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Review

Review

Alcoholic Hepatitis: A Review

Nooshin Hosseini[1], Julia Shor[1], and Gyongyi Szabo[2]

[1]University of Massachusetts, Gastroenterology, University of Massachusetts Medical School, and [2]Professor, Department of Medicine, University of Massachusetts, 364 Plantation Street, LRB-208, Worcester, MA, USA

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Abstract

Alcoholic liver disease (ALD) represents a spectrum of injury, ranging from simple steatosis to alcoholic hepatitis to cirrhosis. Regular alcohol use results in fatty changes in the liver which can develop into inflammation, fibrosis and ultimately cirrhosis with continued, excessive drinking. Alcoholic hepatitis (AH) is an acute hepatic inflammation associated with significant morbidity and mortality that can occur in patients with steatosis or underlying cirrhosis. The pathogenesis of ALD is multifactorial and in addition to genetic factors, alcohol-induced hepatocyte damage, reactive oxygen species, gut-derived microbial components result in steatosis and inflammatory cell (macrophage and neutrophil leukocyte) recruitment and activation in the liver. Continued alcohol and pro-inflammatory cytokines induce stellate cell activation and result in progressive fibrosis. Other than cessation of alcohol use, medical therapy of AH is limited to prednisolone in a subset of patients. Given the high mortality of AH and the progressive nature of ALD, there is a major need for new therapeutic intervention for this underserved patient population.

INTRODUCTION

Alcoholic liver disease (ALD) is the leading cause of alcohol related deaths worldwide. Alcohol contributes to progression of other etiologies of liver disease, and increases the risk of developing hepatocellular carcinoma (Safdar and Schiff, 2004). As an integral part of the fabric of American culture, alcohol consumption is widespread and cuts across socio-economic, regional, and racial lines. Approximately 7% of adult Americans meet DSM-IV criteria for the diagnosis of alcohol abuse or alcohol dependence (Grant *et al.*, 1992; Bowman, 2014; Samhsa, 2014; Agriculture, 2015).

Excessive alcohol consumption can cause a range of injury to the liver, from negligible to fatty infiltration, to cirrhosis over the course of several years (Lefkowitch, 2005). Sustained, excessive alcohol use can cause inflammatory changes in the liver, leading to more serious damage known as alcoholic steatohepatitis, or alcoholic hepatitis. A subset of these patients will eventually develop severe alcoholic hepatitis, which carries a much more dire short-term prognosis. Depending on the degree of inflammation and damage, these conditions may lead to fibrosis and eventually cirrhosis and liver failure (Teli *et al.*, 1995).

The majority of heavy drinkers do not ultimately develop advanced liver disease. This variability in outcomes suggests that various factors, both inheritable and environmental, can contribute to or determine individual patients' susceptibility to advanced liver disease.

PREVALENCE

Alcoholic hepatitis (AH) represents a significant public health burden. In 2007, approximately 56,000 patients were hospitalized with AH across the United States, with an average associated cost of $37,769 per hospitalization (Liangpunsakul, 2011). The mean age of those hospitalized was 53 years; nearly 75% of these patients were male.

The mortality rate associated with AH is staggering. Forty-four percent of all deaths from liver disease in 2003 were attributable to alcohol-induced disease (Yoon and Yi, 2006). One study conducted in Denmark from 1999-2008 found the 28 day mortality rate for patients with alcoholic hepatitis to be 14-24%, with 5 year mortality rate of 56% (Chedid, 1991; Sandahl *et al.*, 2011).

EPIDEMIOLOGY

Several factors have been linked to development of ALD and AH. Alcoholic hepatitis is generally thought to occur with excessive drinking that takes place over a period of at least 20 years, manifesting in the 4th to 5th decades of life (Bellentani *et al.*, 1997, Mezey *et al.*, 1988). Recent studies have shown an increased risk of AH and cirrhosis among individuals drinking more than 30-60 g/day (Becker *et al.*, 1996; Rehm *et al.*, 2010). Patients admitted to the

hospital with cirrhosis and alcoholic hepatitis report a history of drinking greater than 120 g on average per day (Lelbach, 1975; Mezey *et al.*, 1988).

While there is clear evidence that prolonged, heavy alcohol use is associated with ALD, only 35% of excessive drinkers eventually develop steatohepatitis and AH, and only 10% ultimately develop cirrhosis (Friedman, 2008). This suggests that other factors contribute to the overall risk (Liangpunsakul, 2011) (Table 1). These include the pattern of drinking, and type of alcohol consumed and genetic factors. Drinking outside of mealtimes, drinking spirits or beer, and binge drinking are associated with a higher risk of advanced ALD (Bellentani *et al.*, 1997; Wechsler and Austin, 1998; Barrio *et al.*, 2004; NIAAA NIoAAaA, 2004).

