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REVIEW

Emerging concepts in alcoholic hepatitis

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Abstract

Severe alcoholic hepatitis is implicated as a costly, worldwide public health issue with high morbidity and mortality. The one-month survival for severe alcoholic hepatitis is low with mortality rates high as 30%-50%. Abstinence from alcohol is the recommended first-line treatment. Although corticosteroids remain as the current evidence based option for selected patients with discriminant function > 32, improvement of short-term survival rate may be the only benefit. Identification of individuals with risk factors for the development of severe alcoholic hepatitis may provide insight to the diverse clinical spectrum and prognosis of the disease. The understanding of the complex pathophysiologic processes of alcoholic hepatitis is the key to elucidating new therapeutic treatments. Newer research describes the use of gut microbiota modification, immune modulation, stimulation of liver regeneration, caspase inhibitors, farnesoid X receptors, and the extracorporeal liver assist device to aid in hepatocellular recovery. Liver transplantation can be considered as the last medical option for patients failing conventional medical interventions. Although the preliminary data is promising in patients with low risk of recividism, controversy remains due to organ scarcity. This review article comprehensively summarizes the epidemiology, pathophysiology, risk factors, and prognostic indicators of severe alcoholic hepatitis with a focus on the current and emerging therapeutics.

Key words: Immune modulation; Alcoholic hepatitis; Gut microbiota modification; Extracorporeal liver assist device; Apoptosis inhibitors

Core tip: Current research of alcoholic hepatitis pathophysiology *via* translational research has provided insight to novel therapeutic options. Recovery from severe alcoholic hepatitis with assistance of gut microbiota modification, immune modulators, stimulation of liver regeneration, caspase inhibitors, farnesoid X receptors, and extracorporeal liver assist device may be promising.

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INTRODUCTION

Alcoholic hepatitis (AH), is one of the most severe manifestations of alcoholic liver disease. It is a public health issue and worldwide disease associated with high morbidity and mortality. Complications related to alcoholic liver disease result in costly hospitalizations. Current treatment strategies are limited. Abstinence is the first line treatment, however may not improve outcomes in patients with severe AH, defined as discriminant function > 32. The mainstay of therapy is corticosteroids, which have limited efficacy in specific populations. Pursuit of new treatment options for alcoholic hepatitis is the holy grail for patients ineligible or refractory to corticosteroids. The judicious use of early liver transplantation for severe alcoholic hepatitis has been explored although medical and ethical controversy remains. Exploration of maximal medical management with microbiota modification, immune modulation, liver regenerative factors, farnesoid X receptors (FXRs), caspase inhibitors, and extracorporeal liver assist device (ELAD) may be promising for patients with severe alcoholic hepatitis who do not have other options.

Sixty percent of the United States' population reports alcohol consumption[1]. Approximately 8%-10% of the United States population reports heavy alcohol use, which is defined as $\geqslant$ 2 drinks daily in men and $\geqslant$ 1 drink daily in women[2]. One standard drink contains approximately 14 g of alcohol, which is equivalent to 12 ounces (350 mL) of beer (4%-5% wt/vol), 6 ounces (177 mL) of wine (8%-10% wt/vol), and 2 ounces (59 mL) of hard liquor or whiskey (45% wt/vol)[1]. There are progressive and co-existing stages of disease in chronic alcoholism including steatosis, steatohepatitis, fibrosis, and development of compensated to decompensated cirrhosis. In a study examining hospitalized heavy alcohol drinkers with and without alcohol withdrawal, liver biopsies reveal steatosis in 44.9%, alcoholic hepatitis in 34.4%, liver cirrhosis with superimposed alcoholic hepatitis in 10.2%, and cirrhosis only in 10.5%[3]. In other studies, approximately 20% of individuals with chronic alcohol abuse are found to have AH when biopsied[4].

Alcoholic hepatitis is an acute-on-chronic presentation of liver disease with a wide ranging spectrum of mild to florid, life-threatening injury[5]. It is a clinical syndrome associated with recent onset jaundice and coagulopathy in a person who has been a heavy drinker usually for more than a decade[6]. Although long standing alcohol abuse appears to be associated with the development of AH, the exact trigger for development is unclear. Other factors, such environmental and genetic variables may play a pivotal role. The amount and duration of alcohol abuse needed to produce alcoholic hepatitis is variable depending on the individual patient. Alcohol consumption of approximately 40 g daily for women and 50-60 g daily for men is recognized as a minimal threshold amount for patients at high risk of developing AH. Alcohol consumption is usually within less than 60 d prior to onset of jaundice with heavy alcohol use for more than 6 mo for severe alcoholic hepatitis clinical trial inclusion criterias[7].

It has been reported that chronic alcohol abuse and binge drinking are associated with development of liver disease[8,9]. Binge drinking is defined as five or more drinks in men and four or more drinks in women within a period of approximately 2 h at least once a week[10]. Earlier studies implied that weekly binge drinking may be more deleterious than daily consumption of alcohol[2]. More recent studies suggest daily heavy drinkers had increased mortality from liver disease compared to binge drinkers[11]. It has been reported that the combination of chronic alcohol use with a binge drinking pattern may be more detrimental as animal studies showed mice with chronic ethanol fed diet with an addition of single high dose ethanol administration expressed more severe forms of liver injury and steatosis compared to animals with chronic ethanol feeding alone or single high dose of ethanol only[12]. Further studies are needed to delineate the pathophysiology of binge drinking and its' effects on alcoholic hepatitis.

The true incidence of alcoholic hepatitis is unknown. Based on Denmark studies from 1999-2008, the annual incidence rate of alcoholic hepatitis was 46 per 1000000 in men and 34 per 1000000 in women[13]. In the United States, alcoholic hepatitis accounted for 325000 admissions annually in 2010 with average hospitalization cost of $46264. The most common admitting diagnosis for patient hospitalized with AH was hepatic encephalopathy[14].

PATHOPHYSIOLOGY

The pathogenesis of liver disease related to alcohol consumption is not completely elucidated. Most studies simulating alcoholic hepatitis are recreated in animal models using an alcohol and fat infusion method[15]. The etiology of alcoholic hepatitis is complex and multifactorial. Principal factors include steatosis, oxidative stress, altered gut permeability, toxic metabolites, and formation of cytokines result in the initiation of an inflammatory cascade.

Ethanol is oxidized by three metabolic pathways: (1) alcohol dehydrogenase mainly; (2) cytochrome P450 2E1; and (3) catalase (Figure 1) Ten percent of ethanol oxidation occurs in the microsomal cytochrome P450 CYP2E1. Ethanol catalase driven reaction in the liver peroxisome is negligible[16].

Ethanol is metabolized into acetaldehyde *via* the cytosolic alcohol dehydrogenase enzyme within hepatocytes. Acetaldehyde is converted into acetate and reduced nicotinamide adenine dinucleotide (NADH) *via* mitochondrial and cytosolic aldehyde dehydrogenase[17]. NADH is increased as a byproduct of ethanol metabolism.

