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Alcohol-Related Hepatitis: A Review Article

Alcohol-Related Hepatitis

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Abstract

Alcohol-related hepatitis is a unique type of alcohol-associated liver disease characterized by acute liver inflammation caused by significant alcohol use. It ranges in severity from mild to severe and carries significant morbidity and mortality. The refinement of scoring systems has enhanced prognostication and guidance of clinical decision-making in the treatment of this complex disease. Although treatment focuses on supportive care, steroids have shown benefit in select circumstances. There has been a recent interest in this disease process, as COVID-19 pandemic led to substantial rise in cases. Although much is known regarding the pathogenesis, prognosis remains grim due to limited treatment options. This article summarizes the epidemiology, genetics, pathogenesis, diagnosis and treatment of alcohol-related hepatitis.

Key Words: Alcohol; Hepatitis; Epidemiology; Prevalence; Treatment; Clinical Trials

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Core Tip: The aim of this article is to review alcohol-related hepatitis. Despite the increased understanding of the pathogenesis of this disease process, treatment

options remain limited. Our review article focuses on epidemiology, genetics, pathogenesis, diagnosis and treatment. We also discuss complications of alcohol-related hepatitis along with their optimal management and ongoing clinical trials. Further research evaluating therapeutic targets for its management are warranted.

INTRODUCTION

The burden of alcohol-associated liver disease continues to grow with rising cases during and even after the COVID-19 pandemic1-2. Some experts believe that the rise in cases during the COVID-19 pandemic will have long lasting effects on society and healthcare. Alcohol is an integral part of American culture and its widespread use cuts across socioeconomic and racial lines. Alcohol-related liver disease (ALD) can range from hepatic steatosis to end-stage liver disease. Alcohol-related hepatitis (ARH), a form of ALD, is an acute inflammatory syndrome of jaundice and liver injury occurring in patients with significant alcohol use. The severity can range from subclinical to acute severe illness, which is associated with high mortality. The recent trends in ARH hospitalizations in the United States suggest its importance in the current realm of clinical practice.1-4

The prevalence of ARH has been on a rise even prior to COVID-19 pandemic.4 Studies have shown a 53% increase in ARH from 2019 to 2020 with a 64% increase in the latter phase of the pandemic.2 Multiple other studies have shown that the societal disruptions associated with the pandemic have further intensified the rise in cases of ARH. ARH can resolve with abstinence and supportive therapy, however, these measures do not guarantee recovery in all patients. Acute-on-chronic liver failure (ACLF) and development of cirrhosis are the most feared complications of ARH and is associated with significant morbidity and mortality. Thus, identifying patients early during the course of the disease is critical.

PREVALENCE

The true prevalence of ARH is difficult to assess as patients can be asymptomatic and remain undiagnosed. A study by Jinjuvadia *et al*5 evaluating the temporal trends in ARH hospitalizations reported an increase in patients with ARH from 249,884 in 2002 to 326,403 in 2010. Their study included hospitalizations with a primary and secondary diagnosis of ARH. To estimate true prevalence, Ali *et al*4 included patients only with a primary diagnosis of ARH and reported an increase in the total hospitalizations from 67,070 in 2009 to 125,540 in 2019. They also reported an increase in inpatient mortality from 2.48% in 2009 to 3.78% in 2019. The increase in the cases of ARH has been further intensified during the COVID-19 pandemic, especially in younger patients and in women.

ARH is also associated with a significant risk of mortality. Mortality has been estimated to be around 15% at 30 days and 39% at 1 year and has been linked to the severity of the disease5. Patients with mild liver injury have a 20% mortality, while patients with severe liver injury have an overall 40% mortality6. Mortality in patients with higher Maddrey's Discriminant Function (MDF) score (>30), a surrogate marker of severity, is estimated to be between 30-50%7.

In previous years, there has also been an increase in the healthcare burden of ARH hospitalizations. An increase was noted in the mean inpatient cost for ARH hospitalizations from $31,189 in 2009 to $62,229 in 20194. A study by Thompson *et al*8, using commercial insurance claims, examined hospitalized patients between 2006-2013 and reported the average cost per patient is $145,000 in their cohort of 15,546 patients. They also reported the cost surrounding death of ARH was 200-300% higher than the average cost surrounding death.