Gender also plays a notable role in ALD (Baraona *et al.*, 2001). Women's risk for developing severe ALD increases with daily intake of 20–40 g of alcohol, while the threshold for men appears to be 60–80 g (Mezey *et al.*, 1988; Rotily *et al.*, 1990; Bellentani *et al.*, 1997; Lu *et al.*, 2004). Various mechanisms have been proposed in the literature to explain this phenomenon, rooted in differences in alcohol metabolism due to variability in ADH activity, body fat distribution, liver volume, and influence of sex hormones on inflammatory response (Frezza *et al.*, 1990; Seitz *et al.*, 1993; Ikejima *et al.*, 1998; Colantoni *et al.*, 2000).

There are significant geographic differences in the incidence of ALD. Rates of ALD are higher in eastern Europe, southern Europe, and the United Kingdom (Klatskin, 1961; Popova *et al.*, 2007). The lowest rates of ALD are observed in countries with large Muslim populations. The consumption of alcohol in the United States falls in between (Rehm *et al.*, 2013). Ethnicity may be considered a risk. In the US, Hispanics and African Americans show an increased risk of developing ALD compared to whites, and higher mortality from ALD (Stinson *et al.*, 2001; Stewart, 2002).

Alcoholic hepatitis has a strong association with malnutrition (Mendenhall *et al.*, 1995). Protein-calorie malnutrition has been shown to correlate with severity and outcomes of AH, while high fat diets may have a protective effect (Mitchell and Herlong, 1986; Mishra *et al.*, 1989; Mendenhall *et al.*, 1995). Nutrient deficiencies have been implicated in the pathogenesis of severe ALD, including riboflavin, B12, vitamin A and zinc (Corrao *et al.*, 1998). Zinc has been identified as decreasing gut mucosal permeability by disrupting tight junctions, which may play a role in the pathogenesis of AH (Zhong *et al.*, 2010).

Obesity has also been identified as an independent risk factor for ALD, and is thought to potentiate severity of fatty liver disease in heavy alcohol intake (> 50 g/day) (Ekstedt *et al.*, 2009; Hart *et al.*, 2010; Liu *et al.*, 2010; Takahashi *et al.*, 2015; Sookoian and Pirola, 2016).

Other concomitant liver diseases may accelerate alcoholic liver disease, most significantly hepatitis C. Heavy alcohol consumption is believed to act synergistically with hepatitis C in the progression of advanced liver disease (Corrao and Arico, 1998; Hutchinson *et al.*, 2005). Furthermore, in alcoholic hepatitis, the presence of hepatitis C is an independent risk factor for higher mortality at 6 months (Punzalan *et al.*, 2015).

Another factor thought to play a role in ALD risk is hepatic iron and has been identified as a predictor of mortality in alcoholic cirrhosis. The significance and mechanism of iron overload in the development of ALD and AH has not been definitively shown, and remains an area of interest (LeSage *et al.*, 1983; Ganne-Carrie *et al.*, 2000; Gleeson *et al.*, 2006).

Table 1. Disease modifiers for alcoholic liver disease

Disease modifiers	
Alcohol intake	Genetics
Age	Obesity
Sex	Medications
Race	Drugs of abuse
Diet	Other liver diseases
Nutrition	Environmental exposure

GENETICS

Genetic factors affect the risk of ALD as evidenced by monozygotic twin studies (Hrubec and Omenn, 1981; Stickel and Hampe, 2012). Studies on polymorphisms for gene coding for alcohol metabolism, including alcohol dehydrogenase, acetaldehyde dehydrogenase and cytochrome P450 2E1, genes regulating the innate immune response (i.e. IL-1, TNF), and the PNPLA3 gene, showed that certain variants are associated with the risk of alcoholism, and possible association with alcoholic cirrhosis (Khoruts *et al.*, 1991; Menon *et al.*, 2001).

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE

The pathogenesis of alcoholic liver disease involves multiple factors including hepatocyte damage due to alcohol and its metabolites, cholestasis, recruitment and activation of innate immune cells by gut-derived pro-inflammatory danger signals, Kupffer cells, and recruited macrophages and neutrophils in the liver. The perpetual presence of these factors during chronic excessive alcohol use triggers ineffective anti-inflammatory pathways and results in activation of stellate cells and myofibroblasts in the liver leading to fibrosis and alcoholic cirrhosis (Arteel and Crabb, 2016; Louvet and Mathurin, 2015) (Fig. 1).

