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Acute Alcoholic Hepatitis, the Clinical Aspects

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Keywords

alcoholic hepatitis; alcoholic liver disease; diagnosis; clinical outcomes

Introduction

Alcohol is a socially accepted hepatotoxin and its use is common worldwide with geographical variability in consumption patterns driven in part by local cultures and habits. The health-related consequences of alcohol are immense and depend on a number of factors related to the patterns of alcohol consumption, as well as, an individual's co-morbidities and genetic predisposition to alcohol's pathophysiological effects. Alcoholic liver disease (ALD) is a leading cause of advanced liver disease and is the number one cause of death in adults who drink excessively. The majority of liver disease burden in Western countries is attributable to alcohol use (1). An acute form of ALD, alcoholic hepatitis (AH) is regarded as a specific clinical entity characterized by rapid decompensation of hepatic function. The severity spectrum of AH is wide with disease ranging from a subclinical form with good short-term outcomes to severe acute illness associated with high mortality. Early detection of high-risk patients and prompt intervention are needed to improve outcomes in patients with AH and alleviate the healthcare costs associated with severe disease.

Prevalence of alcoholic hepatitis

The exact incidence and prevalence of AH remain unclear, as many patients have subclinical disease and are never diagnosed. One study reported the prevalence of AH in a cohort of 1604 alcoholics to be approximately 20% based on liver biopsy data (2). According to a

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study utilizing the National Inpatient Sample, AH accounted for 56,809 hospitalizations in the United States in 2007 (0.71% of all hospitalizations). The mean age of admitted patients was 53 years, 75% of them were males, and the overall inpatient mortality was 6.8%. Acute renal failure, infections, hepatic encephalopathy, coagulopathy, and ascites were strongly associated with mortality (3).

Patterns of alcohol intake leading to alcoholic hepatitis

AH has been linked to excessive alcohol drinking over a prolonged period of time (typically more than 2 decades). However, it is now recognized that many patients diagnosed with AH report alcohol use over shorter periods of time before diagnosis. Heavy drinking has been defined as ≥ 15 drinks per week for men and ≥ 8 drinks per week for women (2). In an Italian population study, the risk threshold for developing liver damage was ingestion of more than 30 grams of alcohol per day in both men and women. The pattern of drinking was also an important determinant of hepatic damage; specifically, an increased risk was seen in patients drinking without food (4). The type of alcohol use is also important, as the risk of ALD was higher from drinking beer and spirits compared to drinking wine (5).

In practice, most patients diagnosed with AH usually consume more than 100 grams of alcohol per day, with higher consumption being associated with more severe disease. Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as the consumption of 5 or more drinks by a male or 4 or more drinks by a female in about 2 hours, resulting in a blood alcohol concentration of $\geq 0.08\%$ (6). Despite limited quality data, binge drinking is a potential risk factor for AH, and is particularly thought to contribute to the rising incidence of AH in younger individuals. Importantly, a strong relationship between the prevalence of binge drinking and excessive drinking has been demonstrated in epidemiological studies (2). While most patients diagnosed with AH are active drinkers, the disease can still be diagnosed after reducing or stopping alcohol consumption.

Risk factors of alcoholic hepatitis

Aside from the quantity and pattern of alcohol consumption, a number of environmental and individual factors have been associated with the development of AH.

- **Age:** AH is typically diagnosed in adults between with the ages of 40 and 50 years. However as mentioned earlier, younger patients are increasingly being diagnosed with AH likely related to earlier heavy use of alcohol and binge drinking behavior.
- **Sex:** Women are more prone to the toxic effects of alcohol and are at a higher risk of developing liver fibrosis and AH compared to men (7,8). This gender susceptibility is attributed to several factors. Women have lower gastric levels of alcohol dehydrogenase which lead to slower first-pass metabolism of alcohol. They have higher gut permeability leading to higher endotoxin levels after alcohol ingestion that promotes more oxidative stress and hepatic inflammation. Alcohol-mediated cytokine release from macrophages is greater in females. The larger body fat content in women also produces a lower volume of distribution

for alcohol and therefore higher blood alcohol concentration after lower volumes of alcohol ingestion.

