Screening, Diagnosis, and Treatment of Alcohol-Related Liver Disease and Alcohol-Associated Hepatitis

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Abstract: Alcohol-related liver disease is a spectrum of disease in which continued, significant alcohol use can cause progression from fatty changes in the liver to inflammation, fibrosis, and eventually cirrhosis. The rates of alcohol consumption, alcohol use disorder, and alcohol-related liver disease have increased substantially during the past several years. However, the amount of alcohol consumption may not be the only risk factor for such progression of disease. Studies have found several other risk factors, including sex, race, and genetic predisposition, as possible culprits of worsening disease. As a result, clinicians must understand and implement screening tools for early diagnosis and remain up-to-date with the evolving nature of treatment options. This article reviews the diagnosis and treatment of alcohol use disorder as well as the pathophysiology, clinical presentation, and treatment of alcohol-related liver disease, including alcohol-associated hepatitis.

Keywords
Alcohol use disorder, alcohol-related liver disease, alcohol-associated hepatitis, liver transplantation

Harmful alcohol consumption is associated with more than 200 diseases and injury-related health conditions, including chronic liver disease.[1] Not only is the rate of alcohol consumption increasing globally, but also the prevalence of alcohol use disorder (AUD) and alcohol-related liver disease (ALD). In fact, 1 in 12 adults in the United States report heavy alcohol consumption, which can be defined as more than 2 drinks per day for women and more than 3 drinks per day for men, or by participation in binge drinking (consumption of >5 drinks in men and >4 drinks in women over 2 hours).[1,2] In the United States, 1 drink is defined as 14 g of alcohol, which is found in 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of hard liquor. AUD includes binge drinking, heavy drinking, or any alcohol use by pregnant women or anyone younger than 21 years old.[3] AUD involves more than the number of drinks consumed or the type of alcohol consumed, however. To further define and characterize AUD, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* lists 11 different criteria (Table 1), with the severity of AUD defined by the number of criteria met.[4]

AUD and ALD are intertwined. Sustained, excessive alcohol use can cause inflammatory changes in the liver, leading to alcoholic steatohepatitis or alcohol-associated hepatitis (AH).[5] Although hepatic steatosis and

Table 1. *DSM-5* Criteria for AUD[61]

In the past year, have you:
1. Had times when you ended up drinking alcohol more, or longer, than you intended?
2. More than once wanted to cut down or stop drinking alcohol, or tried to, but could not?
3. Spent a lot of time drinking alcohol? Or being sick or getting over aftereffects?
4. Wanted an alcoholic drink so badly you could not think of anything else?
5. Found that drinking alcohol, or being sick from drinking alcohol, often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
6. Continued to drink alcohol even though it was causing trouble with your family or friends?
7. Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink alcohol?
8. More than once gotten into situations while or after drinking alcohol that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
9. Continued to drink alcohol even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
10. Had to drink alcohol much more than you once did to get the effect you want? Or found that your usual number of alcoholic drinks had much less effect than before?
11. Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, restlessness, nausea, sweating, a racing heart, or a seizure? Or sensed things that were not there?

Meeting at least 2 of these criteria indicates AUD. The severity of AUD is defined as: mild = meeting 2 to 3 criteria; moderate = meeting 4 to 5 criteria; and severe = meeting 6 or more criteria.

AUD, alcohol use disorder; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.

possibly fibrosis can be reversed with complete cessation of alcohol consumption, cirrhosis is nonreversible and can progress to further decompensation and hepatocellular carcinoma despite abstinence.[1] Approximately 10% to 20% of patients with ALD develop cirrhosis, with the highest risk in patients with AH.[6] Patients hospitalized with alcohol-related cirrhosis (AC) are twice as likely to die than patients hospitalized with any cause of cirrhosis (13.4% vs 7.3%).[7-9] With this growing burden of disease, understanding the diagnosis, clinical manifestations, and treatment options for both AUD and ALD is essential. This article reviews the diagnosis and treatment of AUD as well as the pathophysiology, clinical presentation, and treatment of ALD, including AH.