During alcohol consumption, alcohol is quickly absorbed in the GI tract resulting in increased blood alcohol concentrations. While most of the alcohol is metabolized in the liver in hepatocytes, alcohol also has substantial direct effects on the GI tract. Alcohol is metabolized in hepatocytes by alcohol dehydrogenase into acetaldehyde, a highly toxic compound with a short half-life, then further by acetaldehyde dehydrogenase into acetate. Both of these key enzymes have a low km and become saturated above the level of about 3-4 drinks of alcohol and higher alcohol concentrations trigger alternate mechanisms for alcohol metabolism that include the Cytochrome

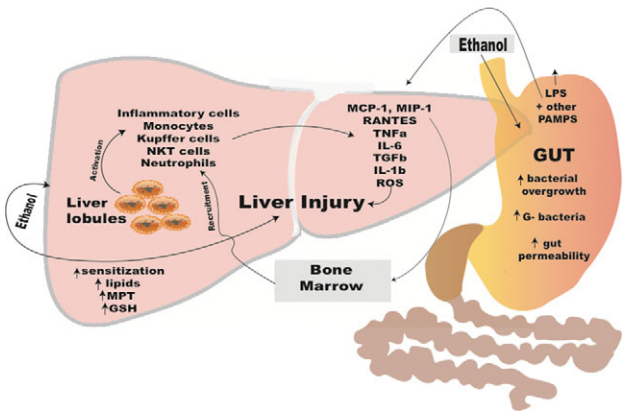

Fig. 1. Pathomechanisms of alcohol-induced liver injury involving the gut-liver access.

P4502E1 system. Upon repeated high doses of alcohol, CYP2E1 is upregulated resulting in accelerated metabolism. This process produces high levels of reactive oxygen species (ROS) in hepatocytes leading to reduced levels of intracellular antioxidants such as s-adenosine methionine (SAME) and glutathione (GSH) (Gao and Bataller, 2011).

Acute binge drinking and chronic excessive alcohol consumption result in liver steatosis that is characterized by accumulation of fat in hepatocytes. Mechanistic studies revealed that key transcription factors such as hypoxia-inducible factor 1 (HIF-1) and regulators of fatty acid metabolism are affected by alcohol in hepatocytes that lead to steatosis (Nath *et al.*, 2011). These include inhibition of PPARα, and upregulation of ADRP (adpocyte differentiation-related protein, also known as perilipin-2), a protein that stabilizes lipid droplets in hepatocytes (Nath *et al.*, 2011). Recent studies also revealed that alcohol results in damage and activation of apoptotic pathways in hepatocytes. Alcohol-induced endoplasmic reticulum (ER) stress activates (Stimulator of Interferon Genes) leading to phosphorylation of IRF3 (Interferon Regulatory Factor 3) that interacts with and activates the mitochondrial apoptotic pathways (Petrasek *et al.*, 2013). Damaged hepatocytes release damage-associated molecular patterns (DAMPs) that are recognized by immune cells in the liver as 'danger' signals leading to a pro-inflammatory response. Some of these danger signals include uric acid and ATP; inhibition of these pathways in animal models of alcoholic liver disease ameliorated liver damage, steatosis and inflammation (Iracheta-Vellve *et al.*, 2015).

A unique and major factor in the pathomechanism of ALD is related to its effects on the GI tract. Numerous studies have demonstrated that alcohol results in a 'leaky gut' via disrupting the tight junctions of the epithelial barrier permitting translocation of microbial components from the intestine to the portal circulation and the liver (Szabo and Bala, 2010). Alcohol use also affects the composition of the gut microbiome which is a contributing factor to ALD. Studies demonstrated that gut 'decontamination' with antibiotics significantly attenuates alcohol-related liver inflammation, steatosis and liver damage (Louvet and Mathurin, 2015). Lipopolysaccharide, a component of the outer wall of gram negative bacteria, is increased in the portal and systemic circulation after acute binge and chronic alcohol use in mice and humans (Szabo and Bala, 2010). LPS is recognized by the Toll-like receptor 4 complex expressed on immune cells and parenchymal cells in the liver and results in upregulation of the inflammatory cascade (Petrasek *et al.*, 2010). In animal models of alcoholic liver disease, gut decontamination with antibiotics or elimination of liver Kupffer cells and macrophages attenuated alcoholic liver disease (Louvet and Mathurin, 2015).

While fat accumulation in hepatocytes characterizes early alcoholic liver disease, activation of the liver resident macrophages, Kupffer cells, is associated with chronic alcoholic liver disease. In addition, there is recruitment of circulating and bone marrow-derived inflammatory cells (monocytes, macrophages and neutrophil leukocytes) into the liver that produce pro-inflammatory cytokines (TNFα, IL-1ß, IL-6, MCP1) (Petrasek *et al.*, 2010; Szabo *et al.*, 2012). The presence of neutrophil leukocytes is a histological hallmark of acute alcoholic hepatitis, correlating with clinical outcomes (Szabo *et al.*, 2012). In acute alcoholic hepatitis, highly elevated circulating levels of pro-inflammatory cytokines, TNFα and IL-1ß, correlate with disease severity and survival (Szabo *et al.*, 2012). Increased peripheral blood neutrophilia represents a diagnostic challenge in alcoholic hepatitis because it can be the result of disease-related inflammation in the absence of microbial infection.