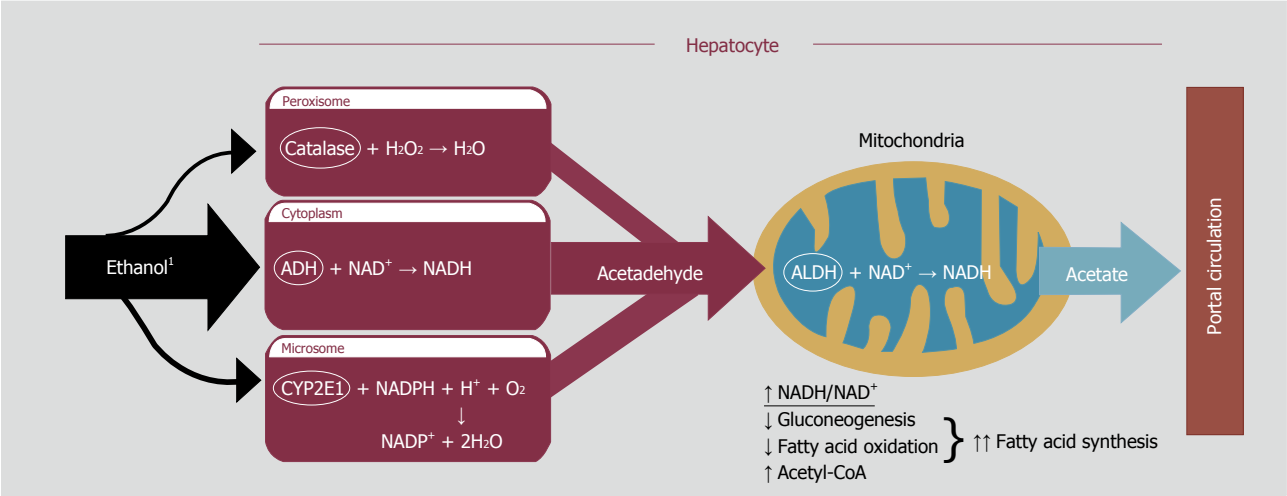

Figure 1 Ethanol metabolism in the hepatocyte. [1]Ethanol inhibits the peroxisome-proliferator-activated receptor α and adenosine monophosphate activated protein kinase with stimulation of sterol regulatory element binding protein 1, a membrane bound transcript factor to promote lipogenesis. ADH: Alcohol dehydrogenase; ALDH: Aldehyde dehydrogenase; NADH: Nicotinamide adenine dinucleotide.

Elevated NADH/NAD$^+$ levels inhibit gluconeogenesis and fatty acid oxidation and is responsible for the high amounts of acetyl-coA found in heavy alcohol users[18]. Acetyl-coA induces fatty acid synthesis by serving as a precursor for fatty acid and cholesterol biosynthesis[19]. In addition, ethanol inhibits the peroxisome-proliferator-activated receptor α and adenosine monophosphate activated protein kinase with stimulation of sterol regulatory element binding protein 1, a membrane bound transcription factor to promote lipogenesis[20-22].

Acetaldehyde is direct hepatotoxin and a known carcinogen[23]. Acetaldehyde form adducts that are potent immunogens to activate inflammatory cytokines[24,25]. The production of reactive oxygen species inducing lipid peroxidation with additional cytotoxic effects of ethanol metabolism induce hepatocyte necrosis[26]. Damage-associated molecular patterns are produced after cell necrosis, which trigger inflammation, fibrosis, and abnormal hepatocyte regeneration[27]. After chronic ethanol consumption, the activity of the microsomal ethanol-oxidizing system increases by 5-10 fold, with an associated rise in cytochrome P-450, CYP2E1. CYP2E1 metabolism increases reactive oxygen species and acetaldehyde production, which diminishes hepatoprotective reduced glutathione and other defense systems leaving hepatocytes to be more vulnerable to oxidative stress[28,29].

The endoplasmic reticulum (ER) regulates protein folding, maturation, misfolded protein degradation, and regulation of new protein entry[30]. When proteins are misfolded in the ER, the unfolded protein response is sensed by the binding immunoglobulin protein/glucose regulated protein 78 (GRP 78). This reaction produces oxidative stress and disassociation of the endoreticulum transmembrane transducers. The transducers are responsible for the activation and recruitment of c-Jun N-terminal (JNK), a stress kinase[31]. Multiple mechanisms, including downstream inflammation and increased oxidative ER stress from hyperhomocysteinemia activates nuclear factor kappa beta (NFKB) and JNK to induce hepatocyte apoptosis *via* caspase activation[32,33]. Deficiencies of B vitamins or homocysteine metabolism mutations seen in chronic ethanol use cause accumulation of homocysteine, which induces the ER stress of the hepatocytes and vascular endothelial cells. In addition, ER stress is associated with fatty acid synthesis *via* the activation of SREBPs (sterol regulatory element-binding proteins), which enhance cholesterol and triglyceride biosynthesis and fibrosis *via* stellate cell activation[34,35].

Ethanol induces gut dysbiosis and alters the permeability[36]. Increased gut permeability allows the endotoxins to infiltrate the liver through the portal vein[37] (Figure 2). Endotoxin levels are measured to be high in patients suffering from alcoholic hepatitis[38]. Bacterial lipopolysaccharide, an endotoxin, binds to the lipopolysaccharide binding protein to form a complex. The complex latches to the CD-14 molecule to activate Kupffer cells and macrophages *via* the toll-like receptor type 4 (TLR-4)[39]. This reaction stimulates mitogen-activated protein kinases [such as extracellular signal-regulated kinase (ERK-1/ERK-2), JNK and p38], NFKB, and activator protein 1 (AP-1). Reactive oxygen species produced by Kupffer cells cause the recruitment of adhesion molecules [intracellular adhesion molecule 1 and vascular adhesion protein 1, chemokines (IL-8 and C-C motif chemokine ligand 2), and inflammatory cytokines (tumor necrosis factor-α, IL-1 and IL-6)[40]. The enhanced inflammatory T-helper-type 1 (TH1) response to alcohol dehydrogenase in alcoholic hepatitis induces additional neutrophil recruitment[41,42]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase is an additional contributor to ROS[6]. Pro-inflammatory cytokine, IL-17 induces the migration of neutrophils into the hepatocytes and stimulates the hepatic stellate cells to produce IL-8 and chemokine CXC motif ligand 1 (CXCL1), which recruit other chemokines to attract other

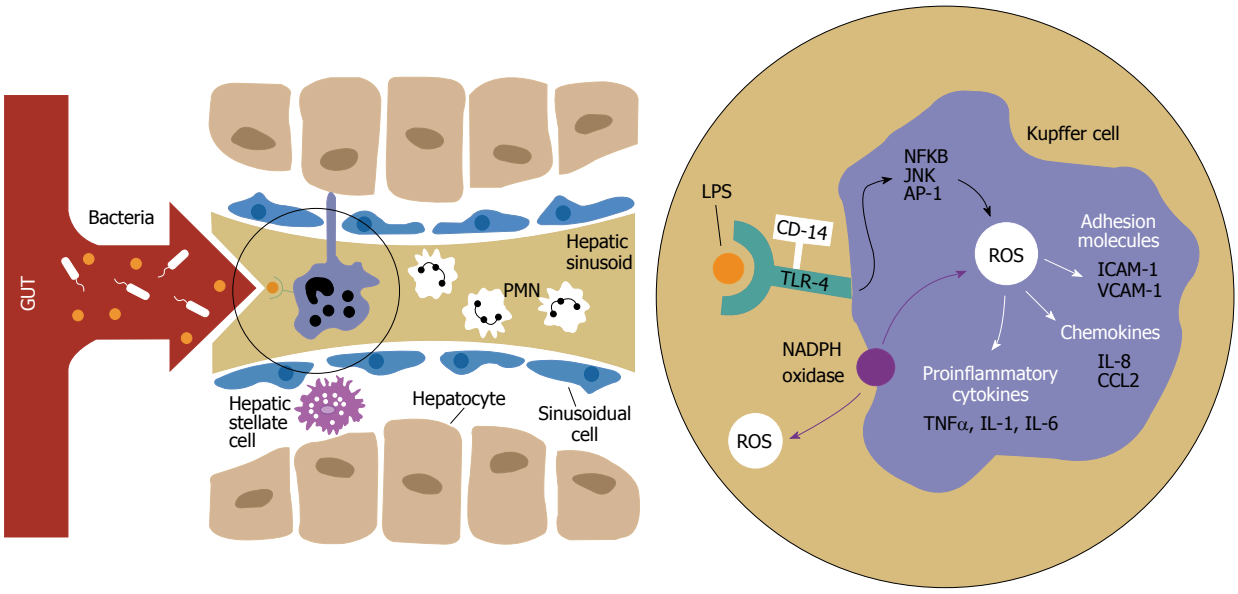

Figure 2 Acetaldehyde induced gut permeability with endotoxemia and inflammatory cascade. LPS: Lipopolysaccharide; TLR-4: Toll-like receptor type 4; ROS: Reactive oxygen species; NADPH: Nicotinamide adenine dinucleotide phosphate-oxidase; NFKB: Nuclear factor kappa beta; JNK: c-Jun N-terminal kinase; AP-1: Activator protein 1; ICAM-1: Intracellular adhesion molecule 1; VCAM-1: Vascular adhesion protein 1; IL-8: Interleukin 8; CCL 2: C-C motif ligand; TNFα: Tumor necrosis factor alpha; IL-1: Interleukin 1; IL-6: Interleukin 6.

neutrophils[43]. IL-22 is stimulated by increased levels of IL-6 and TNF-α. Although IL-22 is produced by TH17, TH22 and natural killer cells, it's receptor is mainly found in hepatocytes. It has a hepatoprotective effect against liver injury and secreted in parallel, to counteract the effects of IL-17[12].