Diagnosis of Alcohol Use Disorder

In a national epidemiologic survey of more than 43,000 participants in the United States, prevalence of AUD increased by almost 35% in women from 2001 or 2002 to 2012 or 2013.[10] Similar drastic increases in rates of AUD were noted in ethnic minorities and participants of lower socioeconomic status. As such, screening for and assessing the level of alcohol use in patients before the development of ALD is of utmost importance. This is best accomplished by obtaining a detailed history of alcohol consumption, which can be limited by underreporting. The National Institute on Alcohol Abuse and Alcoholism recommends a single-question screen of "How many times in the past year have you had 5 or more drinks in a day (for men) or 4 or more drinks in a day (for women)?"[11] If 1 or more episode is reported, further questioning using the Alcohol Use Disorders Identification Test (AUDIT) is recommended. This includes 10 questions on consumption patterns, dependence symptoms, and any alcohol-associated problems.[12] AUDIT has been shown to detect harmful alcohol use in patients who score 8 or higher, or moderate or severe AUD in patients scoring higher than 15 (Table 2).

Completion of AUDIT, however, can be time-consuming for both providers and patients. Alternatively, AUDIT-C, a shorter version consisting of 3 questions, has been developed and validated.[13] Although AUDIT-C cannot provide information on severe alcohol use, it has been shown to perform better than the Cut, Annoyed, Guilty, and Eye (CAGE) questionnaire in identifying alcohol misuse.[14] In a prospective single-site study, patients' alcohol use was assessed using 3 different sources of information: interview by hepatologist, AUDIT-C score, and visit with addiction specialist.[15] Total alcohol consumption, defined as the aggregate of occasional, regular, and excessive drinking, was identified in 21.9% of patients by the hepatologist compared with 36.8% using AUDIT-C, and in 41.1% by the addiction specialist.

Table 2. Alcohol Use Disorders Identification Test

	0 Points	1 Point	2 Points	3 Points	4 Points
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times per month	2-3 times per week	4 or more times per week
How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
How often do you have 6 or more standard drinks on 1 occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the past year have you found that you were not able to stop drinking alcohol once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the past year have you failed to do what was normally expected of you because of drinking alcohol?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the past year have you needed an alcoholic drink first thing in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the past year have you had a feeling of guilt or remorse after drinking alcohol?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
How often during the past year have you been unable to remember what happened the night before because of drinking alcohol?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
Have you or someone else been injured because of your drinking alcohol?	No		Yes, but not in the past year		Yes, during the past year
Has a relative, friend, doctor, or other health care worker been concerned about your drinking alcohol or suggested you cut down?	No		Yes, but not in the past year		Yes, during the past year

A score of 1 to 7 points suggests low-risk alcohol consumption. A score of 8 to 14 points suggests hazardous or harmful alcohol consumption. A score of 15 or more points indicates the likelihood of alcohol dependence (moderate-severe alcohol use disorder).

Additionally, screening for psychiatric comorbidities and abuse of other substances is essential, as these have been shown to occur at higher rates in patients with AUD and can have important implications for maintenance of abstinence and improving long-term outcomes. In a study of more than 10,000 patients with AUD, 47% reported anxiety, 43% reported depression, and 17% reported psychiatric comorbidities.[4] In another survey of US veterans, prevalence of tobacco use increased as severity of AUD rose, further illustrating the importance of screening for other substance abuse conditions in patients with AUD.[16]