Presence of inflammatory cells in the liver sinusoids results in activation of stellate cells characterized by loss of retinoic acid and induction of fibrogenic genes such as alpha-1 smooth muscle actin and collagen-1 production (Louvet and Mathurin, 2015). Activated stellate cells proliferate and produce collagen that contributes to liver fibrosis. Persistent and prolonged activation of hepatic stellate cells and myofibroblasts leads to progressive deposition of collagen, liver fibrosis and in advanced form, bridging fibrosis and cirrhosis.

Research in human, animal models and in vitro systems discovered many important aspects of the pathogenesis of alcoholic hepatitis, yet some critical questions remain unanswered. Why some and not all heavy drinkers develop ALD? What is the trigger for the most severe clinical form of alcoholic liver disease, acute alcoholic hepatitis? Why does alcoholic hepatitis progress even after cessation of alcohol use in most patients?

DIAGNOSIS

Diagnosis of alcoholic hepatitis poses a challenge as it is largely a diagnosis of exclusion. It is made via a combination of clinical suspicion, clinical presentation, laboratory, imaging, and biopsy data. Patients with alcoholic hepatitis frequently present with a combination of typical symptoms including jaundice, abdominal pain, fullness or distention, fever, GI bleeding, or changes in mental status. A recent consensus report defined clinical criteria for the diagnosis of alcoholic hepatitis (Crabb *et al.*, 2016).

PHYSICAL EXAM

Exam findings in alcoholic hepatitis frequently include hepatomegaly, jaundice and fever. Presence of stigmata of chronic liver disease suggests underlying cirrhosis (Lischner *et al.*, 1971; Mendenhall, 1981). Another possible finding in AH is abdominal bruit, which is thought to be caused by increased blood flow in the hepatic artery, however there is conflicting sensitivity and specificity reported in the literature (Sherman and Hardison, 1979; Han *et al.*, 2002).

LABORATORY FINDINGS

Initial laboratory workup for suspected alcoholic liver disease includes CBC, INR, LFTs, GGT, carbohydrate deficient transferrin, and serologies for viral hepatitis. AST and ALT are typically less than 300 iu/L and rarely over 500. The AST is typically higher than the ALT, and 70% of patients have an AST-ALT ratio of greater than 1.5 (Bell *et al.*, 1994; Sorbi *et al.*, 1999; Nyblom *et al.*, 2004). Lab abnormalities in AH may also include an elevated bilirubin, typically greater than 5 mg/dL, with a median of 13, elevated INR and GGT, and low albumin and prealbumin (Poynard *et al.*, 1984; Louvet *et al.*, 2008). Other common hematologic findings include anemia, macrocytosis, leucopenia, lymphocytopenia, and thrombocytopenia (Bell *et al.*, 1994; Mundle *et al.*, 2000; Mathurin *et al.*, 2002; Nguyen-Khac *et al.*, 2011). Recently described biomarkers for chronic alcohol use can aid the diagnosis of AH (Anton and Moak, 1994; Berlakovich *et al.*, 2004; Hock et al., 2005; Hietala et al., 2006; Niemela, 2007; Madhubala *et al.*, 2013).

IMAGING

Abdominal imaging studies, including ultrasound, CT and MRI, may be a useful tool for diagnosing ALD. Imaging findings in patients with AH include hepatomegaly, fatty changes in the liver, evidence of underlying cirrhosis, or ascites (Piekarski *et al.*, 1980; Saverymuttu *et al.*, 1986; Borra *et al.*, 2009). Doppler flow studies of the hepatic artery can be useful as well, and may reveal an elevated peak systolic velocity, or an increase in vessel diameter (Han *et al.*, 2002).

BIOPSY

Diagnosis based on clinical criteria alone carries a 10-50% risk of misclassification of alcoholic hepatitis (Kryger *et al.*, 1983; Mookerjee *et al.*, 2011). EASL Practical Guidelines on Alcoholic Liver Disease recommends the use of liver biopsy in patients with suspected severe alcoholic hepatitis (Mookerjee *et al.*, 2011). Biopsy is recommended in patients with a clinical picture of AH and any of the following factors: 1. Hypotension/massive bleeding on admission, 2. Sepsis at admission, 3. Suspicion of malignant liver disease based on clinical and/or imaging criteria, 4. Uncertain assessment of alcohol drinking history, 5. Cocaine use in the preceding 3 months, 6. Recent use of a potential hepatotoxic substance (Mundle *et al.*, 2000). Consensus of US experts recommends liver biopsies in all patients where the clinical diagnosis of ALD or AH is uncertain.

