**INTRODUCTION**

Alcoholic Hepatitis (AH) is an acute clinical entity characterized by jaundice and coagulopathy occurring in individuals with a history of heavy alcohol use. It is associated with a high mortality rate, as treatment options available to date have been underwhelming. In this review we discuss AH with an emphasis on potential future treatment options.

**Epidemiology**

The true incidence and prevalence of AH is difficult to define, as is the amount and duration of alcohol use needed to cause AH. Most individuals present between the age of 40 and 50. Typically, they have a history of using more than 100g/day over a time period of two decades. AH is more prevalent in men given their higher tendency to abuse alcohol. Binge drinking also increases the risk of AH. In patients with severe AH, the short-term mortality can be as high as 45%.

**Pathophysiology**

Oxidative stress and increased gut permeability are two major mechanisms triggering hepatic inflammation leading to AH. By products of alcohol metabolism via the two major pathways lead to the formation of free radicals and increased oxidative stress. Alcohol is reduced to acetaldehyde and acetate by the enzymes alcohol dehydrogenase and acetaldehyde dehydrogenase, respectively. These enzymes convert NAD to NADH. An increased NADH/NAD ratio leads to the suppression of gluconeogenesis, increased fatty acid (FA) oxidation, and fatty infiltration. Alcohol increases the activity of cytochrome P-4502E1, which also produces free radicals. Decreased levels of glutathione make the liver even more prone to oxidative stress. The release of free radicals leads to the activation of inflammatory cytokines (TNF-α, IL-1 and IL-6), which in turn causes hepatic inflammation. Chronic alcohol use also leads to severe gut dysfunction due to intestinal bacterial overgrowth and the disruption of the tight junctions of the epithelial cells of the gut mucosa. These changes increase the permeability of the gut and cause a leakage of bacteria and endotoxins into the blood stream.

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Increased levels of bacterial lipopolysaccharides (LPS) cause an activation of inflammatory cytokines, eventually leading to hepatic necrosis and inflammation.\(^{16}\) (Table 1.)

**Clinical Presentation**
Symptoms of AH tend to be nonspecific and variable.\(^ {6}\) Elevated bilirubin is considered characteristic of AH.\(^ {17}\) Other findings include fever, right upper quadrant abdominal pain, anorexia, and abdominal distension due to ascites. Severe cases may present with hepatic encephalopathy. Renal failure due to hepatorenal syndrome (HRS) and bleeding due to coagulopathy can also be seen.\(^ {18,19}\) Features of chronic liver disease such as spider angiomata, gynecomastia, and proximal muscle wasting are common. Alcohol withdrawal causing tremors, seizures, delirium, and coma can complicate matters.

Lab abnormalities include elevated bilirubin, mild leukocytosis with neutrophilic predominance, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), anemia, thrombocytopenia, and elevated international normalized ratio (INR). AST/ALT levels are typically below 500 mg/dl with an AST/ALT ratio that is more than two being characteristic of AH. This is attributed to a deficiency of pyridoxal 5’-phosphate in alcoholics, which is required for the enzymatic activity of ALT.\(^ {17,21}\) Reversal of this ratio should lead to the workup for other etiologies of hepatitis.

**DIAGNOSIS**
The diagnosis of AH is a clinical one.\(^ {6}\) A medical history should be obtained in detail with an emphasis on the amount and duration of alcohol intake. Some patients may not have been drinking for a few weeks prior to presentation but may still have AH. This history, in conjunction with lab findings, helps to make the diagnosis. Other etiologies of acute hepatitis need to be ruled out if the clinical features and labs are inconsistent with AH. Although liver biopsy is not routinely indicated, it is recommended if there is a doubt about the diagnosis and an alternate diagnosis is suspected. Pathology shows ballooning hepatocytes,
Mallory-Denk bodies, severe fibrosis (usually micronodular, but sometimes mixed macro- and micronodular) starting from the central vein and extending into the portal triad, and neutrophilic infiltration.\footnote{20}

**Scoring Systems in AH**

Various scoring systems have been developed for AH in order to assist in determining the severity and prognosis, and to guide treatment. The Maddrey discriminant function (DF) score and model for end-stage liver disease (MELD) score are the most commonly utilized.\cite{14,23,24} Other less commonly used ones are the Glasgow alcoholic hepatitis score (GAHS), alcoholic hepatitis histology score (AHHS), and Lille score.