Treatment of Alcohol Use Disorder

Although the severity of liver disease at the time of presentation is a major factor in determining short-term mortality in AH, long-term prognosis of AH and ALD depends on continued abstinence.[17] The adverse effect of ongoing alcohol use on mortality in patients with ALD highlights the importance of AUD treatment,[17] which can include inpatient alcohol rehabilitation, group therapy, individual therapy, and family or couples counseling. Throughout these different sessions, various strategies of

behavioral change can be introduced, including cognitive behavioral therapy, motivational interviewing, and motivational enhancement therapy.[5] In addition, there are several medications that may be administered for relapse prevention. Options approved by the US Food and Drug Administration (FDA) include naltrexone, disulfiram, and acamprosate. Gabapentin, baclofen, topiramate, ondansetron, and varenicline can also be used, but they have not been approved by the FDA for AUD treatment.[5]

Both pharmacologic therapy and behavioral therapy have shown significant efficacy. Mellinger and colleagues studied the effects of AUD treatment utilization on decompensation in more than 66,000 patients with AC.[18] In this study, patients who had a clinic visit for AUD treatment or used FDA-approved relapse medication demonstrated decreased risk of decompensation at 1 year (hazard ratio [HR], 0.85; P<.001 for each). However, only 10% of patients in this study received a face-to-face mental health or substance abuse visit, and only 0.8% received an FDA-approved relapse prevention medication within 1 year of index diagnosis.

Additionally, alcohol biomarkers can provide further objective information and support patients through recovery. Moieties in the urine, blood, or hair can identify metabolites or surrogates of alcohol use and provide further information regarding the time frame of alcohol use. Commonly used biomarkers include phosphatidylethanol, which has a half-life of 10 to 14 days but can be detected longer in patients with chronic, repeated heavy alcohol consumption,[5,19] and urine ethyl glucuronide and urine ethyl sulfate. Phosphatidylethanol is more commonly used and can provide additional information on the amount of alcohol consumed, with lower levels correlating with light or no drinking. Testing of phosphatidylethanol levels has been validated in patients with chronic liver disease at a cutoff of 80 ng/mL for at least 4 drinks per day, with a sensitivity of 91% and specificity of 77%,[20] and therefore can accurately detect surreptitious alcohol use. Although both ethyl glucuronide and ethyl sulfate metabolites are excreted in the urine, they can also be found in blood and hair. Ethyl glucuronide and ethyl sulfate metabolites can usually detect alcohol use up to 5 days prior to testing, but it should be noted that detection times can be prolonged in renal failure, resulting in a longer window of positive results after alcohol ingestion in patients with kidney disease. The development of biomarkers has been pivotal in diagnosing and supporting recovery in patients with AUD and ALD. However, to maintain a therapeutic relationship between provider and patient and improve alcohol use disclosure, the American Association for the Study of Liver Diseases (AASLD) recommends discussing biomarker use with patients before testing.

Pathophysiology of Alcohol-Related Liver Disease

The impact of alcohol on liver disease is complex and multifactorial. The amount of alcohol consumed is correlated with the risk of cirrhosis, with a higher rate of ALD for a given amount of alcohol in women compared with men.[9,21] In a meta-analysis of 7 cohort studies and 2 case-control studies, consumption of 1 drink per day showed an increased risk for liver cirrhosis in women when compared with those who abstain from alcohol consumption long term. Drinking 5 or more drinks per day was associated with a substantially increased risk of cirrhosis in both men (relative risk [RR], 3.80; 95% CI, 0.85-17.02) and women (RR, 12.44; 95% CI, 6.65-23.27).[22] Mechanisms involving hepatocyte damage owing to alcohol and its metabolites, and recruitment and activation of innate immune cells, Kupffer cells, and recruited macrophages and neutrophils in the liver have been implicated in the pathogenesis of ALD.[23] Excessive alcohol use results in the continued presence of these factors, which leads to ineffective anti-inflammatory pathways and eventual activation of stellate cells and myofibroblasts in the liver. These processes can cause fibrosis and AC.