Peripheral neutrophilia is a characteristic finding in alcoholic hepatitis[44]. Normally, neutrophils are recruited to aid in tissue repair and recovery[45]. The innate immunity is impaired in patients with progressive liver dysfunction, contributing to multi-organ failure seen in patients with severe alcoholic hepatitis. Serum analysis of acute alcoholic hepatitis patients compared to patients with alcoholic cirrhosis and healthy controls show a significant reduction in antibacterial innate and adaptive immune responses. An impaired T cell response from AH patients produces fewer interferon gamma when exposed to lipopolysaccharide with impaired neutrophil phagocytosis and defective monocyte oxidative burst when stimulated by bacterial challenge. Defective monocyte oxidative burst reduces the expression of NADPH oxidase, which is responsible for generation of superoxide radicals required for bacterial killing. Higher rates of infection in AH may be explained by this impairment[46]. The T cells of AH patients exhibits increased numbers of PD ligand 1 (PD1), T-cell immunoglobulin and mucin domain 3 (TIM3), and galectin-9, which are ligands responsible for programmed cell death functioning. The blockade of the PD1 and TIM3 can restored the innate and adaptive immunity by increasing T cell and neutrophil antimicrobial activity[47].

Other aldehydes produced along with acetaldehyde contribute to progressive hepatic fibrosis by inducing collagen synthesis. Collagen production activates transforming growth factor β dependent, platelet-derived growth factor, and independent profibrotic pathways to active hepatic stellate cells, which contribute to portal hypertension[48].

RISK FACTORS

Studies have identified risk factors towards the development and progression of liver disease. Patterns of drinking, gender, genetic predisposition, and concomitant liver disease may increase the risk of susceptibility. Simultaneous alcohol consumption with food intake has been published to lower risk of alcoholic liver disease compared to those consuming alcohol alone[9]. Variant genes encoding for alcohol metabolism, such as alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome CYP2E1 might facilitate hepatotoxicity by increasing alcohol tolerance *via* delay of acetaldehyde formation or the metabolism of alcohol through other non-oxidative toxic pathways[49,50]. Acetaldehyde dehydrogenase gene polymorphisms may cause varying levels of alcohol sensitivity in Asians and women, who can develop alcoholic liver disease even if they do not consume alcohol as heavily as others. Women are twice as likely to develop hepatotoxicity with lower amounts and shorter duration of alcohol use compared to men, which may be attributable to gastric alcohol differences and higher proportion of body fat in women in addition to differences in dehydrogenase levels[51-53]. CYP2E1 gene polymorphisms can affect the metabolism of alcohol amongst those with different ethnic backgrounds and alcoholics, however the exact pathogenesis is yet to be eludicated[54].

Variations in patatin-like phospholipase protein 3 (PNPLA3) has a strong association with cirrhosis develop-

ment in Caucasian and Mexican patients with alcoholism[55]. Patients with G allele of PNPLA3 have a higher risk of steatosis and fibrosis, as well as a significantly higher prevalence of alcoholic cirrhosis compared to those with C allele[56]. Recent data published from a genome wide association study found that severe alcoholic hepatitis risk is associated with PNPLA3 rs738409 variant, which until recently has been associated with cirrhosis development. Identification of SLC38A4 variant gene is another novel independent risk locus for severe AH[57].

Caffeine consumption may have a protective effect against development of AH. Recent studies by Chalasani *et al*[58] found the risk of AH was 27% with heavy alcohol users with PNPLA3 genotype CC with regular coffee consumption compared to 86% in heavy drinkers with PNPLA3 genotype GG, who did not consume coffee. PNPLA3 CC genotype subjects who were not regular coffee consumers had a 48% risk of AH. The risk of AH with PNPLA3 GC with and without regular coffee drinking was 37% and 62%, respectively. The risk of AH was 57% in patients with PNPLA3 GG gene who were regular coffee drinkers[58].

Underlying obesity with body mass index (BMI) $\geqslant$ 30 likely potentiates the severity of alcoholic hepatitis. A common pathway is postulated for the generation of steatohepatitis through synergetic or additive effects of heavy alcohol use combined with obesity, although the exact mechanism is not well defined[59]. Diehl *et al*[59] published a paper documenting a supra-additive interaction between obesity and heavy alcohol consumption. One unit of alcohol was equivalent to 8 g. Overweight or obese male subjects who consumed 15 or more alcohol units per week had an increased risk of liver related morbidity and mortality compared to controls. Another United Kingdom study examining 107, 742 women found that subjects with high BMI ($\geqslant$ 25 kg/m^2) who drank $\leqslant$ 15 units of alcohol have an equivalent risk of chronic liver disease development compared to women with low BMI (< 25) who drank $\geqslant$ 15 units per week. Women with BMI $\geqslant$ 25 who drank $\geqslant$ 15 units of alcohol weekly had the poorest outcomes. Even in overweight women who did not drink alcohol, the risk of negative outcomes were present[60].

Alcoholics with other liver co-morbidities, such as hepatitis B, hepatitis C, and hemochromatosis have greater disease severity and likelihood to develop cirrhosis[61,62]. Underlying chronic liver disease may contribute to the development of acute-on-chronic presentation in AH.

HEPATITIS B AND C WITH ALCOHOLIC LIVER DISEASE

The prevalence of hepatitis C patients with alcoholism is approximately 16% compared to the 1.5%-2% prevalence in the general population[63,64]. Patients with concomitant hepatitis C and alcoholism have 2- to 8-fold increase risk of all-cause mortality compared to patients without hepatitis C[65]. Alcohol abuse reduces survival in patients with hepatitis C, especially in women[66]. Hepatitis C viral load was significantly increased within 4 mo when patients had higher amounts of alcohol consumption of 39-100 g/d compared to 0-50 g/d[67]. Alcohol induced liver fibrosis in patients with hepatitis C is dose-dependent and exhibited patients who ingest 30-40 g daily[68]. Mechanisms of the synergistic hepatotoxic effects of chronic alcohol abuse in patients with hepatitis C include altered cell-mediated immunity, increased oxidative stress, increase viral replication, hepatic steatosis, and inflammatory response from iron accumulation[62].

Studies on viral hepatitis and chronic heavy alcohol use are mostly in patients with hepatitis C. Mechanisms of pathogenesis can also be applied to hepatitis B patients. Hepatitis B or C drinkers have an increase risk of hepatocellular carcinoma compared to non-drinkers[69,70]. Alcohol use did not effect viral efficacy in hepatitis B patients treated with entacavir or hepatitis C patients treated with interferon, however alcoholics may be less compliant with medication adherence[71,72]. Elevation of liver enzymes induced by alcohol can cause overtreatment of patients with chronic hepatitis B. It has been published that only 50% of patients with aminotransferase elevation was caused by immune active chronic hepatitis B among other etiologies[73]. Iron deposition is found in > 50% patients with chronic hepatitis C or heavy alcohol consumption, which is not typically seen in hepatitis B[74].