EPIDEMIOLOGY

Alcohol Intake- The amount of alcohol consumption that places patients at risk of ARH is largely unknown. The estimates of the amount of alcohol consumed by patients may

not be accurate as they are based on interviewing patients and family members9. The majority of patients with ARH consume more than 100g/day of alcohol10. American Association For The Study of Liver Disease (AASLD) practice guidelines recommend suspecting ARH in women who consume >40g of alcohol and in men who consume >60g/day for ≥ 6 mo11. It is also pertinent to note that not all patients who drink heavily develop ALD. In a study by Friedman *et al*12, 35% of the patients developed steatohepatitis and ARH, while only 10% of the patient's developed cirrhosis.

The pattern of drinking as well as the type of alcohol consumed also contributes to the risk of developing ARH. Drinking spirits or beer, binge drinking as well as drinking outside of the typical mealtimes has been associated with a higher risk of developing ALD13-15. (Figure 1)

Gender- There are significant differences based on gender. Women are at a higher risk of developing ARH at a lower threshold compared to men. This is attributed to differences in the variability of alcohol dehydrogenase activity, sex hormones, body fat distribution and liver volume between the two genders16-18. There has been an increase in the cases of ARH in women in recent years. A study conducted between 2009-2019 showed an increase in the proportion of women being admitted with ARH from 29.1% to 34.1%4.

Malnutrition- Patients who consume alcohol excessively are often malnourished and can suffer from vitamin deficiencies19. Mortality has been closely related to the severity of protein-energy malnutrition. Patients with severe malnutrition and ARH have an estimated mortality of 80%20. Additionally, depletion of hepatic vitamin A and vitamin E can aggravate liver disease21. Zinc deficiency in patients with excessive alcohol can lead to disruption of mucosal permeability which may play a role in the pathogenesis of ARH.

Concurrent Liver Disease- It is well established that the combination of alcohol misuse and chronic hepatitis C (HCV) increases the incidence of cirrhosis and hepatocellular carcinoma (HCC) and is associated with reduced survival compared to patients with either HCV or alcohol use alone22. Consuming upward of 50g/day of alcohol increases the relative risk of liver disease compared to patients with HCV who do not consume alcohol23. Patients with chronic HCV have been noted to have worse outcomes and higher in-hospital mortality when admitted with ARH24.

While the literature clearly demonstrated worse outcomes in patients with concomitant alcohol misuse and chronic HCV, the data regarding the effect of alcohol use on patients with chronic hepatitis B (HBV) remains understudied. A study by Iida-Ueno *et al*25 revealed that patients with light to moderate alcohol consumption had a 1.5-fold increase of chronic HBV infection while patients with heavy alcohol consumption had significantly accelerated progression to cirrhosis and HCC with 1.3 to 8.4-fold increased risk. Although the mechanism by which alcohol enhances disease progression is less studied in patients with chronic HBV in comparison to patients with HCV, patients with either chronic HCV and HBV should be counseled to avoid alcohol consumption to minimize chances of liver disease progression.

Obesity, Diabetes Mellitus and Metabolic Syndrome-Underlying non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of metabolic syndrome, can be additive to the damage sustained through alcohol misuse and lead to worse outcomes. A study by Siddiqui *et al*26 reported obesity to be an independent predictor of mortality in ARH.

Seasonality- Studies have shown that there might be a seasonal trend to admissions with alcohol use. We have previously reported that in the United States, ARH was highest in the summer months, as compared to the common opinion that ARH hospitalizations are higher in the winter season27.

GENETICS

Significant variability has been noted among patients in regard to the susceptibility of developing ARH as well as the severity of symptoms. This variability has prompted several studies exploring a possible genetic basis for individual response to ARH. Studies have found an alteration in the expression of claudins, osteopontin, CD209, selenoprotein, and bile duct proliferation genes in patients with ARH compared to patients with alcoholic steatosis (AS) and healthy controls without liver disease28. Colmenero *et al*29 identified several genes that were upregulated in ARH including extracellular matrix proteins, fibrogenesis mediators, inflammatory cytokines, and apoptosis regulators. Cytochrome p450 2E1 and angiotensinogen were found to be downregulated. Additionally, certain genes were found to be correlated with the severity of disease features including tissue inhibitors of metalloproteinases-1 and growth-related oncogene α . Epigenetic studies have also shown that a liver affected by ARH has significant alterations in HNF4α-dependent genes, which play a role in impairing metabolic and synthetic function30. A cohort study by Beaudoin *et al* demonstrated an increased risk for developing ARH with a higher total bilirubin in patients with variants in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) and the haptoglobin (HP) genes as compared to other genetic variants associated with chronic liver disease states31.

