Alcoholic Hepatitis

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A 45-year-old woman with a past medical history notable for alcohol abuse over 20 years was brought to the emergency department after being found disheveled and mildly confused. The patient states that she had been "binge drinking" for 6 days. She complained of mild abdominal pain as well as increasing abdominal girth. Physical examination was notable for a low-grade temperature (100.4°F), jaundice, scleral icterus, and a distended abdomen with shifting dullness. Mild tenderness was noted in her right upper quadrant. Liver and spleen were not palpable. Asterixis was present. Notable laboratory values were: white blood cell count, 17,000/μL; aspartate aminotransferase, 240 U/L; alanine aminotransferase, 26 U/L; total bilirubin, 15.1 mg/dL (direct, 9.5 mg/dL); alkaline phosphatase, 355 U/L; international normalized ratio, 1:55; and serum creatinine, 0.7 mg/dL. The patient underwent a diagnostic paracentesis, which showed no evidence of spontaneous bacterial peritonitis. A Maddrey discriminant function score was calculated at 28.3, and a Model for End-stage Liver Disease score was calculated at 21. The patient was admitted to the medical floor with a diagnosis of alcoholic hepatitis.

Liver disease accounts for 2% of deaths and more than 1% of health care spending in the United States.[1,2] Nearly half of these deaths and costs are attributed to alcohol-related liver disease. The spectrum of clinical findings in patients with alcoholic liver disease (ALD) is broad, ranging from fatty liver (steatosis) to alcoholic hepatitis to cirrhosis. This article reviews the fundamental aspects of diagnosis, prognosis, and management of acute alcoholic hepatitis.

DEFINITION AND EPIDEMIOLOGY

Alcoholic hepatitis is a clinical/histopathologic diagnosis first described in 1961 by Becket et al,[3] who applied the term "acute alcoholic hepatitis" to 7 patients who developed abdominal pain, fever, anorexia, and elevated white blood cell count after sustained alcohol consumption. Liver biopsy specimens revealed a diverse inflammatory pathologic presentation including fibrosis, acute lobular inflammatory infiltration, and necrosis.[3] Since then, this clinical/histopathologic syndrome has been a well-recognized cause of morbidity and mortality.

Most US adults imbibe some amount of alcohol, with an average annual consumption rate of 8.4 L per person. There is a direct correlation between per capita ethanol consumption and liver-related mortality rates.[4] Consequently, alcohol prohibition during the 1920s led to a decline in ALD mortality.[5] Although the prevalence of ALD has fallen in recent years, nearly 14 million people in the United States meet diagnostic criteria for alcoholism.[6] According to the Centers for Disease Control and Prevention, ALD caused more than 12,000 deaths in 2001.[7]

There are considerable data suggesting that the amount of alcohol consumed and the duration of consumption on an individual basis relates to the risk of ALD.[8] Consumption of 80 g of ethanol per day (equal to 1 L [34 ounces] of wine, 236 mL [8 oz] of distilled spirits, or 8 12-ounce beers) puts one at a risk for ALD.[6] However, some authors have suggested that the relative risk for disease increases at amounts as low as 30 g/day.[6] ALD can emerge in 3 forms: fatty liver, alcoholic hepatitis, and cirrhosis. The form or severity of liver disease is not predicted by the amount of alcohol consumed. Between 90% and 100% of heavy alcohol consumers will develop fatty liver. Of those with fatty liver, 10% to 35% will develop alcoholic hepatitis, and 20% to 40% of these alcoholic hepatitis patients will progress to cirrhosis.[9] Up to 20% of patients with fatty liver due to alcohol consumption will progress directly to cirrhosis.[9] The variety of presentations of ALD make it clear

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TAKE HOME POINTS

- The diagnosis of alcoholic hepatitis is based on a complete history and physical examination as well as laboratory testing values that are characterized by elevated aspartate aminotransferase/alanine aminotransferase (ratio of these enzymes > 2) levels. At times a liver biopsy is required for confirmation.
- Prognostic indicators such as the Child-Pugh score, Maddrey discriminant function, and Model for End-stage Renal Disease score predict outcome.
- The mainstay of treatment is abstinence, nutritional support, and, for those with poor prognostic indicators, anti-inflammatory measures.
- The decision of whether to begin anti-inflammatory medications in patients with severe alcoholic hepatitis is controversial in the literature and difficult in clinical practice.
- Therapeutic options for severe disease include prednisolone, pentoxifylline, and newer drugs aimed at inhibiting tumor necrosis factor.