HISTOLOGY

Histologic findings can vary based on stage of the disease. Typical features include steatosis, confluent parenchymal necrosis, intrasinusoidal and pericentral collagen, ballooning degeneration, lobular inflammation affecting perivenular regions (in the earliest stages), Mallory bodies (amorphous eosinophilic inclusion bodies) surrounded by neutrophils, foamy degeneration of hepatocytes and cholestasis (Edmondson *et al.*, 1967; MacSween and Burt, 1986; Lefkowitch, 2005) (**Suppl. Table 1**).

Findings of alcoholic liver disease, including perivenular and pericellular fibrosis, which often coexist with AH, may portend future cirrhosis, especially in patients who are co-infected with hepatitis C or continue to drink (Worner and Lieber, 1985; Hall, 1994).

Megamitochondria may be present in milder forms of AH and is associated with a lower incidence of cirrhosis, fewer complications and good long-term survival prospects (Chedid *et al.*, 1986). Increased severity of inflammation (i.e. degree of PMN infiltration and cholestatic changes) is associated with a poor prognosis. Degree of inflammation can also predict response to steroid treatment (Marbet *et al.*, 1987; Nissenbaum *et al.*, 1990; Mathurin *et al.*, 1996) (**Suppl. Table 2**).

COMPLICATIONS

The short-term mortality associated with AH is significant – 30-50% at 3 months. Patients with severe AH can develop encephalopathy, and may require airway protection. One of the most serious complications is acute kidney injury, often can be attributed to hepatorenal syndrome, which is associated with a very poor prognosis. Early volume expansion with albumin or crystalloid should be a priority in patients with creatinine elevated above baseline (Altamirano *et al.*, 2012).

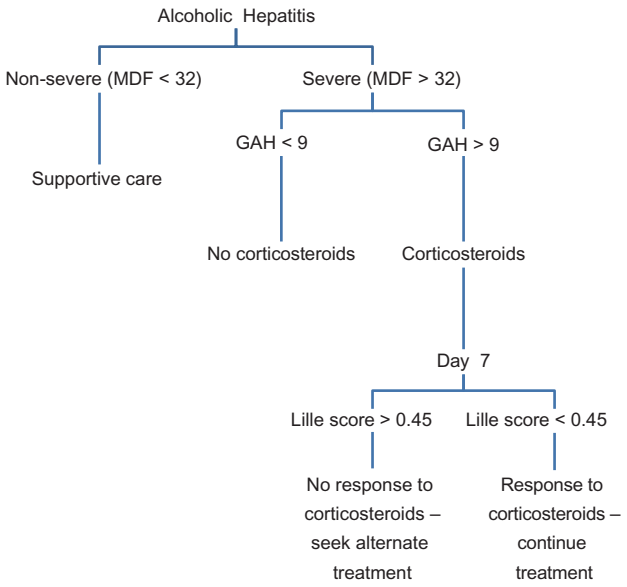

Fig. 2. Treatment algorithm for corticosteroids in alcoholic hepatitis using Maddrey, GAH, and Lille scores.

Infections are also very common. All patients should be screened for infection, particularly when considering therapy with corticosteroids. SBP should be ruled out in all patients with ascites.

A significant number of patients with severe alcoholic hepatitis fail to recover despite treatment and abstinence from alcohol. If recovery has not been reached by 3 months despite the above measures, then the chances of spontaneous recovery are low, and may lead to death. AH can also progress to cirrhosis.

While not necessarily a direct consequence of AH, given that patients with AH likely have underlying ALD, it is important to recognize the increased potential for developing hepatocellular carcinoma (HCC). ALD significantly increases the risk of HCC. The risk for HCC is 3.6 times higher in those with any level of alcohol consumption, as compared to those who abstain from alcohol consumption entirely (Ascha *et al.*, 2010). Among patients with alcoholic cirrhosis, 1–2% develop HCC (Seitz and Stickel, 2007). Furthermore, excess alcohol use may act synergistically with hepatitis C infection, hepatitis B, or obesity to accelerate progression towards HCC (Zakhari, 2013).

MODELS FOR DISEASE SEVERITY, TREATMENT GUIDANCE AND PREDICTION OF SURVIVAL

Decisions regarding treatment of alcoholic hepatitis are contingent upon the patient's prognosis. A number of scoring models for alcoholic hepatitis (discussed below) have been developed to assess severity of disease, predict mortality, and guide treatment (Fig. 2).

The oldest are the Child-Turcotte-Pugh (CTP) and MELD (now sodium-MELD). A Sodium-MELD score of 21 implies a 90 day mortality probability of 20%, and has been used as a threshold for starting corticosteroids in AH (Kamath *et al.*, 2001; Farnsworth *et al.*, 2004). While both scores are used for assessing gravity of disease and mortality, they are less beneficial in guiding prognosis and treatment in AH (**Suppl. Table 2**) (Fig. 3).