DF uses the prothrombin time (PT) and bilirubin levels with the equation to calculate the score being: \(4.6 \times \left[ \text{prothrombin time (sec)} - \text{control prothrombin time (sec)} \right] + (\text{serum bilirubin})\). Patients with a DF \(\geq 32\) have an almost 50% short term mortality (severe AH) and may benefit from glucocorticoid treatment.\cite{25} Individuals with a DF\(< 32\) will not benefit from steroids.

MELD score is typically used for prioritization of liver transplant and to predict mortality in cirrhotic patients, but it has also been used in predicting prognosis in AH. It takes the creatinine, total bilirubin, and INR into account. An increase in the MELD score of \(\geq 2\) points in the first week of hospitalization may independently predict mortality.\cite{22} MELD \(\geq 21\) has a 75% sensitivity and specificity in predicting 3 months mortality (20%).\cite{28}

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GAHS uses age, serum bilirubin, blood urea nitrogen, prothrombin time, and peripheral white blood cell count. This multivariable scoring system also predicts mortality in AH. Patients with a DF \(\geq 32\) and GAH score \(\geq 9\) had higher survival rates after receiving steroids.\cite{26}

AHHS score requires a liver biopsy, which as previously mentioned is not performed routinely for AH. It also predicts severity and 90-day mortality in AH. The stage of fibrosis, degree of neutrophilic infiltration, and type of bilirubinostasis are the major variables predicting severity and prognosis.\cite{27,28} A high stage of fibrosis and presence of bilirubinostasis favors a poor outcome. A higher degree of neutrophilic infiltration and the presence of megamitochondria represents an early stage of hepatocellular injury and represents a favorable prognosis.\cite{29,30,31}

The Lille score helps to identify the response to glucocorticoids. It uses the decrease in bilirubin after one week of glucocorticoid treatment as a marker of response. The score is calculated one week after steroid initiation. Scores of more than 0.45 predict a poor prognosis with 6-month survival rate of less than 25%.\cite{32} Glucocorticoids should be stopped in patients who are steroid non-responders (score \(\geq 0.56\)).

**Treatment**

Treatment of AH with steroids and pentoxifylline has been the mainstay for many years. The importance of nutritional support cannot be understated. It is also vital that the virtues of

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abstinence be stressed to patients. Resources such as alcoholics anonymous should be utilized. The feasibility of early transplant, even in those who are actively drinking, continues to be studied and is advocated by some. There are also many other novel treatments being looked at. While none are ready for widespread usage at this time, they do provide for some potentially exciting opportunities in the future.

**Nutrition**

Most patients with AH have nutritional deficiencies and protein calorie malnutrition.\(^{36}\) Randomized controlled trials have come to different conclusions in regards to the role and survival benefit of enteral nutrition, but poor nutritional status is associated with worse outcomes in AH. All patients should get a calorie count and should receive enough calorie supplementation to meet their needs. Protein intake does not need to be restricted.\(^{33}\) The enteral route is preferred since it maintains gut mucosal integrity, decrease the risk of bacterial translocation, and is cost-effective.\(^{34,35}\)

**Steroids**

Treatment with glucocorticoids is indicated in severe AH (DF\(\geq\)32) or hepatic encephalopathy.\(^{43,44,45}\) Glucocorticoids decrease the levels of TNF and IL8, ultimately decreasing inflammation.\(^{46,47}\) Prednisolone is the steroid of choice since it does not require conversion to any active metabolites in the liver,\(^{48}\) although it is contraindicated in renal failure, active gastrointestinal bleeding, uncontrolled hyperglycemia, acute pancreatitis, psychosis, and infection.\(^{49,50}\) Prednisolone 40 mg/day orally is given for four weeks, followed by a gradual taper over the next two weeks in patients who are steroid responders.\(^{25}\) Response to steroids is determined by the Lille score, calculated one week after the start of steroids.

**Pentoxifylline**

Pentoxifylline acts by inhibiting phosphodiesterase and decreasing the levels of TNF.\(^{37,38}\) It is known to decrease the incidence of HRS in AH.\(^{39,40,41}\) The studies and trials conducted to date, including the STOPAH study, have concluded that pentoxifylline has no impact on mortality in AH. It may be used as an alternative therapy in patients with severe AH in whom steroids are contraindicated or in patients with renal failure.\(^{52}\) It is not recommended in patients who are steroid non-responders. The combined use of pentoxifylline and steroids has not demonstrated a mortality benefit and is not recommended.\(^{42}\)

**Liver Transplant**

Liver transplant is considered in those with severe AH who have failed medical management. Studies have shown a significant long-term mortality benefit in patients who underwent liver transplantation. Six month and two-year survival were significantly higher in patients who received early liver transplant despite being active drinkers upon presentation.\(^{52}\) Most transplant centers require a minimum of six months of abstinence before considering liver transplant. Given that severe AH carries a high mortality, many patients do not survive long enough to meet this criterion. Although early liver transplant in AH has good outcomes, patient selection is very difficult. Alcohol relapse after transplantation is a challenge, and it is therefore no surprise that ethical and sociocultural factors play a big role. More studies are needed in order to create better criteria for transplant eligibility.