The PNPLA3 gene in particular has been identified to play a significant role in the pathogenesis of several liver diseases, as it belongs to a group of lipid-metabolizing enzymes. The I148M variant, a single-nucleotide polymorphism of the gene, is associated with an increased risk for developing hepatic steatosis, non-alcoholic steatohepatitis (NASH), ALD, cirrhosis, and hepatocellular carcinoma (HCC)32. Despite these correlations, the precise function of the PNPLA3 gene is yet to be fully understood. Palmer *et al*33 demonstrated that variants in the PNPLA3 gene in Hispanic-American and African-American patients is significantly associated with the

development of hepatic steatosis, and other studies have shown that these groups suffer from higher mortality rates due to ALD. Levy *et al*34 reported that patients of Hispanic ancestry presented with ALD at a significantly earlier age than patients of Caucasian or African-American background, though the mechanisms remain unclear and may be related to the gene variants described by Palmer *et al* as well as health care disparities. Future studies can help to elucidate the underlying mechanisms of these discrepancies and the potential of gene-targeted therapy in the management of ARH.

PATHOGENESIS

The pathogenesis of ARH involves acute inflammation superimposed on chronic ALD. Initial hepatic injury results from the metabolism of ethanol into acetaldehyde by alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1). As ethanol builds up as a result of increased consumption, acetaldehyde also accumulates in the liver and begins to exert toxic effects35. Acetaldehyde leads to the formation of adducts, in the form of bonds with proteins, lipids, and DNA. This in turn impairs the normal function of the affected proteins and lipids and leads to DNA damage. CYP2E1 further contributes to liver injury by the production of reactive oxygen species (ROS) which leads to hepatocyte injury36. This is thought to occur as a result of lipid peroxidation and interaction with proteins and nucleic acids, leading to hepatocyte necrosis37. (Figure 2)

The oxidation of ethanol and acetaldehyde leads to an increase in the levels of Nicotinamide Adenine Dinucleotide (NADH), which enhances lipogenesis in the liver38. Fatty infiltration of the liver is also a result of increased gut permeability due to alcohol ingestion, leading to higher levels of lipopolysaccharides present in the portal circulation39. Endotoxin, a lipopolysaccharide present in cell walls of gut microbiota, forms a protein complex and binds to the CD14 receptor on Kupffer cells in the liver40. The activation of Kupffer cells leads to the release of tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine41. TNF-α exerts its hepatotoxic effects by causing

hepatocyte apoptosis and stimulating the release of other cytokines42. Higher levels of TNF-α are correlated with an increased severity of ARH, demonstrating the significance of the cytokine in the pathogenesis of ARH43.

The stimulation of Kupffer cells also lead to an increase in polymorphonuclear leukocyte infiltrate in the liver, as a result of chemotactic factors such as interleukin-844. The multifactorial process of inflammation superimposed on alcohol-induced hepatic damage leads to the impairment of liver function observed as systemic illness and laboratory abnormalities in ARH. A thorough understanding of the pathogenesis of ARH can aid in its treatment, and further studies elucidating the precise mechanisms involved may improve treatment modalities and outcomes.

DIAGNOSIS

Physical Examination

Physical examination can range from benign to profoundly abnormal45. Patients may have signs of malnutrition/sarcopenia manifested as temporal or thenar muscle wasting. Jaundice and scleral icterus may be apparent in patients with more severe disease while subtle signs of jaundice can be noted sublingually or in the tympanic membranes in patients with less severe disease. The presence of spider angiomas, gynecomastia in men and caput medusa is uncommon in patients with ARH in the absence of cirrhosis. Right upper quadrant tenderness to palpation along the enlarged hepatic border is common, with the liver edge extending into the pelvis and crossing the midline in severe cases. Some studies have reported a bruit over the liver as a feature of severe ARH in >50% of patients46. Splenomegaly can often be appreciated as well even in the absence of cirrhosis. Fluid wave, shifting dullness and frank abdominal distention signifying large-volume ascites can be seen in severe cases. Lower extremity swelling progressing to anasarca can also be seen in severe cases. Finally, asterixis can be seen in patients with significant hepatic dysfunction.