- **Ethnicity:** Hispanics are more likely to develop AH at a younger age compared to Caucasians, and both Hispanics and African Americans are more likely to develop ALD (11,12). It is not clear whether this racial susceptibility is due to genetic variations, different patterns of alcohol use/abuse, differences in socioeconomic status, and/or access to medical care.
- **Obesity:** Obesity is an independent risk factor for cirrhosis in alcoholic patients and potentiates the severity of AH. The synergy between obesity and heavy alcohol intake likely is the results of similar disease mechanisms for both ALD and non-alcoholic fatty liver disease (11).
- **Malnutrition:** Protein-calorie malnutrition is a major risk factor for developing AH and is an indicator of poor outcomes and decreased survival in patients with established AH (12).
- **Co-existent hepatitis C virus (HCV) infection:** The combination of alcohol use and HCV infection has been associated with rapid progression to fibrosis and higher incidence of cirrhosis than either factor alone. In patients with AH, the presence of HCV infection was demonstrated as an independent risk factor for higher mortality at 6 months (13).
- **Hereditary factors:** Monozygotic twins were shown to have a higher concordance rate for alcoholic cirrhosis than dizygotic twins (14). Variations in the genes for cytochrome P450 2E1 (CYP2E1) and alcohol dehydrogenase (ADH); the major enzymes involved in alcohol metabolism, affect alcohol-driven tissue damage in addition to having a proposed influence on patterns of alcohol consumption and dependency, which in turn can predispose individuals to AH (15).

Clinical Presentation

Symptoms/Signs

The diagnosis of AH is primarily based on the clinical presentation (Box 1). Obtaining an accurate alcohol consumption history on presentation is crucial although not always feasible. In symptomatic individuals, progressive jaundice is the main presenting feature, and a history of heavy alcohol use is typically elicited. Other clinical features can include fever, anorexia, weight loss, fatigue, generalized weakness, and nausea and vomiting. Patients can have complications related to portal hypertension such as ascites and variceal hemorrhage, even in the absence of underlying cirrhosis. Patient with AH are also prone to develop encephalopathy secondary to severe hepatic dysfunction. With most AH patients being active drinkers, they can exhibit severe forms of alcohol withdrawal after suddenly decreasing or discontinuing their alcohol use. Within the first 24 hours after the last drink, tachycardia, hypertension, irritability and hyperreflexia can occur. Over the next few days more dangerous complications including seizures and delirium tremens can arise. On physical exam tender hepatomegaly can be present, and occasionally a hepatic bruit can be

auscultated likely related to increased flow through the hepatic artery. Classical non-specific signs of liver disease such as parotid enlargement, Dupuytren's contractures, dilated abdominal wall veins and spider nevi can be present (16).

Laboratory Findings:

No single laboratory marker can definitively establish the diagnosis of AH but a number of biochemical derangements can be seen in these patients. The classical finding is an elevated aspartate aminotransferase (AST) to 2–6 times the upper limit of normal (usually less than 300 IU/L) and elevation of alanine aminotransferase (ALT), to a lesser extent, resulting in an AST:ALT ratio $\Rightarrow$ 2 (17). Leukocytosis with an elevated neutrophil count, anemia and hyperbilirubinemia are common. Leukocytosis can be a feature of AH itself, part of the systemic inflammatory response syndrome (SIRS), or an indication of underlying infection. In severe cases of AH, serum albumin can be low and coagulopathy with a prolonged prothrombin time (elevated international normalized ratio) is common. Patients with AH are also prone to renal injury and approximately 7% can be diagnosed with hepatorenal syndrome type 1 (18).

Ruling out infection

Patients with AH are especially prone to developing bacterial infections and about 25% of patients with severe AH are infected at the time of presentation (19). Indeed, infection is a leading cause of mortality in those with severe disease. Therefore, close monitoring for symptoms and signs of infection is crucial and screening for infections is warranted on admission as well as repeatedly during the hospital stay in patients who experience clinical deterioration. Routine blood and urine cultures should be obtained and paracentesis should be performed in those with ascites to evaluate for bacterial peritonitis. Importantly, patients with AH frequently have SIRS criteria that can be related to the overall inflammatory nature of the disease itself or can reflect an active bacterial infection. Regardless of the exact etiology, SIRS triggers a cascade of events that culminate in multi-organ failure, and an increased mortality risk is associated with increasing presence of the SIRS parameters.