Alcohol is absorbed in the gastrointestinal tract and metabolized in hepatocytes by alcohol dehydrogenase and acetaldehyde dehydrogenase, ultimately yielding acetate. Both enzymes become saturated after 3 to 4 drinks of alcohol, and alternative mechanisms of alcohol metabolism are subsequently activated. These alternative pathways produce high levels of reactive oxygen species and reduced levels of intracellular antioxidants. Additionally, chronic excessive alcohol consumption and binge drinking can lead to downregulation of hepatic β oxidation of fatty acids and progressive fat accumulation, which can often lead to inflammation and steatohepatitis. Alcohol use can also damage and activate apoptotic pathways in hepatocytes, resulting in the release of damage-associated molecular patterns, which are recognized in the liver as danger signals and cause a proinflammatory cascade response.[23] Further, recruitment of circulating and bone marrow–derived monocytes, macrophages, and neutrophil leukocytes into the liver produces proinflammatory cytokines, a histologic hallmark of acute AH. Inflammatory cells in the liver sinusoids result in activation of stellate cells and myofibroblasts, leading to deposition of collagen, liver fibrosis, bridging fibrosis, and cirrhosis.

In the intestinal lumen, alcohol can disrupt the tight junctions of the epithelial barrier, creating what is termed a leaky gut. This results in translocation of microbial products from the intestine to the portal circulation and liver. Increased levels of lipopolysaccharide, a component

of the outer wall of gram-negative bacteria, have been found in animal models and humans with acute binge drinking and chronic alcohol use. Lipopolysaccharide is recognized by toll-like receptor 4 on macrophages and activates further inflammatory signaling pathways.[23]

Despite these mechanisms of injury, only 35% of patients with harmful alcohol use develop steatohepatitis and AH, and only 10% to 20% develop cirrhosis, suggesting the presence of concomitant risk factors. Bellentani and colleagues demonstrated that patterns of drinking such as drinking outside mealtimes, drinking hard liquor or beer, and binge drinking are associated with a higher risk of advanced ALD.[24] Women have been identified to be at greater risk for ALD, with increased risk associated with consumption of 20 g to 40 g of alcohol per day compared with 60 g to 80 g for men.[5] These sex-based differences may be owing to variations in alcohol metabolism, body fat distribution, liver volume, and influence of sex hormones on inflammatory responses. Studies of monozygotic twins have demonstrated genetic susceptibility as well. Polymorphisms in genes regulating alcohol metabolism such as alcohol dehydrogenase 2 (*ADH2*) and aldehyde dehydrogenase 2 (*ALDH2*) have been strongly linked to risk of AUD but have not been shown to increase risk of liver disease.[5,25] Patatin-like phospholipase domain–containing protein 3 (*PNPLA3*) polymorphisms and membrane-bound O-acyltransferase domain–containing 7 (*MBOAT7*) genes, on the other hand, have been associated with increased risk of AC and AH.[5,26-29] Ethnic predisposition can also have an impact, as studies have demonstrated increased risk of developing alcoholic steatohepatitis and AH in Hispanic participants compared with non-Hispanic White and African-American participants.[5,30,31] Finally, other concomitant liver diseases can accelerate ALD and promote rapid development of advanced fibrosis and cirrhosis, particularly in patients with nonalcoholic fatty liver disease, hepatitis C, and hemochromatosis.[23]

Clinical Presentation and Diagnosis of Alcohol-Related Liver Disease

ALD is defined as a clinical histopathologic spectrum ranging from steatosis, AH, and liver fibrosis ultimately leading to cirrhosis. ALD can be difficult to diagnose clinically because many patients may not disclose alcohol use and most patients remain either asymptomatic with silently progressive disease or present with nonspecific symptoms such as fatigue. As such, patients with significant alcohol use should be evaluated for possible ALD, which includes screening with serum liver tests and ultrasonography. In patients with ALD, transaminase levels are generally below 400 IU/L, with an elevated aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio.[9]

Even after taking a clinical history of a patient's alcohol intake, differentiating between nonalcoholic fatty liver disease and ALD can remain challenging. Because many patients may not disclose alcohol use, clinicians should have a high clinical suspicion for AH, particularly in patients who present with acute jaundice, AST greater than ALT, and high international normalized ratio. Additionally, discriminant indices, such as the ALD/nonalcoholic fatty liver disease index, have been developed to help differentiate these clinical entities.