HEMOCHROMATOSIS WITH ALCOHOLIC LIVER DISEASE

Hepcidin is a peptide produced in the liver for delivery of iron through the ferroportin transporter. When hepcidin levels are decreased in patients with progressive liver disease, iron is accumulated in the hepatocytes[75]. Concomitant iron accumulation and ethanol toxicity may be associated with increased production of oxidative stress. Patients with hemochromatosis who consumed more than 60 g of alcohol per day were 9 times more to develop cirrhosis than who consumed less[76]. Elevated hepatic iron concentration is associated with higher mortality in alcoholic cirrhosis patients[77]. Iron accumulation seen in alcoholic liver disease and hepatitis C is independent risk factor for hepatocellular carcinoma development[76]. Fifty percent of patients with hereditary hemochromatosis develop fibrosis with a 200-fold risk of hepatocellular carcinoma development[78].

NASH AND ALCOHOLIC LIVER DISEASE

Patients with risk factors for non-alcoholic steatohepatitis (NASH) are identified with insulin resistance, obesity, hyperlipidemia, and metabolic syndrome in the setting of minimal alcohol use compared to alcoholic liver disease patients[79]. Differentiating between alcoholic and NASH can be challenging as imaging, laboratory studies, and histologic findings can be non-diagnostic. Attaining a careful alcohol consumption history is cardinal, but can

be unreliable. Histologically, patients with NASH tend to have more advanced fatty degenerative hepatocytes, while there is generally a greater neutrophillic predominance and frequency of Mallory Denk bodies in hepatocytes with alcoholic liver disease. Mallory-Denk bodies are misfolded protein aggregates induced from ER stress, which are deposited into ubiquitin-rich cytoplasmic inclusions within ballooned hepatocytes[80,81]. Mallory-Denk bodies can be present in chronic cholestasis, Wilson's disease, NASH, and amiodarone toxicity. They are not exclusively seen in alcoholic hepatitis[82]. Patients with alcoholic liver disease tend to higher rates of perivenular fibrosis, phlebosclerosis, cholestasis, and ductal proliferation compared to NASH patients[83]. Using logistic regression, Dunn *et al*[84] identified mean corpuscular volume, AST/ALT ratio, body mass index, and gender as the key variables to differentiating alcoholic liver disease from NASH patients of Caucasian ancestry. The alcoholic liver disease/nonalcoholic fatty liver disease index (ANI) created was found to have good diagnostic capacity compared other previous proposed biomarkers. ANI > 0 was consistent with an alcoholic liver disease diagnosis, while an ANI < 0 was likely due to nonalcoholic fatty liver disease. ANI is not as reliable in cirrhotic patients with Model of End-stage Liver Disease (MELD) score > 20, as well in patients with concomitant alcoholic and NASH disease[84]. A 20-year observational study of patients with uncomplicated hepatic steatosis concluded that 1.2% of non-alcoholic fatty liver disease patients developed cirrhosis compared to 22% of alcoholic fatty liver disease patients[85].

CLINICAL PRESENTATION

Symptoms of alcoholic hepatitis are nonspecific. Patients can experience fatigue, right upper quadrant abdominal pain, anorexia, fever, and weight loss. Development of jaundice may occur in a rapid fashion. Patients with alcoholic hepatitis can develop tender hepatomegaly, ascites, hepatic encephalopathy, upper gastrointestinal bleed, and sarcopenia. Signs of chronic alcohol abuse such as spider angiomata, splenomegaly, palmar erythema, gynecomastia, parotid gland enlargement, testicular atrophy, and Dupuytren's contractures may be present. Characteristic laboratory studies demonstrate a 2:1 aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio with typical values less than 300-400 mg/dL. Serum ALT levels are typically lower than AST in alcoholic hepatitis due to a reduced ALT activity in vitamin B6 depleted hepatocytes and mitochondrial injury causing release of mitochondrial AST[86]. Higher levels of aminotransferases may point towards an additional factor inducing hepatotoxicity (*e.g.*, superimposed ischemic hepatitis, drug induced liver injury, rhabdomyolysis, or acute viral hepatitis). Bilirubin levels can be as high as 30 mg/dL with severe coagulopathy, leukocytosis, anemia, and new onset of renal failure is seen in patients with hepatorenal syndrome[40,87]. Severe alcohol withdrawal can be a life-threatening when patients develop delirium tremens, seizures, coma, and cardiac arrest. Treatment with hemodynamic stabilization, airway protection, and benzodiazepines are necessary[88]. There is a higher prevalence of patients having alcohol withdrawal in alcoholic hepatitis compared to alcoholic cirrhosis[3]. Multiple electrolytic disturbances have been identified in patients with alcoholic hepatitis, such as hypokalemia, hypophosphatemia, and hypomagnesaemia among others. Supplementation with thiamine, folic acid, and correction of glucose, potassium, magnesium, and phosphate is recommended[23].

DIAGNOSIS

Alcoholic hepatitis is mainly a clinical diagnosis. If there is confirmed abstinence for more than 2 mo or the patient reports less than 4 drinks daily on average, alcoholic hepatitis is less likely. Liver biopsy is considered to a gold standard for diagnosis of alcoholic hepatitis, however they are not considered to be routinely performed for AH evaluation in United States. In a review of 11 randomized controlled trials requiring biopsy proven AH, 1409 of 1668 (84.5%) of the liver biopsies confirmed histologic alcoholic hepatitis with increased diagnostic accuracy of 96% when total bilirubin was > 80 μmol/L (> 4.7 mg/dL). The authors concluded that a histologic diagnosis was not necessary for diagnosis and management of AH based on these parameters[89]. Nevertheless, if clinical diagnosis is not clear or appears multifactorial, a liver biopsy can be considered. Caution must be executed when there is severe portal hypertension and coagulopathy. If the benefits outweigh the risks, a transjugular approach can determine the wedge hepatic venous gradient and portal pressures and is recommended when a patient has severe coagulopathy or ascites[90]. Other causes of liver disease, including decompensated alcoholic cirrhosis, sepsis, and biliary obstruction must be ruled out. Abdominal imaging usually shows steatosis and/or cirrhosis with splenomegaly, which is non-specific in alcoholic hepatitis[91].

Cardinal histologic findings of alcoholic hepatitis include ballooning hepatocytes, Mallory-Denk bodies, and neutrophilic infiltration in the setting of macrovesicular steatosis with fibrosis and lobular distortion[92].

MORTALITY PREDICTORS/PROGNOSIS

Clinical scoring systems have been developed to predict outcomes in patients with alcoholic hepatitis and guide treatment. Maddrey's discriminant function, Glasgow score, and MELD score help determine if corticosteroids need to be initiated, while the Lille score evaluates if they need to be continued.

The Maddrey's score incorporates the serum bilirubin and prothrombin time to produce a discriminant function score (DF). A DF > 32 is characterized as severe alcoholic hepatitis and has high short-term mortality of

approximately 50%. Patients with a DF > 32 may benefit from corticosteroid therapy. A DF < 32 is classified as mild or moderate in severity with mortality rate of 10%. Corticosteroid treatment is not beneficial in this patient group[93].

The MELD score predicts mortality in alcoholic hepatitis and survival in cirrhotic patients. MELD score performs as well as the DF in 30-d mortality prediction. Corticosteroid therapy reduces short term mortality in patients with MELD score of > 11 or bilirubin > 8 mg/dL with ascites[94]. A retrospective study determined that an increase in MELD ⩾ 2 within the first week of hospitalization is independently associated with in-hospital mortality[95]. A study by Dunn *et al*[96] found that a MELD ⩾ 21 has a 75% sensitivity and specificity to predict mortality with an estimated 90-d mortality of 20% for patients with this score. A MELD ⩾ 21 can be applied to treatment guidelines for corticosteroid administration.