Laboratory findings

Patients with suspected ARH should undergo a broad laboratory workup including comprehensive metabolic panel (CMP), complete blood count (CBC), international normalized ratio (INR), and gamma glutamyl transferase (GGT). Serologies for HAV, HBV and HCV should also be obtained to rule out alternative/concomitant infectious causes. Typical laboratory findings in ARH consist of elevated white blood cell count, thrombocytopenia, low sodium, potassium and magnesium. Other findings include total bilirubin >3 mg/dL, elevated alanine transaminase (ALT) and aspartate transaminase (AST) with levels usually <400 U/L, AST:ALT ratio >2, GGT >100 U/mL, INR >1.5, and albumin <3.0 g/L47. Other sequelae of chronic alcohol use such as macrocytic anemia can also be seen. (Figure 3)

It is pertinent to rule out alternative/concomitant causes of liver disease such as Wilson's disease, autoimmune liver diseases and iron overload syndromes. This is especially important in patients with severe disease who may be considered for liver transplantation, as these diagnoses will have significant implications on patient's ability to qualify for an urgent transplant as well as pre-and post-transplant management. Making these diagnoses can be challenging as patients with ARH may have multiple metabolic derangements. For example, patients with ARH may have decreased ceruloplasmin levels in the setting of hepatic dysfunction leading to suspicion of Wlison's disease. If there is a significant clinical concern for Wilson's disease, patients should undergo a slit lamp examination for Kayser-Fleischer rings as well as a 24-hour urine copper collection. Ferritin levels as well as iron saturations in patients with ARH can be markedly elevated in ARH therefore genetic testing for HFE gene mutation should be considered48. A clinical suspicion of autoimmune liver disease, especially in the setting of elevated autoimmune markers (antinuclear antibody (ANA), anti-smooth muscle antibody (SMA), antimitochondrial antibody (AMA), anti-liver kidney microsomal antibody), should prompt consideration of liver biopsy. Alpha-1-

antitrypsin levels can be artificially elevated in the setting of acute illness; genetic testing should be considered if clinical suspicion is sufficiently high.

Imaging

Abdominal imaging can be effective in the initial evaluation of suspected ARH however, it cannot serve as the sole basis for the diagnosis. Abdominal ultrasound (US) computed tomography (CT) scan and/or magnetic resonance imaging (MRI) will likely reveal and enlarged liver with smooth contours and decreased attenuation, and in more severe cases, an enlarged spleen, ascites and other sequelae of portal hypertension. The presence of smooth hepatic borders, as opposed to the nodular contour, can help to differentiate ARH from cirrhosis49. (Figure 4)

BIOPSY

The European Association for the Study of the Liver (EASL) clinical practice guideline in 2014 stated that the "presence of acute steatohepatitis can be suspected on the clinical and biochemical grounds, but a definitive diagnosis of acute steatohepatitis requires liver biopsy"50. AASLD practice guidelines in 2019 recommend performing biopsy for confirmation if there are potential confounding factors such as11:

Ischemic hepatitis (e.g. severe upper GI bleed, cocaine use within 7 days or hypotension)
Suspected drug-induced liver disease
Uncertain alcohol use assessment
Atypical laboratory tests (AST<50 or >400 IU/L, AST/ALT <1.5), ANA>1:160 or SMA >1:80

Liver biopsy is controversial, especially in patients with coagulopathy and ascites. Percutaneous biopsy may be performed in most patients, but transjugular biopsy is preferred in patients with severe thrombocytopenia and prolonged international

normalized ratio (INR). Liver biopsy is also recommended in patients suspected of having additional etiology for ACLF.

HISTOLOGY

Histology in patients with alcohol-related liver disease can range from steatosis to steatofibrosis51-52. Steatofibrosis is defined as steatosis with fibrosis, with or without hepatitis. Histological features include steatosis, hepatocyte ballooning, neutrophil-rich inflammation in the lobular parenchyma, necrosis, apoptosis and Mallory-Denk bodies (MDB)53. The predominant mode of hepatocyte injury is *via* ballooning degeneration, followed by lytic necrosis and apoptosis. The hepatocytes become swollen, with clumping of intermediate filaments and loss of cytokeratin 8 and 1851. The swelling in hepatocytes can be attributed to severe ATP depletion and an increase in intra-cellular calcium, resulting in loss of plasma membrane volume control, oncotic necrosis and disruption of the intermediate filament network. The majority of changes in ALD are seen in the centrilobular region of hepatic lobe as they contain enzymes such as alcohol dehydrogenase, which are critical in alcohol metabolism54.

It is pertinent to note there are histological similarities between NASH and ARH53. The differentiation is based on clinical information regarding alcohol intake, however some features are seen more commonly in ARH as compared to NASH. (Table 1)

Apoptosis can be triggered by oxidative stress. Apoptotic hepatocytes, also known as councilman bodies or acidophil bodies, are visualized as shrunken cells, chromatin condensation and cellular fragmentation55. MDB contain eosinophilic material, located primarily in the perinuclear location in the cytoplasm of hepatocytes56. They are formed due to the misfolding of aggregated keratin filaments. MDB demonstrate immunoreactivity with antibodies to keratin 8,18 and p62. Portal inflammation is milder as compared to other etiologies of liver disease. Portal inflammation, when present, is accompanied by ductular reaction and periportal inflammation57. Other features of this

disease include glycogenated nuclei, megamitochondria, cholestasis and hemosiderin deposits58. Iron deposition can also occur in patients with ALD59-60. Based on the index of suspicion, concomitant hereditary hemochromatosis should be ruled out.

