possible for patients to have a minimum of 60 to 100 g of dietary protein daily, provided that other measures to control encephalopathy are taken. In rare instances, it may be necessary to restrict dietary proteins. In these cases, alternatives include provision of high-quality protein via a parenteral route or giving oral amino acid supplements enriched selectively in branched-chain amino acids.⁴³

Management of Alcoholic Hepatitis

The majority of patients with alcoholic hepatitis have mild disease with a negligible effect on short-term mortality rates. In patients with severe alcoholic hepatitis characterized by encephalopathy, jaundice, coagulopathy, or azotemia, however, the 30-day mortality rate may be in excess of 50%.¹⁰ The strongest prognostic

factor is hepatic encephalopathy. Short-term mortality risk may be predicted by a discriminant function value based on bilirubin level and prothrombin time.⁴⁴ More recently, the Model for End-Stage Liver Disease (MELD) score, calculated from serum bilirubin and creatinine levels and international normalized ratio, has been used to assess disease severity and predict short-term mortality.⁴⁵

The strong evidence of immunologic and inflammatory liver injury in patients with alcoholic hepatitis has provided a rationale for the use of glucocorticoids. The equivalent of 30 to 40 mg of prednisolone daily is given for 30 days, followed by rapid taper and withdrawal over 2 to 4 weeks. Glucocorticoid treatment is indicated only in severe alcoholic hepatitis (characterized by encephalopathy, hyperbilirubinemia, and/or coagulopathy), in which significant benefit, including reduction of mortality, has been demonstrated.^{10,44,46} Steroids have no proven benefit in the treatment of mild alcoholic hepatitis. Glucocorticoids are relatively contraindicated in the presence of gastrointestinal bleeding, infection, or acute renal failure (demonstrated by a serum creatinine concentration of greater than 2.5 mg/dL).

Pentoxifylline (PTX), a hemorrheologic agent that lowers blood viscosity, has been shown to decrease portal hypertension and to have an inhibitory effect on TNF and other inflammatory cytokines. TNF is one of the key factors involved in hepatocellular damage and also causes vasoconstriction that could contribute to renal insufficiency. Significant improvement in short-term survival in patients with severe acute alcoholic hepatitis after 1 month's treatment with PTX has been demonstrated recently in a single study.⁴⁷ The benefit of PTX appears to be related to a significant decrease in the risk of developing hepatorenal syndrome and renal failure.

Various other agents, including anabolic steroids (oxandrolone),⁴¹ thyroid antagonists (propylthiouracil),⁴⁸ promoters of hepatic regeneration (insulin, glucagon, glucose),^{49,50} anti-fibrogenic agents (colchicine, penicillamine),⁵¹ antioxidants (*S*-adenosylmethionine),⁵² phospholipids, calcium channel blockers,⁵³ and hepatoprotective bile acids (ursodeoxycholic acid),⁵⁴ have been studied in clinical trials for treatment of alcoholic hepatitis, but none of them have been found to be consistently beneficial or to improve survival.⁵⁵

Management of Alcoholic Cirrhosis

Once cirrhosis is diagnosed, survival rates are most strongly affected by presence or absence of ongoing alcohol use, severity of hepatic functional failure, presence and severity of complications of cirrhosis, and development of hepatocellular carcinoma.¹¹ Cirrhotics

with active alcoholic hepatitis exhibit progressive deterioration of liver function. Following prolonged abstinence with resolution of alcoholic hepatitis, liver function typically stabilizes and improves. Persistent complications of cirrhosis that fail to resolve with abstinence, such as ascites or encephalopathy, are indicative of a poorer prognosis. The traditional Child-Turcotte-Pugh classification and the newer MELD score both are good indicators of short-term and medium-term prognosis in patients with alcoholic cirrhosis.⁵⁶

In general, medical management of alcoholic cirrhosis focuses on eliminating alcohol and treating complications, including variceal hemorrhage, hepatic encephalopathy, ascites, and spontaneous bacterial peritonitis. Serial liver imaging (every 6–12 months) and serum α -fetoprotein levels (every 3–6 months) to screen for hepatocellular carcinoma should be considered.

Orthotopic Liver Transplantation

Orthotopic liver transplantation is widely employed in patients with end-stage liver cirrhosis. Controversies surrounding liver transplantation in patients with a history of alcoholism focus on the risk of recidivism, potential noncompliance with medical care, concurrent damage to other organs such as the heart and pancreas, the shortage of donor organs, and adverse public opinion.⁵⁷ Nevertheless, patients with history of alcoholism can successfully undergo transplantation following a period of abstinence from alcohol (typically at least 6 months), provided there is commitment to sustained sobriety. The waiting period is necessary in part to permit resolution of alcoholic hepatitis, and many patients exhibit enough improvement with prolonged abstinence that liver transplantation is no longer necessary.⁵⁸

Liver transplantation should be considered in abstinent patients with complications of alcoholic cirrhosis or significant hepatic functional impairment (Child-Turcotte-Pugh class B or C). Although most patients undergoing liver transplantation are younger than 60 years, selected patients between 60 and 75 years may be offered transplantation if they are otherwise in excellent health. The process usually begins with strong encouragement of sobriety in a formal program of substance abuse evaluation, treatment, support, and monitoring. Additional evaluation may be pursued once a commitment to sobriety is apparent.

Evaluation for orthotopic liver transplantation consists mainly of a search for complicating factors that may represent relative or absolute contraindications to transplantation. Examples include severe cardiovascular or pulmonary disease, malignancy outside of the

liver, sepsis, and psychosocial problems that may jeopardize the patient's ability to follow medical regimens after transplantation. In particular, patients with end-stage ALD may have other diseases caused by alcohol, such as cerebral dysfunction, chronic pancreatitis, cardiomyopathy, peripheral neuropathies, and skeletal myopathies, that must be identified and evaluated.

Advances in surgical techniques, organ preservation, and immunosuppression have resulted in progressive improvement in post-transplant survival over the past 2 decades. Currently, the 1-year survival rate for patients who underwent liver transplantation for ALD averages 85%, and the 5-year survival rate is more than 70%, with quality of life being good or excellent in most cases.⁵⁹ These results are comparable to or better than those observed in patients transplanted for other chronic liver diseases.⁶⁰ Relapse of alcohol abuse following liver transplantation in well-selected patients is unusual; more than 85% of former alcoholics remain alcohol-abstinent, and of those who resume drinking, the majority drink only moderately (< 3 drinks/week).^{61,62}

CONCLUSION

ALD is the most common hepatopathy in the western world and is a leading cause of liver transplantation. ALD comprises a wide spectrum of pathology ranging from mild fatty infiltration to advanced cirrhosis. Although the association between alcohol abuse and liver disease has been known for centuries, the exact mechanisms of alcohol-induced liver injury remain incompletely understood.

The only treatment of ALD that has been proven to be of value, albeit with limited success in improving mortality, is the combination of abstinence from alcohol and supportive care, including adequate nutrition. During the past 3 decades, several pharmacologic interventions have been investigated in the treatment of ALD. To date, none are clearly effective, although some trials support the use of glucocorticoids in severe alcoholic hepatitis, particularly in patients with a discriminant function value greater than 32. **HP**

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