The Lille score monitors the change in total bilirubin after the first week of corticosteroids to identify the response of patients with severe alcoholic hepatitis. Patients with Lille score > 0.45 indicates poor response to corticosteroids and predicts a 6-mo survival of < 25%. Non-responders are recommended to stop corticosteroids due the risk of infection[97]. Recently, a study showed that Lille score on day 4 was as good as day 7 to predict 90-d mortality and reduces unnecessary steroid exposure[98]. A meta-analysis of five randomized clinical trials with prednisolone treated subjects with severe alcoholic hepatitis showed an improved survival benefit when sub-classified based on Lille score. Complete responders (Lille score ⩽ 0.16), partial responders (Lille score 0.16-0.56), and null responders (Lille score ⩾ 0.56) has 28-d survival rates of 91%, 79% and 53%, respectively. Corticosteroids had a significant effect on 28-d survival in subjects with Lille score ⩽ 0.56[99]. Side effects of steroids include infections, hypokalemia, osteopenia, and weight gain. Fungal infections, especially Aspergillosis are common in the steroid treated group[100].

Another prognostic score is the Glascow alcoholic hepatitis score (GAHS), which incorporates age, serum bilirubin, blood urea nitrogen, prothrombin time, and peripheral white blood cell count. Patients with a DF ⩾ 32 and a GAHS < 9 did not show benefit from treatment with corticosteroids. For those patients with a GAHS ⩾ 9, there was a significant improvement in survival for patients who received corticosteroids. Day 28 survival was 78% for those treated with corticosteroids compared to 52% for the placebo group[101].

Altamirano and his group published the Alcoholic Hepatitis Histologic Score system in order to predict the 90-d mortality. The degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria were independently associated with 90-d mortality. The factors identified patients with a low (0-3 points), moderate (4-5 points), or high (6-9 points) mortality within 90 d (3%, 19% and 51%, respectively). The disadvantage of this scoring system is that it requires a liver biopsy, which is not routinely performed in the majority of alcoholic hepatitis patients[102].

Factors associated with increased mortality from alcoholic hepatitis include: Older age, acute kidney injury, elevated bilirubin level, coagulopathy, leukocytosis, alcohol consumption > 120 g/d, infection, hepatic encephalopathy, upper gastrointestinal bleed, and bilirubin to gamma glutamyl transferase ratio > 1[103-106].

Metabolomic profiling

Metabolomic profiling is recently constructed to identify biochemical markers in liver-related disease[107]. In a study by Rachakonda *et al*[108], metabolomic profiles were able to differentiate alcoholic cirrhotics *vs* severe alcoholic hepatitis patients with 100% accuracy. The features related to the pathogenesis of alcoholic hepatitis were confirmed by several findings in this study. Severe alcoholic hepatitis was associated with enhanced triglyceride lipolysis, impaired mitochondrial fatty acid beta oxidation, upregulation of omega oxidation, and decreased plasma membrane remodeling. Although there was an increase in measured bile acids found in severe alcoholic hepatitis, intestinal dysbiosis was suggested due to low deoxycholate and glycodeoxycholate levels. Other changes seen in severe alcoholic hepatitis include increased glucose consumption by the pentose phosphate pathway, altered tricarboxylic acid cycle activity, and enhanced peptide catabolism. Altered levels of small molecules related to glutathione metabolism and antioxidant vitamin depletion were observed[108]. Another study performed by Rachakonda *et al*[109] showed that patients with severe alcoholic hepatitis were found to have higher levels of serum resistin and plasma activation inhibitor-1 levels with decreased serum leptin levels. Levels of inflammatory cytokines, such as tumor necrosis factor α, IL-6, IL-8, and IL-15 were higher in patients with severe alcoholic hepatitis. IL-6 levels of ⩾ 38.66 pg/mL were found to have significantly decreased mean survival rates[109].

BIOMARKERS

The development of biomarkers sensitive to the detection of alcoholic hepatitis can be helpful for prognostication. Selected-ion flow tube mass spectrometry breathe testing was able to identify increased levels of acetaldehyde, trimethylamine, acetone, and pentane in patients with alcoholic hepatitis with underlying cirrhosis compared to those with liver cirrhosis and acute decompensation from etiologies other than alcohol. These biomarkers represent breakdown products of ethanol metabolism in alcoholic hepatitis. Given the small sample size, larger studies will need to be performed for validation of results[110].

Other markers, such as procalcitonin, lipopolysaccharide, liver progenitor cell proliferation, soluble TNF receptor 1, microRNA profiling, and IL-22 serum

levels are being studied for clinical application towards prognostication of alcoholic hepatitis[104,111-115].

ABSTINENCE AND MEDICATIONS TO PREVENT RECIDIVISM

The most important primary intervention for alcoholic hepatitis management is abstinence counseling[116]. Abstinence can improve survival in patients with alcoholic liver disease by improving histologic features of hepatocyte injury with reduction of portal hypertension and progression into cirrhosis[5]. Two thirds of patients abstaining from alcohol have significant improvement within 90 d[117]. A 30% decrease in survival rate is seen in patients with compensated cirrhosis who continue to use alcohol compared to those who are abstinent[118,119]. Continued interventions, such as combination psychotherapy with cognitive behavioral therapy, peer driven support counseling, motivational enhancement therapy, and comprehensive medical care can reduce recividism[120]. Risk of recidivism is as high as 67% to 81% over the course of one year[121].

Medications to maintain abstinence have been investigated. FDA approved medications are disulfiram, naltrexone, and acamprosate[122]. Disulfiram was first approved in 1983[123]. Other agents have been explored due to poor tolerability and lack of evidence to support its efficacy[124]. Disulfram is not recommended for use in cirrhotic patients as the literature describes cases of fulminant hepatitis requiring liver transplant[125]. Naltrexone is an opioid antagonist used to decrease alcohol cravings, however it can cause hepatocellular injury[126]. Nalmefene works in a similar mechanism of action to naltrexone, but does not have the risk of hepatocellular injury and has a longer half-life[127]. Acamprosate is structurally similar to gamma amino butyric acid and is associated with reducing alcohol withdrawal symptoms based on 15 controlled trials. As a maintenance medication, it can decrease the relapse rate and relapse severity compared to placebo[128]. In a recent randomized, double-blind study in the United States, there was no evidence of efficacy for acamprosate compared to placebo among alcohol-dependent individuals recruited from a primary care setting[129]. These patients did not receive extensive multidisciplinary counseling. In the COMBINE trial, there was no substantial benefit for patients treated with acamprosate *vs* naltrexone or intensive abstinence counseling. The PREDICT study is a randomized clinical trial conducted in Germany, which compared its data to the COMBINE study. The primary outcome examined the first occurrence of heavy drinking. PREDICT found neither acamprosate nor naltrexone to supply any additional benefit compared with placebo[130].

There are few medication options to prevent recidivism in advanced chronic liver disease. Baclofen is γ aminobutyric acid B-receptor antagonist, which is minimally metabolized in the liver. It is one of the few treatments studied in cirrhotic patients. Addolorato *et al*[131] performed a randomized double-blinded placebo-controlled in alcoholic-dependent cirrhotics with baclofen 10 mg three times daily for 12 wk in the treatment arm. Seventy-one percent of maintained abstinence compared to 29% in the placebo group. Baclofen may be beneficial to achieving and maintaining abstinence safely in Child-Pugh class A, B and C cirrhotic patients[131]. Gamma hydroxyl butyrate may be well tolerated in patients with decompensated cirrhosis with alcohol withdrawal symptoms due to the short half-life of 4-6 h. Further studies need to be performed before recommendations on efficacy and safety can be made[132]. None of the medications discussed have been studied in the context of alcoholic hepatitis and remains a challenge to medical practitioners.