Ruling out other liver diseases

Other causes of acute liver injury such as drug-induced liver injury, viral hepatitis, autoimmune hepatitis, Wilsonian crisis and cholangitis should be ruled out while evaluating patients with suspected AH. Liver, vascular, and biliary imaging are required to exclude biliary or vascular disorders as well as hepatocellular carcinoma.

Diagnosis

Clinical prognostic scoring models of alcoholic hepatitis

Based mainly on laboratory parameters, a number of scoring models are used to assess severity of AH, predict mortality and guide decisions for initiation of specific therapies (20–23). For more information on scoring models please see Pierre M. Gholam: Prognosis and Prognostic Scoring Models for Alcoholic Liver Disease and Acute Alcoholic Hepatitis, in this issue. The Maddrey discriminant function (DF) remains widely utilized in the initial assessment of patients with AH. A value of ≥ 32 signifies severe disease and has been used

as a threshold for initiation of corticosteroid therapy in the absence of other contraindications (20). The role of the model for end-stage liver disease (MELD) score has been evaluated in assessing AH severity. A MELD score of 21 has been reported to have the highest sensitivity and specificity to predict mortality in patients with AH, estimating a 90-day mortality of 20% for patients with this score (21). A MELD score of 21 has also been used as a threshold for starting corticosteroids (24). In addition to MELD's role in the initial assessment of AH patients, a progressive increase in MELD score in hospitalized AH patients is associated with significantly poor outcomes and higher in-hospital mortality (25). While the Glasgow alcoholic hepatitis score (GAHS) and the ABIC (age, serum bilirubin, INR, and serum creatinine) scores have been shown to predict survival outcomes in patients with AH, their use has been limited due to lack of external validation studies (22, 23). Finally, the Lille score was designed to assess the response of patients with severe AH to corticosteroid therapy. It is calculated based on five pretreatment variables (age, albumin, prothrombin time, bilirubin at day 0 of treatment, presence or absence of renal insufficiency,) and the change in bilirubin at day 7 of treatment. A Lille score ≥ 0.45 is associated with 75% mortality at 6 months, indicating that corticosteroids should be discontinued due to lack of response (26).

Role of liver biopsy

Although the diagnosis of AH is suspected based on clinical and biochemical data, a definitive diagnosis may require histological confirmation and a liver biopsy remains the "gold standard" diagnostic tool. According the guidelines of American Association for the Study of Liver Diseases, a liver biopsy should be considered when contemplating medical treatment for patients with a clinical diagnosis of severe AH, and in patients without a clear underlying diagnosis (27). Findings on liver biopsy in AH include steatosis, hepatocyte ballooning, neutrophil infiltration, Mallory bodies (aggregated cytokeratin intermediate filaments and other proteins) and scarring with a typical perivenular distribution compared to the periportal fibrosis observed in chronic viral hepatitis. Limitations of liver biopsy include cost, sampling errors and inter-observer variability. The percutaneous approach carries the risk of serious complications such as bleeding, infection, pneumothorax, hemothorax and organ puncture (28). The utility of liver biopsy in patient with AH is particularly controversial as many are coagulopathic, have thrombocytopenia and/or ascites, all of which can complicate or prevent a percutaneous liver biopsy. Therefore, a transjugular liver biopsy is preferred in this setting but is not widely available outside tertiary medical centers.

Histological prognostic scoring of alcoholic hepatitis

In addition to aiding in the diagnosis of AH, liver biopsy may have a role in determining AH prognosis. A recent multicenter study has tested and validated an alcoholic hepatitis histologic score (AHHS), and showed its accuracy in predicting short-term mortality in patients with AH (29). This study included 121 patients with biopsy-proven AH as the initial set, with subsequent testing and updating of the score in a test set of 96 patients, then validation in an independent set of 109 patients. The AHHS was generated using 4 histological features that independently predicted short-term survival: stage of fibrosis, degree of neutrophil infiltration, pattern of bilirubinostasis, and presence of mega-mitochondria. Optimal cutoff values to define different severity categories were: 3 and 6

points (sensitivity of 98%, 72% and specificity of 20%, 75%, respectively). Using these cutoff values, the AHHS identified patients with AH as having low (0–3 points), moderate (4–5 points), or high (6–9 points) 90-day mortality rates. None of the individual histological features assessed by the AHHS were useful in predicting response to corticosteroids. This study also demonstrated an association between the pattern of bilirubinostasis and the risk of developing a bacterial infection during hospitalization, as nearly 50% of patients with canalicular/ductular bilirubinostasis or hepatocellular plus canalicular/ductular bilirubinostasis developed a bacterial infection during hospitalization. The degree of bilirubinostasis itself progressed with increasing levels of serum bilirubin. Table 1 summarizes the AHHS calculation.