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that factors other than amount of alcohol consumed play a role in the pathogenesis of the disease.

BASIC ETHANOL METABOLISM AND RISK FACTORS FOR DISEASE

The liver is the primary site of ethanol metabolism. Within the hepatocyte, the enzyme alcohol dehydrogenase (ADH) metabolizes ethanol to acetaldehyde. In the mitochondria, acetaldehyde dehydrogenase (ALDH) then metabolizes acetaldehyde to acetate. When these pathways become overwhelmed due to chronic substantial ethanol abuse, the microsomal ethanol oxidizing system (MEOS) becomes increasingly important. Cytochrome P450 2E1, the central enzyme of MEOS, is induced primarily in the smooth endoplasmic reticulum and converts ethanol to acetaldehyde, which is then metabolized to acetate by ALDH.[10] The cytochrome P450 2E1 enzyme has the capacity to generate reactive oxygen intermediates, such as superoxide radicals, which play a role in causing hepatocellular damage.[11] In addition, a portion of ingested ethanol is metabolized directly in the stomach by gastric ADH.

Genetic and acquired differences in these metabolism pathway enzymes may explain why some persons are more susceptible to disease than others. Differences in polymorphisms of cytochrome P450 2E1 as well

as this enzyme's role in the metabolism of acetaminophen may explain why some are protected while others progress to disease. In addition, women have a two- to fourfold greater risk than men for developing ALD for a given amount of alcohol consumed. This increased risk is thought to result from women having less naturally occurring gastric ADH and therefore having a greater amount of ethanol detoxified by the liver.[12]

Hepatitis C virus (HCV) infection is a major risk factor for progression of ALD. Approximately 30% of alcoholics have antibodies to HCV; these patients with concurrent HCV infections are more likely to have severe disease, decreased survival, and higher rates of hepatocellular carcinoma.[13] Although the pathogenesis is unclear, it is thought that the interaction of alcohol with HCV results in decreased immune-mediated viral killing or enhanced virus gene expression.[14] Concurrent *Helicobacter pylori* infection is also a risk factor for developing ALD, which may be due to an associated gastritis leading to decreased gastric ADH and thus a greater amount of ethanol presenting to the liver.[15] Hepatitis B virus infection, obesity, and malnutrition also predict more severe disease.[16]

DIAGNOSIS
Clinical Findings

The diagnosis of alcoholic hepatitis is made by a thorough history, physical examination, and laboratory evaluation. All patients must have a history of alcohol ingestion. The history should focus on the amount of alcohol consumed and the duration of consumption as well as on other potential liver toxic behaviors (eg, intravenous drug use, current medications with liver toxicity, comorbid illnesses). Fever is seen in approximately 25% of patients, hepatomegaly in approximately 75%, and jaundice in up to 60%. Between 30% and 60% of patients have ascites.[17] The presence of ascites does not necessarily prove that a liver is cirrhotic, as ascites may be a transient effect of hepatic inflammation on portal flow.[18] Abdominal pain is usually mild in alcohol hepatitis; if severe pain is present, another intra-abdominal process should be sought, such as gallbladder or pancreatic disease. Skin stigmata of liver disease (eg, palmar erythema, spider angiomata) suggest underlying cirrhosis.

The levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in patients with alcoholic hepatitis. Classically, the ratio of AST to ALT in alcoholic hepatitis is greater than 2. These ratios can help distinguish alcoholic hepatitis from other causes of liver disease. A ratio greater than 2 occurs in 70% of patients with alcoholic hepatitis as compared

with 26% of patients with postnecrotic cirrhosis, 8% with chronic hepatitis, and 4% with viral hepatitis.[19] The biopsy findings of nonalcoholic steatohepatitis (NASH) and alcoholic hepatitis are similar. However, NASH and viral hepatitis are usually characterized by an AST/ALT ratio of less than 2.[20] Levels of serum transaminases do not correlate with disease activity.[21] ALT and AST levels in alcoholic hepatitis rarely exceed 300 U/L; if transaminases exceed this level, other diseases or concomitant diseases (eg, acute viral hepatitis) should be considered. Other laboratory abnormalities in alcoholic hepatitis include leukocytosis (which, if not due to infection, may correlate with hepatic disease activity), increased prothrombin time and partial thromboplastin time, increased bilirubin level, thrombocytopenia, and red blood cell macrocytosis.