TREATMENT

Nutritional supplementation

Patients with alcoholic hepatitis and cirrhosis have nutritional deficiencies and sarcopenia. Protein calorie malnutrition is associated with short and long term mortality[133]. Vitamin A, Vitamin D, thiamine, pyroxidine, folate, and zinc are common vitamin deficiencies seen in alcoholics[134]. Early studies from the Veterans' Association found 100% of the 363 alcoholic hepatitis patients had protein calorie malnutrition[135]. The degree of malnutrition is associated with the severity of liver disease. AASLD and EASL guidelines recommend enteral nutritional therapy in AH patients, however the evidence remains controversial[2,136]. Moreno *et al*[137] randomized 136 biopsy confirmed severe alcoholic hepatitis patients to receive either intensive enteral nutrition *via* feeding tube plus methylprednisolone or conventional nutrition plus methylprednisolone for 14 d. There is no significant difference in the six-month survival between the groups with 44.4% deaths in the intensive enteral nutrition arm and 53.1% of the controls. The study results were likely affected by being underpowered. The mortality rate at one and six months are lower in the intensive enteral nutrition group compared to the control, but the results are not statistically significant. Of note, 48.5% of the patients had the enteral tube discontinued prematurely. Five patients had serious adverse events related to enteral nutrition, such as aspiration pneumonia, hyperglycemia, and hepatic encephalopathy exacerbation. Nevertheless, this study implies that patients receiving < 21.5 kcal/kg per day have a significantly lower survival rate with increased risk of infection and hepatorenal syndrome at 6 mo compared to those with better nutritional rates. Patients with nutritional requirements of $\geqslant$ 65 g/d of lipids and $\geqslant$ 77.6 g/d of protein have better six-month survival rates[137,138]. Further investigation needs to be pursued to delineate the role of nutrition in AH patients.

Corticosteroids

Patients with mild alcoholic hepatitis (DF < 32) have a 10% mortality rate when not treated with prednisolone.

Supportive care is warranted[139]. Multiple treatment options have been studied, however only prednisolone have remained the mainstay of therapy[91,136]. Corticosteroids have a wide range of immune modulatory functions including suppression of pro-inflammatory transcription factors: NFKB and activator protein 1 (AP-1), which lower circulating levels of TNF-α and IL-8[140,141]. Prednisolone use is indicated in patients with DF > 32 or hepatic encephalopathy, but contraindicated in active infection, gastrointestinal bleeding, acute pancreatitis, or renal failure[142,143].

Studies examining the combination of prednisolone and pentoxifylline treatment produced mixed results[144,145] or showed no added benefit of pentoxifylline[146,147]. The Steroids or Pentoxifylline for Alcoholic Hepatitis trial is the largest randomized clinical trial to date, which examined the short and long term mortality of patients with severe alcoholic hepatitis. Results show no reduction in all cause mortality at 28 d for patients treated with prednisolone or pentoxifylline. However, there is a non-significant mortality benefit at 28 d in the prednisolone treated group, which is not seen at 3 and 12 mo[148]. Corticosteroids may have some benefit within the first month, but cannot be generalized to a provide long term value.

The meta-analysis of 22 randomized clinical trials performed by Singal *et al*[90] show a reduction in short-term mortality in patients with severe alcoholic hepatitis treated with steroids *vs* placebo. Corticosteroids with N-acetylcysteine (NAC) compared to corticosteroids alone may be effective in improving short-term mortality[149]. More recently, Thursz *et al*[150] performed a meta-analysis of 9 randomized clinical trials comparing the use of corticosteroids, pentoxifylline, or both for the treatment of severe alcoholic hepatitis. They found that corticosteroid treatment improved 28 d survival compared to pentoxylline and control group. There is no added benefit of treatment with combination group of corticosteroids and pentoxifylline[151].

Pentoxifylline

Pentoxifylline inhibits tumor necrosis factor, a cytokine responsible for the inflammatory cascade initiation seen in alcoholic hepatitis. One out of four randomized controlled trials showed a mortality rate of 25% in pentoxifylline treated patients with DF > 32 compared with 46% in the placebo group. The benefit seen was mostly to prevent hepatorenal syndrome[151]. It can be an alternative for patients who have contraindications to steroids or early renal failure, however is not recommended as a first line agent.

N-acetylcysteine

Oxidative stress produced from alcoholic hepatitis depletes gluthathione levels. NAC is an antioxidant substance, which is a pro-drug to the precursor of gluthathione. Moreno *et al*[137] produced a randomized clinical trial of NAC *vs* placebo, which shows no significant difference[129]. In 2006, Phillips *et al*[152] found that corticosteroids are superior to NAC for short-term survival. Nguyen-Khac *et al*[153] examined the use of NAC with corticosteroids in a 2011 randomized clinical trial. They found patients with combination therapy have improved one-month survival compared to patients treated with corticosteroids. There are fewer cases of infections and hepatorenal syndrome in the combination treatment arm. Nevertheless, there is no significant difference in survival at 6 mo[153]. Further studies are needed to evaluate the efficacy of NAC.

Other anti-TNF alpha inhibitors

Anti-TNF alpha inhibitors, such as infliximab and etanercept is not recommended for the treatment of alcoholic hepatitis. Although early pilot studies of corticosteroids and infliximab show an improvement in the Maddrey score within the first month, later studies have shown anti-TNF alpha inhibitors are associated with increased death from infections[113,154,155].

Liver transplantation

Liver transplantation may be considered as a last option for patients with alcoholic hepatitis when medical treatment has failed or is contraindicated. Most liver transplant centers require a minimum abstinence of six months prior to donor allocation consideration. Given the donor organ scarcity, the risk of recividism is feared for patients with alcoholic hepatitis undergoing liver transplantation[156].

Data regarding the 6-mo rule as a predictor of long-term sobriety remains controversial[157]. Based on a systematic review, there is no difference in early alcohol use in patients transplanted for alcoholic liver disease *vs* non-alcoholic liver disease at: 6 mo (4% *vs* 5%) and 12 mo (17% *vs* 16%). At 7 years post-OLT, 32% of the patients with alcoholic liver disease reports using alcohol. Although comparable rates of any alcohol use are reported in patients transplanted for alcoholic liver disease and non-alcoholic liver disease, the risk of heavy drinking appears much higher in alcoholic liver disease patients[158]. There is a wide variation among post-liver transplant alcohol relapse rates reported in the literature, ranging from 20% to 50%. Heavy drinking rates range from 10% to 20%[159]. The duration of pre-transplant abstinence does not appear to correlate with post-transplant survival[160], however studies for long term follow-up of the graft in patients transplanted for alcoholic hepatitis with continued alcohol abuse requires further investigation.

Mathurin *et al*[161] reports the results of a multicenter European trial which carefully selected corticosteroid refractory AH patients whom were deemed to have a low risk of recividism after liver transplantation. The episode of AH is deemed as the patient's first liver decompensating event. Other inclusion criteria includes: Close and supportive family members, absence of severe coexisting or psychiatric disorders, and a covenant to adhere to life-long alcohol abstinence. The study reports

no alcoholic relapse within the initial 6-mo follow-up period. Three of 26 patients transplanted for refractory alcoholic hepatitis later resumed drinking alcohol: One at 720 d, one at 740 d, and one at 1140 d after transplantation. Despite counseling by an addiction specialist, 2 patients remained daily consumers (30 g/d and > 50 g/d), whereas 1 consumed alcohol occasionally (approximately 10 g/wk). None of them had graft dysfunction[161].

Im *et al*[162] applied inclusion criteria similar to Mathurin's European trial for early liver transplantation in severe alcoholic hepatitis in the United States. The low candidate acceptance rate (20%) and the high survival rates for transplanted AH patients compared to controls (89% *vs* 11%) is comparable to the findings in Mathurin's study. Two patients (25%) had alcohol use post OLT. One patient self-reported a "slip" of 60 g and 15 g of alcohol use at day 84 and 260, respectively. Serial urine ethanol testing and self-reporting were negative thereafter. One patient had alcohol relapse, which is defined as: Four or more drinks daily or at least one drink for 4 or more days in succession after liver transplantation. When the subject with alcohol relapse was further analyzed, it was deemed that the hepatic decompensation was not the patient's first event and the subject had poor insight to disease prior to transplant. Limitations to the study include small sample size (n = 9) and short follow-up period (median = 765 d)[162].