As the disease progresses, fibrosis begins in perivenular region (Zone 3) and extends to the perisinusoidal region in patients giving classic "chicken-wire fibrosis". Trichrome stain visualizes the fibrosis. If the injury continues, fibrosis progresses resulting in nodule formation and finally cirrhosis. An orcein stain, can be beneficial in later stages to differentiate broad bands of fibrosis from areas of collapse, which can occur in superimposed ARH54.

A histological severity score including cytokeratin 8 and 18, has shown good accuracy in predicting 90-day survival61. Alcoholic hepatitis histologic score (AHHS) was created using parameters such as degree of fibrosis, degree of neutrophil inflammation, type of bilirubin stasis, and presence of mitochondria62. This score has been shown to be predictive of 90-day mortality. Trepo *et al*63 combined the expression patterns of 123 genes with the MELD score to create gene-signature plus MELD (gs-MELD) scoring system. This helped in discriminating patients with poor and good 90-day survival with an AUROC of 0.86. This score outperformed other models including MELD plus Lille. This is not yet commercially available for use, however may hold promise for the future.

COMPLICATIONS

Complications of ARH include infection, kidney injury, gastrointestinal bleeding, and acute liver failure amongst others. (Figure 5)

Infection

Patients with ascites are at risk for developing spontaneous bacterial peritonitis (SBP), a life-threatening infection of the peritoneal cavity. SBP is almost exclusively seen in

patients with ascites and is a result of bacterial translocation of enteric microflora into the ascitic fluid with concurrent failure of liver-related defensive mechanisms due to cirrhosis64. Additionally, patients with ARH are often treated with corticosteroids, further suppressing the immune response and increasing the risk of serious infection. Treatment of SBP is usually with a third-generation cephalosporin, such as ceftriaxone, which can also be used prophylactically in patients with decompensated cirrhosis or known patient with cirrhosis who presents with gastrointestinal bleeding.

Despite the well-known association of SBP with ALD, several studies demonstrate that infection due to pneumonia and urinary tract infection (UTI) is more common in severe ARH than SBP65. Infection overall is a major cause of mortality in severe ARH, with the majority being bacterial in nature66-67. A recent meta-analysis68 found pneumonia to be the most common infection in severe ARH at 23%, followed by UTI at 10%. In comparison, SBP accounted for only 7% of infections. Patients with acute severe ARH have also been shown to have a greater level of immunosuppression compared to patients with cirrhosis, as they were found to have reduced T-lymphocyte and neutrophil activity69. Furthermore, obesity has been associated with increased susceptibility to infection in patients with ARH70. A high index of suspicion is needed in monitoring infectious signs and symptoms in patients with ARH as these patients often lack typical signs of infection such as fever or abdominal pain and may present instead with progressive hepatic decompensation. A low threshold for initiation of antibiotic therapy is advised and can be initiated empirically while infectious work-up is in progress.

Acute Kidney Injury (AKI)

AKI is a common complication in hospitalized patients with ARH and can be due to pre-renal, intrinsic renal and post-renal causes. Pre-renal AKI continues to be the most common etiology, while the most feared etiology is hepatorenal syndrome (HRS). These entities can be differentiated *via* volume expansion challenge (25% albumin 1 g/kg for

48 h). Renal US can be used to rule out post-renal causes. Diuretics should be discontinued in patients with AKI.

Another etiology that should be considered in patients with ARH is acute tubular necrosis (ATN) secondary to cholemic nephrosis, or bile salt nephropathy and should be suspected in patients with prolonged severe cholestasis. Hyperbilirubinemia can also lead to formation of tubular casts, which can lead to acute tubular necrosis (ATN)71. Evaluation of fractional excretion of sodium/urea as well as urine microscopy is beneficial to identify the etiology of kidney disease. Workup for AKI in patients with ARH is presented in Figure 6.

The most feared complication, hepatorenal syndrome, results from renal artery vasoconstriction secondary to splanchnic vasodilation seen in liver disease72. Patients with ARH and other ALD often develop dilation of the splanchnic vasculature in response to increased hepatic resistance, which in turn leads to activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, and arginine vasopressin system. The activation of these vasoconstrictor systems leads to constriction of the renal arteries and subsequent AKI due to decreased renal blood flow often in the setting of decreased cardiac output73. The development of AKI in patients with ARH is associated with a significantly higher mortality rate compared to patients without AKI, 65% vs. 7% ($p<0.0001$) respectively74.