Two scores have been approved to define severity of the disease and to determine when coritocosteroid therapy is recommended –

Maddrey Discriminant Function

Laboratory Values Involved
1. Serum total bilirubin
2. Prothrombin time
3. Control prothrombin time

DF = (4.6 x [prothrombin time (sec) -control prothrombin time (sec)]) + (serum bilirubin)

	Non-severe Disease	Severe Disease
MDF score	< 32	> 32
Short-term mortality	10 %	30–60%
Corticosteroids?	No	Yes

Fig. 3. Maddrey Discriminant Function (MDF). Scores are used to predict mortality and for guiding treatment with coritcosteroids.

Model for End-stage Liver Disease (MELD)

Laboratory Values Involved
1. Serum total bilirubin
2. Serum creatinine
3. INR for prothrombin time

MELD = (0.957 x log(creatinine) + 0.378 x log(bilirubin) +1.12 x log(INR) +0.643) x 10

MELD Score and Mortality Risk	
Score	**3 Month Mortality Risk**
22	10%
29	30%
33	50%
38	80%

Fig. 4. Model for End-stage liver disease (MELD) scoring system.

the Maddrey Discriminant Function score (MDF) and the Glasgow Alcoholic Hepatitis Score (GAHS).

The Maddrey Discriminant Function score is the most widely used scoring system for AH. It functions as a guide for treatment, predictor of severity of disease, and as a predictor of individual mortality. The calculation incorporates both serum bilirubin and PT at time of diagnosis. Disease is classified as severe (DF > 32) and non-severe (DF < 32). Short-term mortality for a DF < 32 is predicted at 10%, and 30-60% for DF > 32. As such, patients who fall within the 'severe' category are most likely to benefit from treatment (see Treatment section below) (Maddrey *et al.*, 1978). This scoring system is the most widely used in determining whether or not to start corticosteroid treatment (Fig. 4).

The Glasgow Alcoholic Hepatitis Score was developed for use as a more accurate predictor of overall outcomes than the MDF. Given the potential contraindications to corticosteroid therapy, GAHS helps select patients with severe alcoholic hepatitis who would most benefit from treatment. The score is a function of age, leukocyte count, serum urea, bilirubin, and PT. A score above 9 is associated with a poor prognosis. Patients with both MDF > 32 and a GAHS > 9 treated with corticosteroids showed improvements in both 28 day and 84 day survival. Conversely, patients with a MDF < 32 and a GAHS of < 9 treated with corticosteroids had no survival benefit (Forrest *et al.*, 2005) (**Suppl. Table 4**).

The ABIC score predicts the 3-month mortality of patients with AH, but is not widely used to predict severity of disease or for starting corticosteroids. It is calculated using age, bilirubin, INR and creatinine. The ABIC score further stratifies the severity of alcoholic hepatitis into low (< 6.71), intermediate (6.71-8.99), and high (> 9.0) classes. These classes correspond to a 90-day mortality of 0%, 30%, and 75%, respectively (Dominguez *et al.*, 2008) (**Suppl. Table 3**).

In addition to assessing severity of patients with AH, the Lille score is used to assess response of patients to steroid treatment. The calculation uses age, albumin, PT, and bilirubin on day 0 of treatment. It also takes into account the presence or absence of renal insufficiency and the change in bilirubin at day 7 of treatment. A score of < 0.45 is associated with a 15% mortality at 6 months, while a score of 0.45 or greater predicts a 75% mortality. After corticosteroids are initiated, a score of 0.45 or greater on day 7 indicates a lack of response to treatment (Louvet *et al.*, 2007). There is also data to suggest that the Lille score at day 4 can be also predictive of response to treatment. Initial scoring systems were dependent upon factors on the day of presentation. However, as evidenced by the Lille score, early improvement in liver function impacts short-term mortality, and thus repeated testing and calculation of scores may be useful during hospitalization (**Suppl. Table 5**).

Recently, new scoring systems that incorporate histologic information have been developed. The Alcoholic Hepatitis Histologic Score (AHHS) incorporates 4 pathologic findings from biopsy specimens that are independently associated with survival. These include the stage of fibrosis, neutrophil infiltration, evidence of cholestasis, and presence of megamitochrondria. Patients are then stratified into categories of mortality within 90 days (Altamirano *et al.*, 2014).

Per EASL 2018 guidelines, of the above scoring models, only two are approved to define the severity of AH and thus to establish when steroids should be initiated – the MDF and GAHS scores. Along the same lines, strict rules for cessation of therapy should be applied, by identifying early non-response to corticosteroid treatment, by using the Lille score (European Association for the Study of the Liver, 2018).