A three-year pilot by Lee examined 2 groups of patients selected to receive a liver transplant: Severe alcoholic hepatitis as the first episode of liver decompensation *vs* alcoholic cirrhotics with ⩾ 6 mo of abstinence. Early liver transplant provided excellent short-term survival in both groups. There were similar rates of alcohol relapse in both groups: 23.5% *vs* 29.2%. Although lacking statistical significance, patients transplanted for AH had higher rates of harmful drinking post-transplant compared to the control group (23.5% *vs* 11.5%, P = 0.42). The data was particularly concerning given the two out of the four patients with harming drinking patterns died secondary to recurrent alcohol use (alcohol overdose and medication noncompliance with graft failure, respectively)[163].

Although preliminary results may appear promising, ethical issues pertaining to organ shortage, sociocultural concerns about judicious organ allotment, and recividism risk remain[164]. The feasibility of patient selection through strict psychosocial assessment is limited by resources. An addiction psychiatrist experienced in liver transplant may not be readily available in all centers. Liver transplantation for refractory severe acute alcoholic hepatitis should be judiciously employed in highly selected individuals who are at low risk of recidivism[165].

New therapeutic options for alcoholic hepatitis are needed. Corticosteroid use are helpful in 50% of cases, however they are associated with a higher rate of infections and do not offer long term survival benefit. Treatments targeting gut dysbiosis, innate immunity, inflammation pathways, and apoptosis are currently being studied (Table 1).

NEW THERAPEUTIC OPTIONS

Gut microbiota modification: Probiotics

Animal studies mimicking alcoholic hepatitis have observed changes in microbial translocation and dysbiosis[166]. Patients with alcoholic hepatitis have abnormalities in bacterial overgrowth, intestinal mucosal damage, increased gut permeability with bacterial translocation, and resulting endotoxemia[167]. The use of probiotics to modify gut bacteria are studied for the treatment of alcoholic hepatitis. Animals studies by Wang *et al*[168] concludes *Lactobacillus* rhamnosus treatment reduced alcohol-induced hepatic inflammation by attenuation of TNF-α production *via* inhibition of TLR-4 and TLR-5 mediated endotoxin activation. A pilot study with mild alcoholic hepatitis patients who received *Bifidobacterium bifidum* and *Lactobacillus plantarum 8PA3* for five days shows significantly reduced ALT, AST, lactate dehydrogenase, total bilirubin, and restoration of gut flora compared to placebo. Other studies have showed that alcoholic cirrhotics have cytokine reduction with reduced liver disease severity and hospitalization when treated with probiotic VSL#3[169,170]. Rifaximin is studied for the role of bacterial overgrowth in decompensated alcoholic cirrhotics. Rifamixin administered for 28 d decreased endotoxemia in the systemic and splenic circulation with reduction in portal hypertension. Currently, there are clinical trials examining the role of Lactobacillus rhamnosus, rifaximin, fecal microbiota transplantation, and antibiotics in AH patients[99].

Immune modulators

Chronic ethanol stimulation increases the production of inflammatory cytokines and chemokines to induce liver injury. Multiple mechanisms are proposed to modulate the innate immune system. It is not clear if animal and cellular models can be extrapolated for use in humans. Based on animal studies, IL-22 is a hepatoprotective cytokine. Chronic-binge ethanol fed mice treated with recombinant IL-22 protein induced activation of hepatic STAT3 to prevent alcohol-induced steatosis, liver injury, and oxidative stress in a study by Ki *et al*[12]. IL-22 down regulates the expression of fatty acid transport protein. It is found to have antioxidant, apoptotic, proliferative, and antimicrobial properties with minimal side effects[11]. IL-17 levels produced by TH17 cells are elevated in patients with alcoholic hepatitis. IL-17 induces neutrophil recruitment and stimulates hepatic stellate cells to secrete chemokines, such as IL-8 and CXCL[171,172]. Alcoholic hepatitis patients with expression of these chemokines in the liver are correlated with worsening severity of portal hypertension and patient survival[173,174]. Therapeutic agents targeting the reduction of CXCL and IL-17 with IL-22 upregulation can be a new treatment

Table 1 New potential treatments for alcoholic hepatitis

Treatment	Class	Mechanism of action
Probiotics	Gut microbiota modification	Reduction of bacterial endotoxins and translocation
IL-22 recombinant protein	Immune modulation	Hepatoprotective: Antioxidant, apoptotic, proliferative, and antimicrobial properties
G-CSF	Growth factor	Liver regeneration
Obeticholic acid	Farnesoid X receptor	Improvement in cholestasis
Emricasan	Caspase inhibitor	Apoptosis, inflammation, and fibrosis inhibitor
Anakinra (Pentoxifylline + Zinc)	IL-1 receptor	Decreases hepatic inflammation
SAMe	Glutathione precursor	Decreases oxidative stress
Metadoxine	Antioxidant	Decreases oxidative stress and steatosis
ELAD	Extracorporeal human hepatic cell-based liver treatment	Toxin removal, reduction of inflammation, liver regeneration

IL: Interleukin; G-CSF: Granulocyte colony-stimulating factor; ELAD: Extracorporeal liver assist device; SAMe: S-adenosil-L-methionine.

strategy[54,175].

Liver regeneration: Granulocyte colony-stimulating factor

Bone marrow-derived stem cells can populate the liver and differentiate into hepatic cells when faced with liver insult. Experimental studies show that granulocyte colony-stimulating factor (G-CSF) promote the mobilization of bone marrow stem cells to ameliorate liver injury and enhance the proliferative capacity of hepatocytes[176]. G-CSF mobilizes CD 34+ cells, increases hepatocyte growth factor, and induces proliferation of hepatic progenitor cells within 7 d of administration in patients with alcoholic cirrhosis with biopsy proven alcoholic steatohepatitis[177]. In a pilot study, 46 patients with severe alcoholic hepatitis were randomized to receive G-CSF $\geqslant$ 5 μg/kg for 5 d with standard medical therapy (pentoxifylline with nutrition) *vs* standard medical therapy alone. Findings shows a statistically significant number of peripheral CD 34+ cells and improvement of Child Pugh score, MELD, and discriminant function for up to 3 mo in the G-CSF group. Ninety day survival benefit is seen in G-CSF group compared to placebo[178]. The addition of corticosteroids would be helpful in delineating the survival benefit. A clinical trial testing the efficacy of G-CSF in the management of patients with severe alcoholic hepatitis whom have failed corticosteroids is needed.

FXR/obeticholic acid

FXRs are nuclear hormone receptors that participate in bilirubin metabolism. Bile acids are the physiologic ligands of FXRs, which regulate bile acid, carbohydrate, and lipid metabolism. In addition, they modulate liver regeneration after injury. FXR activation is protective against cholestatic and fatty liver injury. In a murine model, mice were fed an ethanol or control diet. FXR impairment is exhibited in the ethanol group. FXR agonist therapy is found to be hepatoprotective, likely from suppression of microsomal CYP2E1 enzyme upregulation[179]. FXR activation is shown in other studies to prevent and improve liver fibrosis in mice[180,181].

Obeticholic acid is a selective FXR. A phase 2 clinical trials shows obeticholic acid improved insulin sensitivity and markers of liver inflammation in patients with diabetes and nonalcoholic fatty liver disease. Phase 2 clinical trials are exploring obeticholic acid in patients with alcoholic hepatitis.