Non-invasive diagnostic modalities

Given the limitations and potential complications of liver biopsy, there is a need for alternative non-invasive methods for AH diagnosis and assessment of disease severity. Analysis of breath biomarkers including volatile organic compounds and elemental gases have been recently evaluated in the diagnosis of AH. A study reported a diagnostic model using the combination of the breath levels of trimethylamine and pentane to distinguish patients with AH from those with acute liver decompensation from causes other than alcohol or controls without liver disease (30). This model known as TAP provided accurate prediction for the diagnosis of AH with 90% sensitivity and 80% specificity for a TAP score of 36 or higher. The levels of exhaled trimethylamine had a low level of correlation with the severity of AH based on MELD score. These results still need to be externally validated.

Outcomes

Short-term and long-term survival

The natural history of AH is variable and depends on the severity of the disease, whether treatment is initiated or not, and abstinence from further alcohol use. In a pooled analysis of 19 clinical trials of AH, the overall mortality was about 34% among 661 patients randomized to placebo (31). The 1-month mortality rate in trials that included patients with severe AH was approximately 23%. The leading cause of death in these patients was liver failure followed by gastrointestinal bleeding and infection. The high short-term mortality of severe AH was also demonstrated in a meta-analysis of 5 randomized controlled trials which evaluated the role of corticosteroid treatment (32). The 28-day mortality rate in 197 non-corticosteroid-treated patients with severe AH was 34.3%. Short-term mortality in patients with mild-moderate AH is less well reported but is generally low.

While the high short-term mortality associated with severe AH is well reported, long-term survival following AH is not as well described. A recent study demonstrated a significant correlation between the long-term survival following an episode of AH with abstinence from alcohol (33). In this study, the estimated 5-year overall survival rate was 31.8%, with a 3-fold higher survival rate in abstainers compared to relapsed and continued drinkers. About half of the patients surviving the index hospitalization died during the study follow up period.

Progression to cirrhosis

Many patients already have underlying alcoholic cirrhosis at the time of initial AH presentation. In those without cirrhosis, progression to cirrhosis primarily depends on continued consumption of alcohol, but an older study reported that about 10%–20% of patients with AH progress to cirrhosis every year, with 70% of all patients ultimately developing cirrhosis (34). Women diagnosed with AH are a higher risk of progression to cirrhosis than men despite abstinence (35). Total abstinence from alcohol use can lead to complete return of normal liver histology in about 10% of patients with AH.

Recidivism

Abstinence from alcohol use is the cornerstone of management in patients with AH and complete sobriety is vital for recovery of liver injury. Data on the prevalence and patterns of recidivism after the diagnosis of AH is limited and its impact on patient survival is conflicting. Studies have reported a recidivism rate of 28% at 6 months and 37% at 12 months in patients with severe AH (36, 37). A more recent retrospective study from the United Kingdom analyzed data from 109 patients hospitalized for severe AH, with an aim of assessing their long-term outcomes including survival and recidivism (33). During a median follow up of 40.7 months from hospitalization, 63 patients died (57.8%) including 22 who died during the index hospitalization. The other 41 patients had a median survival of 30.2 months. Among 87 patients surviving the index hospitalization, 57% were drinking at time of last follow up including two-thirds who continued to drink and one-third who relapsed after initial abstinence. Another 8% suffered an alcohol relapse but were eventual abstainers at time of last follow up. Abstinence at last follow-up was the only independent predictor of long-term outcome with 5-year survival being approximately 3-fold higher in abstainers (75.3%) compared to relapsed drinkers (26.8%) and continued drinkers (21.0%) ($P=0.005$). Importantly, this study showed that the survival benefit from sobriety in AH was not apparent until 18 months following discharge (HR 2.714, 95% CI 0.995–7.404, $P=0.051$), and that transient abstinence is of little benefit in AH patients indicating the need for immediate and sustained sobriety. Therefore, medical therapy to decrease alcohol relapse after recovery from AH should be considered to lower the high rate of recidivism. Interestingly, among 12 patients who underwent a liver biopsy in this study, 11 (91.7%) had underlying cirrhosis, and an additional 83 had evidence of cirrhosis based on imaging studies, for a total of 86.2%, consistent with prior reports of the high prevalence of cirrhosis in patients diagnosed with AH (33).