**Granulocyte Colony Stimulating Factor (G-CSF)**

G-CSF acts by mobilizing the hematopoietic stem cells that cause liver regeneration.\(^{53,54}\) It also increases the bactericidal activity of neutrophils.\(^{57,58}\) Studies have shown that G-CSF leads to the production of CD34\(^+\) stem cells and induces proliferation of hepatic progenitor cells which can lead to liver regeneration.\(^{55,56}\) This leads to decreased infections, improved DF score, and increased three month survival.\(^{59}\) The studies conducted so far have only compared GCSF with pentoxifylline or with normal controls not receiving any pharmacological treatment. None of the studies have compared outcomes with patients on steroids. The treatment may improve survival in patients who are steroid ineligible or steroid refractory, but this needs to be further researched.

**Extra Corporal Liver Support**

Various biologic and non-biologic liver support systems are being developed and studied in AH.
Extracorporeal cellular therapy (ELAD) is a biologic system that uses liver cells (C3Acells). These cells have anti-inflammatory and antioxidative properties that help regenerate the liver. Non-biologic liver support devices use the concepts of plasma exchange and albumin dialysis. Some examples of such devices are single pass albumin dialysis (SPAD), molecular adsorbent recirculating system (MARS), and fractionated plasma separation and adsorption (PROMETHEUS). MARS therapy has been shown to decrease serum bilirubin and serum creatinine. It also leads to clearance of hepatic encephalopathy. The favorable effects of albumin dialysis in patients with severe AH suggest that the procedure used alone or in combination with other pharmacological therapies may play a role in the future. However, prior to being used further it has to be proven to be effective in well-designed randomized controlled trials, especially in terms of improving both short- and long-term survival. The outcome of ELAD depends on the severity of AH and organ dysfunction. Patients with acute renal failure, severe coagulopathy, age >50 and MELD >28 have worse outcomes with ELAD. ELAD can work as a bridge therapy for liver transplant in younger patients who do not have renal failure or severe coagulopathy.

N Acetyl Cysteine (NAC)
N Acetyl cysteine acts by replenishing glutathione levels, which tend to be depleted in AH. NAC alone is not an effective treatment for AH. That being said, the combined use of NAC and steroids decreases the risk of infections and hepatorenal syndrome. Combination therapy also decreases short term mortality but has no long-term survival benefit. Further studies are needed before making the combination therapy of NAC and steroids a standard of care in AH.

Stool Transplant / Fecal Microbiota Transplant (FMT)
Studies looking at healthy donor fecal microbiota transplant (FMT) have shown improved survival at one year in steroid ineligible patients. In one trial, patients with severe alcoholic hepatitis were transplanted for seven continuous days with the goal of modulating patient gut bacteria. Microbiota analysis was subsequently performed, with similar profile found between donors and recipients at the one-year mark.

Immune Modulation
One potential therapy target is chemokines. These molecules, especially CCL20, play an important role in alcoholic hepatitis due to upregulation. Targeting this molecule, along with IL8, is being studied in order to see if a safe and effective therapy may be developed. Secukinamab is an anti IL-17a monoclonal antibody, currently used for rheumatoid arthritis, that may play a role in AH. IL-10, anti-osteoponin, and anti-TNF agents are also being looked at to see if they might be effective against AH. Osteoponin is an extracellular protein matrix that is highly expressed in alcoholic hepatitis and may be a good potential target for treatment as well.

Granulacytapheresis
This is a technique in which granulocytes and monocytes are removed from patient blood. It is well tolerated, may be beneficial in steroid non-responders, and is under further study in AH patients.

CONCLUSION
Alcoholic hepatitis is a relatively common condition that can have deadly consequences for patients, and is burdensome for society at large given the loss of productivity and costs that are associated with it. Fortunately, research continues to elucidate the pathophysiology of the disease and this may potentially lead to new breakthroughs in treatment. Novel treatments such as FMT deserve further study, as does early transplantation. Despite these advances, nutrition and abstinence are two relatively simple interventions that need to be the cornerstone of any treatment regimen going forward.

References
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31. Stewart RV, Dincsoy HP. The significance of giant mitochondria in liver biopsies as observed by light microscopy. Am J Clin Pathol. 1982;78:293–8