The clinical diagnosis of alcoholic hepatitis has sensitivities and specificities ranging above 90% when compared to the gold standard liver biopsy.[22] Liver biopsy should be considered if the diagnosis is uncertain, if there may be more than 1 disease process involved, or if overt signs of liver failure are present.

Pathologic Findings

The hallmark of alcoholic liver disease is inflammatory change around the central vein (ie, peri-central changes) of the hepatic lobule. Viruses typically affect the periportal areas. Macrovesicular steatohepatitis (large fat droplets within the cell that push the nucleus to side) and microvesicular steatohepatitis (small fat droplet accumulations with nuclei remaining in the center) are seen in 60% to 90% of patients. Neutrophilic infiltration can be seen in 50% to 85% of patients with alcoholic hepatitis; monocyte infiltration is seen with viral pathogens. Mallory (eosinophilic) inclusions, a nonspecific finding, may be seen in 70% to 75% of patients. Sinusoidal and septal fibrosis, with or without cirrhosis, may be seen as well.[19,23]

PROGNOSIS

Current treatment guidelines are based upon prognostic indicators. Mild alcoholic hepatitis is generally not dangerous and patients will likely be asymptomatic. Overall mortality rates in patients hospitalized with alcoholic hepatitis approach 15%, usually from the severe complications of sepsis and hepatorenal syndrome, but may exceed 50% in patients with encephalopathy and other clinical predictors of poor outcome (discussed below).[24] Some patients will improve without treatment, while others will not improve despite aggressive therapy; it is therefore valuable to identify the patients for whom treatment may be beneficial.

Table 1. Prognostic Tools Used in Alcoholic Hepatitis

Child-Pugh Classification

Parameters	Points Assigned*		
	1	2	3
Ascites	Absent	Slight	Moderate
Total bilirubin, mg/dL	< 2	2–3	> 3
Serum albumin, g/dL	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

*A score between 10 and 15 points is considered decompensated disease and is associated with a 35% to 45% 2-year survival.

Maddrey Discriminant Function

$$DF = 4.6 \text{ (patient's prothrombin time} - \text{control time)} + \text{total serum bilirubin [mg/dL]}$$

Model for End-Stage Liver Disease (MELD) Score

$$3.8 \times \log_e \text{(total bilirubin [mg/dL])} + 11.2 \times \log_e \text{(INR)} + 9.6 \times \log_e \text{(creatinine [mg/dL])} + 6.4$$

INR = international normalized ratio.

Several prognostic indices have been used over the last half century. The Child-Pugh score, developed in 1964 to risk stratify patients undergoing shunt surgery, was an early tool used to prognosticate patients with alcoholic hepatitis (**Table 1**). This index is used less frequently because it relies on subjective data (eg, degree of ascites, encephalopathy).[25] Most current treatment guidelines and literature use the Maddrey discriminant function, which is calculated based on the patient's serum bilirubin level and prothrombin time prolongation (Table 1).[26] The score is used to help discriminate between patients who have high 30-day mortality rates and those who do well; values above 32 indicate severe disease. Mortality rates in patients who receive no treatment and have scores greater than 32 may exceed 45%.[26]

Recent studies indicate that the Model for End-Stage Liver Disease (MELD) score, originally used as a severity index for patients with end-stage liver disease, may be a more valuable model than the Child-Pugh score or the Maddrey score in patients admitted with alcoholic hepatitis (Table 1). Admission MELD score greater than or equal to 18 (positive predictive value [PPV], 47%; negative predictive value [NPV], 97%), first-week MELD score greater than or equal to 20 (PPV, 51; NPV, 98), and first-week change in MELD score greater than 2 (PPV, 35; NPV 96) are significantly associated with in-hospital mortality.[27,28]

Table 2. Proposed Therapeutic Approach to Alcoholic Hepatitis: Risk Stratification with Maddrey Discriminant Function Score* or Model for End-Stage Liver Disease

Lower Risk	Higher Risk
DF score ≤ 32	DF score > 32
Admission MELD score < 18	Admission MELD score ≥ 18
Supportive care	Nutritional supplements
Abstinence	Consider prednisolone or pentoxifylline or other anti-TNF agents (future)
Rehabilitation	
Counseling	

Note: It is very important to rigorously rule out infection prior to starting immunosuppressive medications.

Adapted from O'Shea RS, McCullough AJ. Treatment of alcoholic hepatitis. Clin Liv Dis 2005; 9:125. Copyright 2005, with permission from Elsevier.