Recurrent alcoholic hepatitis

Recurrence of AH has been reported to account for 2.4–18% of diagnosed AH episodes (37,38). The recurrent episodes of AH followed short periods of recidivism with marked clinical and biochemical improvement during the intervening periods of abstinence. Recurrent episodes of AH have been reported to be more severe and protracted, as reflected by worse prognostic scores including DF (70.4 ± 27.9 versus 50.5 ± 10.9 , $p=0.014$) and MELD score (26.2 ± 3.7 versus 22.1 ± 1.5 , $p=0.008$) as well as having a higher prevalence of complications (38). When compared to other AH patients who had recidivism, those who developed recurrent AH had similar mortality (about 57%) but a higher number of hospital

admissions than expected. As mentioned, earlier, these findings indicate that recidivism itself rather than the presence or absence of recurrent AH is the more important predictor of poor outcomes in patients with AH.

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Synopsis

Alcoholic hepatitis is an acute form of alcoholic liver disease with variable severity. The disease develops in patients who usually have a history of prolonged and recent alcohol abuse. The diagnosis is clinical and depends on history, physical examination, and a number of laboratory derangements. Liver biopsy is diagnostic but not universally performed, and non-invasive diagnostic modalities are under development. A number of scoring systems are used to assess severity of disease, predict mortality and guide decisions for initiation of specific therapies. The natural history and long-term outcomes of alcoholic hepatitis including mortality, progression to cirrhosis and recurrence vary, and are, in part, dependent on abstinence from alcohol use.

Key Points

- The incidence of alcoholic hepatitis is variable and depends on the amount, duration and patterns of alcohol consumption; most patients diagnosed usually consume more than 100 grams of alcohol per day.
- Risk factors include age, female gender, ethnicity, obesity, malnutrition, coexistent hepatitis C virus infection, and genetic susceptibility.
- Diagnosis is based on the clinical presentation in a patient with a history of alcohol abuse.
- Common laboratory derangements include elevated AST to 2–6 times the upper limit of normal (usually less than 300 IU/L), the ALT level less than 200 IU/L with classical AST:ALT ratio > 2 , leukocytosis, hyperbilirubinemia, and prolonged prothrombin time.
- Several scoring models have been developed to assess disease severity and guide therapeutic decisions.

Box 1:**Alcoholic Hepatitis Signs and Symptoms**

Nausea/vomiting

Abdominal pain (right upper quadrant and/or midepigastic)

Fatigue

Weakness

Anorexia

Jaundice

Fever

Increased abdominal girth with ascites

Hepatic encephalopathy

Variceal bleeding

Tender hepatomegaly

Hepatic bruit

Stigmata of chronic liver disease:

- Spider angiomas
- Palmar erythema
- Gynecomastia
- Parotid enlargement
- Increased collateral vessels on anterior abdominal wall
- Dupuytren's contractures

Table 1:**Alcoholic Hepatitis Histological Score**

Component	Points
Stage of fibrosis	No fibrosis or portal fibrosis 0 Expansive fibrosis 0 Bridging fibrosis or cirrhosis +3
Degree of neutrophil infiltration	No or mild +2 Severe 0
Pattern of bilirubinostasis	No 0 Hepatocellular only 0 Canalicular/ductular +1 Hepatocellular plus canalicular/ductular +2
Mega-mitochondria	No +2 Yes 0
- Score is calculated by sum of all points - Alcoholic hepatitis severity: mild (0–3 points), intermediate (4–5 points), severe (6–9 points)	

Data from Altamirano J, Miquel R, Katoonizadeh A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology* 2014;146:1231–9.e1–6.