Caspase inhibitors

Alcohol exposure causes hepatocytes to release extracellular vesicles in a caspase-dependent manner to elicit apoptosis and macrophage activation[182]. Apoptosis may trigger abnormal liver tissue repair, inflammation, regeneration, and fibrosis[183]. Caspase inhibitors may decrease apoptosis and inflammation in a variety of liver diseases. Emricasan is a pan-capsase inhibitor studied in patients with hepatitis C and NASH. In clinical trials, emricasan significantly reduces the aminotransferase activity in non-cirrhotic hepatitis C patients. Similar trends are observed in patients with NASH and hepatitis B, however statistical analysis was not performed on these groups[184]. In NASH studies, mice fed a high fat diet demonstrates a five-fold increase in hepatic apoptosis and 1.5-fold and 1.3-fold increase in caspase-3 and -8, respectively. Mice with emricasan administration demonstrates a reduction in inflammation and fibrosis compared to placebo. Based on the positive preliminary data found in murine NASH models, clinical trials evaluating emricasan for benefit in patients with alcoholic liver disease are ongoing. Thus far, a phase 2 clinical trial concluded that Child Pugh A and B cirrhotic patients with baseline MELD $\geqslant$ 15 who are treated with emricasan showed significant improvement compared to placebo in MELD scores, Child-Pugh scores, bilirubin levels, and INR in preliminary data[185].

Combination therapy: Anakinra-blocks IL-1 beta receptor, pentoxifylline and zinc vs methylprednisolone

Alcohol-induced liver injury activates Kupffer cells, which stimulation production of inflammasomes and IL-1β, which initiate the inflammatory cascade. Effects include liver inflammation, steatosis, injury, and fibrogenesis. Pharmacological inhibition of IL-1 signaling has a hepatoprotective effect. There was recovery from acute-on-chronic alcoholic liver injury[186]. Anakinra, an IL-1

receptor antagonist combined with pentoxifylline and zinc is being studied in phase 2 and 3 clinical trials to examined the efficacy against corticosteroids.

S-adenosil-L-methionine

S-adenosil-L-methionine (SAMe) is a direct precursor of glutathione, which serves as a major physiologic defense mechanism against oxidative stress. A recent pilot study randomized two groups of twenty patients each with severe alcoholic hepatitis treated with prednisolone 40 mg daily *vs* prednisolone 40 mg with intravenous SAMe 800 mg for 28 d. After the first week, intravenous SAMe regimen was converted to oral doses of 1200 mg/d for two months. The response rate measured by the Lille's score is significantly improved in the prednisolone and SAMe (95% of patients) compared to the prednisolone only group (65%). Hepatorenal syndrome occurred in 20% patients in the prednisolone group, but none in the combination treatment group. Difference between the groups regarding 28-d mortality could not be inferred. Although not statistically significant, the six-month survival rate is 90% in the prednisolone plus SAMe group *vs* 75% in the prednisolone group. Larger trials are needed to validate the study results[187].

Metadoxine

Metadoxine is an antioxidant, which aids in gluthathione metabolism and inhibits hepatic steatosis[188]. The addition of metadoxine with corticosteroids is found to improve 30 and 90 d survival rates. The metadoxine and corticosteroid group is found to have a better treatment response based on Lille's score, lower rates of hepatorenal syndrome, and decreased development and/or progression of hepatic encephalopathy compared to the corticosteroid group. There are no significant adverse side effects[189]. Another study combined metadoxine with either prednisone or pentoxifylline for 30 d. The group receiving metadoxine combined with prednisolone or pentoxifylline had increased three and six-month survival rate of 50% compared to the 20% survival rate in the prednisolone or prednisone only group. The rates of hepatorenal syndrome and hepatic encephalopathy development are significantly less in the metadoxine group, however infections are not[190]. Additional studies with a greater sample size are needed to increase the power of future studies.

ELAD

There are ongoing Phase 3 clinical trials of ELAD for acute severe alcoholic hepatitis[191]. Patients with acute renal failure, severe coagulopathy, and MELD > 28 have worse outcomes with ELAD. There are no survival differences between the ELAD over the control group in day 28 and 91. Pre-specified exploratory analysis of 101 patients < age 47 showed an improved 3-mo survival in the ELAD group compared to the control group (81.4% *vs* 67.2%). When analyzed for patients less than 50 years old, creatinine < 1.3 mg/dL, bilirubin $\geqslant$ 16 mg/dL, and INR $\leqslant$ 2.5, the 3-mo survival rate was 94% in the ELAD group and 68% in the control group. The most recent ELAD trial, VTL-308 incorporates the new inclusion and exclusion criteria[192]. The preliminary results are eagerly awaited. There are limitations to the use of ELAD, including high cost and stringent inclusion criteria. Patients are usually monitored in the intensive care use with frequent monitoring and blood draws. Currently, there are limited centers performing ELAD research and the patient selection criteria excludes: Alcohol use > 6 wk, persons > 50 years old, severe coagulopathy, and advanced renal failure.

Many therapies have been studied for alcoholic hepatitis without proven efficacy. Treatment with antioxidants, including vitamin E and silymarin do not have a survival benefit in alcoholic hepatitis or cirrhosis patients. Colchicine, amlodipine, propylthiouracil, anabolic steroids, and insulin and glucagon combinations are not effective in patients with alcoholic hepatitis[45].

FUTURE RESEARCH

Most of the understanding of alcoholic liver disease pathogenesis stem from animal models of alcoholic liver disease recreated *via* ad libitum or intragastric ethanol feeding. Recent publications propose a new model of ad libitum feeding with 40% intake of caloric intake from a Western diet high in cholesterol and saturated fat combined with 60% ethanol *via* intragastric infusion to simulate a "true" model of alcohol hepatitis, where contributing factors such as obesity and alcohol abuse are taken into account. This model recreates findings seen in chronic alcoholic liver disease with superimposed alcoholic hepatitis when a weekly binge dose of ethanol is added. However, the model could not emulate the acute-on-chronic hepatic decompensation seen in alcoholic hepatitis[193,194]. The search for molecular targets through genomic studies holds the future direction of answering unsolved questions about alcoholic hepatitis pathogenesis. Further study of IL-22's antioxidant, anti-apoptotic, anti-steatosis, antibacterial, proliferative effect, and other hepatoprotective properties in conjunction with the inflammatory and immunomodulatory function of corticosteroids is underway[12,195]. Recent literature highlights the use of biospecimens (*i.e.*, liver tissue, peripheral serum, stool) for *in vitro* and *in vivo* studies as a new approach to finding targets for therapy[194]. New findings eludicated under such methods, include impaired bacterial killing from monocyte oxide burst dysfunction and defective T cell function in AH subjects. Although the reversal of defective monocyte oxidative burst is not restored by the IFN-gamma, the negative regulator of Janus Kinase responsible for suppressing cytokine signalling-1 was discovered to have increased expression[46]. Restoration of T-cell interferon gamma production, reduction in production of IL-10 producing T cells, and improvement in neutrophil antibacterial function occurs when antibodies against PD1 and TIM3

are blocked[47].

CONCLUSION

Alcoholic hepatitis is increasingly recognized as a form of acute-on-chronic liver failure in patients with underlying alcohol-related disease[196,197]. Patients with severe alcoholic hepatitis remain a challenging population to treat. New treatment options for AH involving gut microbiota modification, immune modulation, promotion of liver regeneration, apoptosis inhibitors, farnesoid receptors, and ELAD appear promising thus far, however the research is still in the preliminary phases. Currently, early liver transplantation for severe AH failing standard medical therapy is not universally implemented and further investigation is warranted. Solving the complex pathophysiology of alcoholic hepatitis through translational studies with clinical application is challenging. The study of new animal model simulating "true" AH and use of genomic analysis to provide molecular targets are emerging into present day practice. The utilization of clinical trials fuelled by constant evolving concepts discovered *via* translational research will help determine the endpoints and safety of the new therapeutic options to bridge the gap of a disease with high morbidity and mortality.

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