Treatment of hepatorenal syndrome is complex, with most studies supporting the use of vasoconstrictors in combination with albumin administration. Terlipressin, a vasopressin analogue, has shown promising results in the treatment of hepatorenal syndrome as it was found to be superior to both placebo and octreotide75. It has recently been approved in the United States by the Food and Drug Administration (FDA) for the management of hepatorenal syndrome. Liver transplantation is the treatment of choice in patients with HRS as renal dysfunction is potentially reversible

with the correction of hepatic failure76. Interestingly, obesity has been found to be associated with decreased survival in acute ARH, and this is thought to be due to an increased risk of developing renal failure77.

Acute On Chronic Liver Failure (ACLF)

Severe ARH can lead to acute-on-chronic liver failure (ACLF) , a condition that is associated with increased mortality in patients with ARH and is commonly seen during the course of the disease78. ACLF manifests as worsening jaundice and coagulopathy and is usually triggered by a precipitating event. Current literature shows that ARH serves as a common precipitating event for the development of ACLF79. A prospective cohort study demonstrated that 65% of patients with severe ARH had ACLF at the time of diagnosis or within a 6-month follow-up period80. Given the poor prognosis of ACLF, early liver transplantation is becoming more commonplace in the treatment of severe ARH, with recent literature supporting its use with stringent patient selection criteria.

Portal Hypertension and Cirrhosis

Many patients with ARH also have portal hypertension or will develop portal hypertension at some point during their disease course potentially leading to variceal hemorrhage. Overall one-month mortality in moderate to severe ARH is 23%, with the most common causes of death being liver failure, gastrointestinal bleeding, and infection81. The one-month mortality in non-severe ARH is 6%, however the rate increases to 13% after one year82.

Long-term follow-up in patients with ARH over 4 years revealed the probability of developing cirrhosis to be 10-20% per year and up to 70% of patients will ultimately develop cirrhosis83. In another study, about 40% of the patients were diagnosed with cirrhosis on biopsy, 5 years after the episode of ARH84. The probability of developing cirrhosis is associated with continued alcohol use, as Rehm *et al*85 demonstrated in a

meta-analysis that there is a close dose-dependent relationship between ongoing alcohol use and the risk of progression of ALD to liver cirrhosis. Pares *et al*86 found an 18% risk of progression to cirrhosis in patients who abstained from alcohol after 20 mo compared to 23% in patients with continued alcohol consumption.

PREDICTION MODELS

Maddrey's Discriminant Function (MDF) is a commonly used prognostic indicator in the management of ARH as it is specific for ARH and has shown to be relatively accurate in predicting short-term outcomes87. The MDF score incorporates two of the major indices of liver function, prothrombin time (PT) and total bilirubin with the formula 4.6 × (prolongation of prothrombin time in seconds) + bilirubin (μmol/L)/17. MDF score of <32 signifies mild to moderate ARH with 30-day survival estimated at 80-100%. MDF score ≥32 is considered to be severe ARH with a 30-day survival of only 50%, and these patients warrant corticosteroid administration for treatment of their disease88. (Table 2)

Lille Model is used to evaluate treatment response to corticosteroids and includes age, initial serum albumin, change in total serum bilirubin at day 7 of treatment, renal insufficiency, and initial MDF score89. Patients with a Lille score of <0.45 had an average 6-month survival rate of 85%, compared to just 25% in patients who scored ≥0.45 after 7 days of treatment (p <0.0001). The Lille model is primarily used in conjunction with the MDF to guide treatment of ARH. Patients who score ≥0.45 after receiving corticosteroid therapy for 7 days are considered for discontinuation of steroids and initiation of alternative treatment modalities, as continuation of steroids is of little benefit in these patients.

Model for End-stage Liver Disease (MELD) was initially created to assess the mortality risk in patients with portal hypertension undergoing transjugular intrahepatic portosystemic shunts (TIPS) procedure however, it has now become a validated tool in

assessing patients with a variety of liver pathologies90. MELD differs from MDF in that it incorporates serum creatinine and uses INR rather than PT. The formula for MELD is 9.57 × loge(creatinine) + 3.78 × loge(total bilirubin) + 11.2 × loge(INR) + 6.43. In comparison to the MDF, the MELD has been shown to be superior in predicting outcomes of patients with ARH. Several studies have demonstrated this effect, further supporting the use of MELD in patients with ARH91-94. Patients with a MELD score ≤11 have mild disease associated with a very low mortality rate. Patients who score >21 are considered to have severe ARH93.