DF = discriminant function; MELD = Model for End-Stage Liver Disease; TNF = tumor necrosis factor.

*Although the MELD score has recently been shown to be the best prognostic indicator,[27,28] it has not yet been studied as well as the Maddrey DF.

MANAGEMENT

Abstinence from alcohol is the foundation of treatment for any patient diagnosed with ALD in that it delays progression of disease and is necessary for future consideration of transplant candidacy. Supportive medical care is standard in all hospitalized patients with alcoholic hepatitis. These measures include treatment of any coexistent alcohol withdrawal, maintenance of appropriate volume status (which may be difficult in patients with underlying cirrhosis and ascites), and thorough evaluation for infection.

Mortality remains high in patients with elevated discriminant functions and MELD scores despite supportive care, and additional pharmacotherapy has been studied to improve outcomes in these patients. Because inflammation plays a role in disease progression, anti-inflammatory treatment with steroids by far has been the most thoroughly examined therapy. In a meta-analysis that included 11 randomized trials (10 placebo controlled) involving patients treated with corticosteroids for acute alcoholic hepatitis, the relative risk for 30-day mortality was 0.63 (0.41 if only the highest quality studies were used).[29] It is important to note that most of the studies used in this meta-analysis excluded patients with infections, gastrointestinal bleeding, renal failure, or pancreatitis. In patients with fever and leukocytosis, infection should be rigorously excluded prior to administration of immunosuppressants.

The American College of Gastroenterology currently recommends the use of glucocorticoids for patients with a Maddrey score over 32 and/or encephalopathy.[30] The treatment should be prednisolone (which has less hepatic metabolism than prednisone) 40 mg/day for 4 weeks then tapered over 2 weeks.[30] **Table 2** outlines therapy based on scoring indices. Despite these recommendations, the decision to treat patients with alcoholic hepatitis with anti-inflammatory medications continues to be highly debated in the literature. Overall, the evidence leans in favor of the use of corticosteroids in carefully selected patients with acute alcoholic hepatitis. Still, the treating physician has to make a difficult decision in starting a potentially dangerous medicine (a corticosteroid, with its known risks) in a patient already at high risk of developing an infection or dying. To complicate this matter further, the sickest of these patients may stand to benefit the most from the treatment.

Other anti-inflammatory medications have been studied. It has been shown that tumor necrosis factor-α (TNF-α) is elevated in patients with alcoholic hepatitis and may play a pathologic role in alcoholic hepatitis by inducing programmed cell death. Pentoxifylline is a phosphodiesterase inhibitor that has multiple effects on immune markers and notably lowers the levels of TNF-α. One randomized controlled trial (N = 101) showed a significant short-term survival benefit in patients with Maddrey discriminant function scores greater than 32 treated with pentoxifylline.[31] TNF blockade with etanercept (a soluble TNF-α receptor:FC fusion protein) and infliximab (a chimeric mouse-human anti-TNF-α monoclonal antibody) also has had promising results in limited early studies.[32,33]

Patients with alcoholic hepatitis typically are severely malnourished. One study involving 363 patients with alcoholic hepatitis found that all had evidence of protein-calorie malnutrition.[34] The level of malnutrition correlated with a worse prognosis. These findings have led to trials investigating nutritional supplementation in hospitalized patients. Although results have been mixed, the American College of Gastroenterology recommends enteral nutritional support for patients with alcoholic hepatitis, with specific protein and calorie daily requirements met using amino acid supplementation if needed.[30] Branch chain amino acids are not recommended because of their increased cost and because there is no evidence that conventional amino acid preparations precipitate hepatic encephalopathy.[35]

SUMMARY

ALD is a costly and deadly illness. Hospital physicians should be comfortable managing any manifestation of ALD, especially acute alcoholic hepatitis, which may

portend a poor outcome. Diagnosis of alcoholic hepatitis is made by patient history, physical examination, and focused laboratory evaluation. If necessary, a liver biopsy may be performed and is the diagnostic gold standard. A thorough search for a coexistent infection is necessary. Physicians should be able to gauge their patients' prognosis using the Maddrey discriminant function and the MELD score. Current treatment recommendations include supportive care, and depending on the above prognostic indicators, the judicious use of corticosteroids. Pentoxifylline has shown benefit, and other anti-inflammatory agents are under investigation.　　**HP**

ACKNOWLEDGMENT

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