TREATMENT

The standard of care for patients with alcoholic liver disease and alcoholic hepatitis has not changed in the last several decades, yet mortality of patients with alcoholic hepatitis remains high. This demonstrates a major gap in development of new therapies and highlights the lack of attention to the alcoholic hepatitis patient population.

TREATMENT OF ALCOHOLIC LIVER DISEASE AND MODERATE ALCOHOLIC HEPATITIS

Patients with high risk and/or excessive alcohol use should be consulted to stop alcohol use. Alcohol cessation is difficult or unachievable for most patients due to addiction (Lazo and Mitchell, 2016). In the absence of full alcohol cessation, reduction of alcohol use not to exceed 2 drinks in men and 1 drink in women per day could be an acceptable initial intervention. Treating alcohol addiction is most effective with psychiatric help or participation in formal withdrawal programs. Medical interventions for alcohol addiction should also be considered.

There is no specific treatment for alcoholic liver disease at this time. Patients should be advised that continued alcohol use confers high risk of developing alcoholic hepatitis. In patients with decades or longer of excessive alcohol use, the likelihood of alcoholic liver

fibrosis and cirrhosis increases and cirrhosis may develop even after cessation of alcohol use. Women should be advised about the greater probability of developing ALD and cirrhosis at shorter duration and doses of alcohol use compared to men even after stopping alcohol use (Lazo and Mitchell, 2016).

Previous studies showed no or limited benefit of antioxidants or PTU. Given the massive activation of pro-inflammatory cytokines in severe alcoholic hepatitis, anti-TNF therapies were used in experimental settings however showed no early benefit. All of the studies involving TNFα or TNF receptor blockade had to be discontinued due to the increased rate of infections (Petrasek and Szabo, 2016). This is not unexpected as chronic excessive alcohol users are immunocompromised and have poor anti-bacterial and anti-viral host defense mechanisms. Small studies found that administration of SAME as antioxidant had some benefits. In patients with severe alcoholic hepatitis, administration of N-acetyl-cystamine (NAC) also provided benefit. Administration of a probiotic, lactobacillus GG, or zinc were shown to improve gut permeability in animal models and patients with alcoholic liver disease.

Moderate alcoholic hepatitis is clinically defined as elevated AST, AST/ALT ratio greater than 1.5, increased bilirubin and MELD < 19 in the setting of recent excessive alcohol use and no other etiologies of liver disease (Crabb *et al.*, 2016). As of 2018, there is no specific treatment for moderate alcoholic hepatitis. Some providers use pentoxifylline for 28 days but there are studies in patients with moderate and severe alcoholic hepatitis that show limited benefit to support this practice. The most effective therapy associated with improvement of alcoholic hepatitis is alcohol cessation.

TREATMENT OF SEVERE ALCOHOLIC HEPATITIS

Severe alcoholic hepatitis is defined as Maddrey discriminant factor > 32 and/or MELD > 20 (Crabb *et al.*, 2016). These patients are typically hospitalized and often require intensive care due to their risk for sepsis-like clinical presentation, cardiovascular instability, infection, all complicated by alcohol withdrawal in most acute presentations. The clinical syndrome of acute alcoholic hepatitis is characterized by a sepsis-like presentation due to sterile inflammation and cytokine 'storm' in the absence of a clear source of infection. The diagnostic challenge is that the low grade fever, tachycardia, and hypotension may also be heralding infection in these patients. Development of multi-organ involvement, most frequently hepatorenal syndrome and ARDS requiring mechanical ventilation, is associated with poor clinical outcome. Standard of care in the US in patients with acute alcoholic hepatitis (MDF > 32) is prednisolone 40 g for 28 days, shown to improve 6 month mortality (Petrasek and Szabo, 2016). Several studies have evaluated pentoxifylline alone in severe alcoholic hepatitis however results were controversial (Petrasek and Szabo, 2016). Co-administration of prednisolone and pentoxifylline failed to provide added benefit over steroids alone, with the exception of reduction in hepatorenal syndrome (Thursz *et al.*, 2015).

Patients with acute severe alcoholic hepatitis are managed by active supportive therapy. Intake of at least 3,000 daily calories is associated with improved survival (Petrasek and Szabo, 2016). If steroids were started, evaluation of the Lille score on day 7 has good prognostic value (Louvet *et al.*, 2007).

In addition to the limited benefit of steroid therapy, it carries increased risk of infections and its use is limited to a narrow patient population. In patients with hepatic encephalopathy, recent acute GI bleeding and established or suspected infection, steroids should be avoided. There is a major need for new and effective therapy in alcoholic hepatitis, and several recent clinical trials are ongoing in the United States and other countries to develop new therapies. Some of the new interventions aim to inhibit inflammation by administration of a recombinant IL-1 receptor antagonist, IL-22 to improve gut barrier function and liver immunity, or use an orally administered FXR agonist that affects bile acid metabolism, gut permeability and presumably inflammation (Szabo, 2017).