Glasgow Alcoholic Hepatitis Score (GAHS) was developed in order to present a model with increased specificity than MDF and a more accurate cutoff score than MELD. The GAHS incorporates many of the same parameters as the MDF and MELD, but differs in its inclusion of the peripheral white blood cell count95. The inclusion of an inflammatory component is thought to provide a more accurate predictor of mortality in ARH, and has been shown to be superior to MDF in predicting 28-day and 84-day mortality. The cutoff point delineating severe ARH from non-severe is a GAHS score of ≥9.

Age, Serum Bilirubin, INR, Serum Creatinine (ABIC) score is another scoring system that was developed to predict mortality in patients with ARH96. The ABIC score includes liver function as well as kidney function and has a formula of (age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8). This model is validated for predicting 3-month survival rates in ARH based on stratification of the severity of disease. Patients are classified based on their ABIC score into low (< 6.71), intermediate (6.71-8.99), and high (> 9.0) mortality risk. These classes correspond to a 90-day mortality of 0%, 30%, and 75%, respectively. Despite its efficacy in death risk stratification, the ABIC score does not play a major role in treatment or in determining whether corticosteroid administration is indicated.

TREATMENT

The management of ARH involves reducing hepatic inflammation by targeting pro-inflammatory and immunologic substances acutely and reversing alcohol-induced hepatotoxicity in the long term. The mainstay of treatment in ALD is abstinence from alcohol. A retrospective study by Lackner *et al*97 demonstrated a 5-year mortality rate of 13% in early ALD and 43% in decompensated ALD. Abstaining from alcohol showed an improvement in survival in patients with both early and decompensated ALD. A meta-analysis by Xie *et al*98 determined that patients with ALD see an improvement in survival rates after approximately 1.5 years of abstinence. However, studies have also shown that histological improvements in ALD can be observed in patients as soon as 2 wk after discontinuation of alcohol consumption99.

Many of the traditional pharmacologic agents used to promote abstinence from alcohol such as disulfiram, naltrexone, acamprosate, and topiramate are of limited use in ALD as they may be hepatotoxic and lack data supporting their usage100. Baclofen, a selective gamma-aminobutyric acid (GABA)B receptor agonist, has been studied as a potential agent of choice in patients with ALD as it has minimal hepatic clearance. A recent multi-site randomized control trial101 of patients with and without ALD demonstrated that low-medium dose baclofen at 30-75 mg daily led to a significant improvement in alcohol abstinence.

Nutritional supplementation is a vital component in the treatment of ALD. Malnutrition is common in patients with ALD, and the severity of malnourishment is correlated with the severity of liver disease102. The AASLD recommends a diet of at least 2000 kcal/day with at least 1.5 g protein/kg/day in patients with ALD103. These patients suffer from nutritional deficiencies and appropriate nutritional supplementation should be provided as nutritional deficiencies have been shown to be associated with worse outcomes104.

Treatment of mild to moderate ARH, as defined by an MDF score <32, consists mainly of supportive care and management of complications such as ascites, hepatic encephalopathy, and acute alcohol withdrawal syndrome105. Ascites is managed primarily through sodium restriction and diuresis. Patients with ascites generally have decreased sodium excretion, warranting a daily sodium restriction of 2-4 g/day. AASLD guidelines recommend that for the first episode of ascites, aldosterone antagonists alone can generate an adequate response with few side effects106. On the contrary, if the patient has long-standing ascites, anasarca or hepatic hydrothorax, the recommended regimen is a combination of an aldosterone antagonist and loop diuretic.

Hepatic encephalopathy is managed primarily with lactulose and rifaximin in order to promote the excretion of toxic metabolites *via* stool and improve the biodiversity of gut flora. Acute alcohol withdrawal is treated with benzodiazepines such as lorazepam on a scheduled regimen or symptom-triggered dose in accordance with protocols such as the Clinical Institute Withdrawal Assessment (CIWA). Lorazepam has been shown to be the safest agent in its class in patients with liver disease due to minimal hepatotoxicity and is therefore the drug of choice107. Use of long-acting benzodiazepines, such as chlordiazepoxide, should be avoided in patients with significant hepatic dysfunction due to decreased rate of hepatic metabolism and potential for rapid accumulation leading to progressive decline in mental status108.