Finally, the rapid deterioration of patients with chronic alcoholic hepatitis prompted some liver transplant centers to consider liver transplantation as a last resource (Mathurin *et al.*, 2011). A recent study from Europe demonstrated a high success rate in patients who received liver transplantation (Mathurin *et al.*, 2011). Both graft and recipient survival were average or better than in liver transplantation for other indications and alcohol recurrence was avoided in most patients with close postoperative management (Mathurin *et al.*, 2011).

TREATMENT OF ALCOHOL ADDICTION

The most challenging aspect regarding care of patients with alcoholic hepatitis is alcohol addiction that results in craving and often, relapse. The care of patients before and after hospital discharge should include plans for mitigating alcohol addiction that may include different strategies such as behavioral treatments and/or voluntary admission to an alcohol withdrawal program, participation in Alcohol Anonymous (AA) and/or pharmaceutical drugs to reduce physical symptoms of addiction and alcohol craving. The drugs Acomprosate and Naltrexone are approved for the treatment of Alcohol Use Disorder (AUD) and are most usually used although have limited effects (Miller *et al.*, 2011). The safety and efficacy of most of these drugs have been established in addicted individuals who had no concurrent diagnosis of alcoholic liver disease or alcoholic hepatitis. The use of Acomprosate is safe in patients with existing liver disease however, Naltrexone has potential liver toxicity in patients with existing liver disease. There are other emerging drugs not approved in all countries like Topiramate, Ondasentron, Gabapentin, Varenicline and Baclofen. These drugs are NOT approved for AUD in the USA (although baclofen is now approved in France only for AUD), but their use could be considered as an off-label treatment in a case-by-case scenario. Furthermore, baclofen is the only medication formally tested in patients with advanced liver disease, as shown by a few clinical trials (Addolorato *et al.*, 2007; Morley *et al.*, 2018). Of special interest for this review, a retrospective study conducted at UCLA indicated the safety and utility of baclofen in AUD patients with alcoholic hepatitis when the total bilirubin level approaches 10 mg/dl (Yamini *et al.*, 2014).

There are several cognitive-behavioral (CBT) therapy options for substance abuse disorders, including alcohol addiction that should be considered in patients with alcoholic liver disease and alcoholic hepatitis (McHugh *et al.*; and NIAAA website). These can be used alone or combined with pharmacologic treatments. Brief interventions that involve 1-4 short counseling sessions with a trained interventionist can help to reduce alcohol use (NIAAA website). Motivational interviewing (MI) is an approached that is based on assessing ambivalence toward behavior change in alcohol use. MI is usually offered in an individual format. Motivational enhancement therapy (MET) helps individuals to resolve their ambivalence about engaging the treatment for their alcohol use disorder (NIAAA website). MET can be successful in alcohol addicted people to improve their engagement in treatment and reduces their problem drinking (Principles of Drug Addiction Treatment, 2019a, Principles of Drug Addiction Treatment, 2019b; Alcohol Alert, 2005; McHugh *et al.*, 2010).

CONCLUDING REMARKS

Research in human, animal models and in vitro systems discovered many important aspects of the pathogenesis of alcoholic hepatitis, yet some critical questions remain unanswered. The standard of care for patients with alcoholic liver disease and alcoholic hepatitis has not changed in the last several decades, yet mortality of patients with alcoholic hepatitis remains high (15-50%). This demonstrates a major gap in development of new therapies and highlights the lack of attention to alcoholic hepatitis. The primary means for therapy for patients with alcoholic hepatitis involves corticosteroids, and is limited to a narrow patient population, and has limited benefit and a high side effect profile. More recent therapies aim to inhibit inflammation by targeting cytokine mediated pathways, and by improving gut barrier function. Finally, the rapid deterioration of patients with alcoholic hepatitis has prompted some centers to consider transplantation as a last resort, which remains controversial. It is clear that given the grim outcome and excessive costs associated with alcoholic hepatitis despite major advances in medical therapies over the past several decades, however, there is a wide gap between our understanding of alcoholic hepatitis and treatment, and a glaring need for new therapeutic advancements in this area.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *Alcohol And Alcoholism* online

CONFLICT OF INTEREST STATEMENT

Dr. Szabo consults for and received grants from Allergan. She consults for Terra Firma, Glympse Bio, Quest, Arrow, GLG, Salix, and Tobira. She received grants from Gilead, Genfit, Intercept, Verlyx, Novartis, SignaBlok, and Shire. She holds intellectual property rights with Up to Date. The co-authors declare no conflict of interest.

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