The most well-studied treatment modality in severe ARH, classified as an MDF score ≥32, is the use of corticosteroids. Its use was validated in the "Steroids or pentoxifylline for alcoholic hepatitis" (STOPAH)109 trial, which included 1053 subjects with ARH. There was a 28-day mortality benefit in patients treated with prednisolone. On the contrary, no mortality benefit was observed in the prednisolone group after 90 days or 1 year, adding further evidence that the positive effects of steroids in severe ARH are limited to short-term. (Figure 7)

A meta-analysis of 5 randomized control trials110 revealed a significant improvement in 28-day survival among patients with severe ARH treated with corticosteroids (79.97±2.8% *vs* 65.7±3.4%, $P = 0.0005$). A more recent meta-analysis111 of 11 randomized control trials found similar results in short-term mortality benefit, however also demonstrated that corticosteroid treatment did not decrease mortality rate after 6 mo. The primary mechanism by which corticosteroids exert their effect in severe ARH is by blunting the immune response and inflammation that contributes to mortality112. The standard regimen for treatment of severe ARH is administration of prednisolone 40 mg daily113. Contraindications to steroid administration include active infection, gastrointestinal bleeding, acute pancreatitis, and renal failure, as steroids can acutely exacerbate these conditions114.

STOPAH109 trial reported that incidence of serious infections occurred in 13% of patients in the prednisolone group compared to 7% in patients who were not treated with prednisolone ($P = 0.002$). However, a recent meta-analysis115 found that corticosteroid administration in severe ARH reduced 28-day mortality from liver-related death with no significant change in mortality from bacterial infection or gastrointestinal bleeding. The study also found a higher incidence of fungal infection in steroid-treated patients. Pentoxifylline was previously used in the management of ARH. Its use has been limited based on the results of STOPAH trial, in which use of pentoxifylline was not associated with mortality benefit.

Liver transplantation (LT) has been controversial in the treatment of ARH, as patients with ALD have historically been considered poor candidates for transplantation due to concern for continued alcohol use after transplantation. However, recent trends have shown an opportunity for LT to gain a larger role in the treatment of ARH with strict selection criteria for candidates, as demonstrated in several studies116. A prospective trial by Mathurin *et al*117 showed a significantly improved 6-month survival rate in patients with severe ARH (MDF >32, Lillie >0.45) who received LT compared to

controls without LT (77% and 23% respectively, p <0.001). However, selection criteria were remarkably strict, as only patients with no prior episodes of hepatic decompensation, strong family support, complete commitment to abstinence, and consensus among all care providers were accepted for LT, which was less than 2% of all patients admitted with ARH during the study period. A more recent trial by Weeks *et al*118 demonstrated a 97% 1-year survival rate in patients who received LT for severe ARH, however had an alcohol use relapse rate at 17% due to less strict inclusion requirements (including patients with recent hepatic decompensation). A recent large multi-center retrospective analysis (ACCELERATE-AH)119 found a 94% 1-year survival rate and 84% 3-year survival rate with a 11% relapse rate. Of note, median MELD score was 39 and median Lille score was 0.82 for patients who received LT.

In summary, LT should be considered for patients with life-threatening ARH who have failed medical therapy and who have a low likelihood of alcohol relapse based on predetermined medical and social criteria. The proportion of candidates meeting these criteria may be relatively low, however stringent patient selection can aid in avoiding improper use of donor organs while dramatically improving survival rates. A study reported that the rates of relapse-free survival and hazardous relapse-free survival did not differ between the patients who received early transplantation compared to those who were transplanted after 6 mo of bstinence120.

THERAPIES/CLINICAL TRIALS UNDER INVESTIGATION

Multiple therapies are currently under clinical trial for the management of ARH. While the discussion regarding all the therapies under investigation is beyond the scope of this article, information regarding the various mechanisms and clinical trials currently targeting this disease is presented in the Table 3 below.

CONCLUSION

Alcohol-related hepatitis remains a disease process with high morbidity and mortality. Despite research advances in pathogenesis of this disease process, limited progress has been made in management of this condition. Abstinence remains critical in maximizing the chances of hepatic recovery; corticosteroids continue to play a role in select populations. Given the grim prognosis and increasing prevalence of ARH, research efforts are aiming at inhibiting inflammatory cytokine pathways that lead to progressive hepatic damage. In the meantime, many centers around the world are resorting to liver transplantation as salvage therapy. The COVID-19 pandemic exacerbated the pre-existing trend of rising cases of ARH. Urgent societal and government interventions are needed to prevent the ongoing rise in ARH cases in addition to intensifying research efforts in identifying and testing therapeutic targets for this complex disease process.

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