Alcohol-Associated Steatosis

Patients with alcohol-associated steatosis tend to remain asymptomatic. Although an enlarged liver may be found on physical examination, elevated levels of AST and γ-glutamyltransferase (GGT) are often the best indicators of recent excessive alcohol consumption. Steatosis can be seen on various imaging modalities, and therefore liver biopsy is generally not needed for diagnosis of alcohol-associated steatosis. Although liver ultrasonography detects moderate to severe steatosis with a sensitivity and specificity of 90%,[9,32] magnetic resonance imaging can more accurately quantify fat, given its ability to assess fat throughout the entire volume of the liver.[5,33]

Alcohol-Related Cirrhosis

Seventy percent of patients with compensated AC are asymptomatic, and physical examination may reveal hepatosplenomegaly, spider angioma, and muscle wasting.[9,34] Laboratory studies can also be helpful in deciphering early ALD with elevated mean corpuscular volume, AST, ALT, alkaline phosphatase, or GGT, whereas elevated bilirubin or prothrombin time or decreased albumin or platelet count can suggest advanced ALD with development of portal hypertension. Cirrhosis will often be diagnosed at times of decompensating events, such as ascites, jaundice, gastrointestinal bleeding, hepatic encephalopathy, or development of hepatocellular carcinoma.[5,9] In patients without decompensation, fibrosis can be assessed using the Enhanced Liver Fibrosis (ELF) score or the FibroTest, both of which combine serum laboratory values into specific algorithms. For a cutoff of 10.5, the ELF score has a specificity of 79% for F3 fibrosis and 91% for F4 fibrosis. For a cutoff of 0.58, the FibroTest has a specificity of 67% for F3 fibrosis and 89% for F4 fibrosis.[9,35] Radiologic studies such as transient elastography, which uses velocity of shear waves in the liver tissue to determine liver stiffness, can also be used to estimate the extent of fibrosis. Using a threshold value of 15 kilopascals in individuals with harmful alcohol use, transient elastography has a sensitivity of

86% and specificity of 95% for diagnosis of advanced fibrosis or cirrhosis. However, it is important to screen for active alcohol use prior to these testing modalities, as liver stiffness can decrease with 2 weeks of abstinence.[9,36] Additionally, the threshold value for detection of fibrosis may need to be adjusted according to AST and bilirubin levels, as elevations reflect hepatic inflammation that may overestimate the degree of fibrosis present.[9,35,37] Magnetic resonance elastography, another radiologic test to assess fibrosis, utilizes magnetic resonance imaging with low-frequency vibration to evaluate liver stiffness. Although it serves as a useful tool, particularly in patients with obesity or ascites, magnetic resonance elastography is overall limited by cost and availability.[9]

Alcohol-Associated Hepatitis

Patients with AH can have a broad spectrum of presentation ranging from jaundice to liver failure. Regardless of clinical presentation, the presence of AH is associated with the fastest rate of disease progression and, in severe cases, higher risk of acute or chronic liver failure. In the absence of symptoms, the diagnosis of AH depends on histologic findings. In symptomatic AH, patients typically present with jaundice, serum bilirubin levels greater than 3 mg/dL, and elevated transaminase levels (but typically <400 IU/L) with elevated AST to ALT ratio, and have consumed at least 1 alcoholic drink within 8 weeks of presentation of jaundice.[5] Prior to making a diagnosis of AH, other causes of liver disease, biliary obstruction, and hepatocellular carcinoma should be ruled out.[9,38] Although symptomatic patients with AH can be identified by these criteria, liver biopsy may be needed in uncertain cases. Further, patients with AH may or may not have underlying cirrhosis, which can be difficult to clinically distinguish. Noninvasive measures of fibrosis, particularly with AH, can overestimate fibrosis. Therefore, fibrosis should be assessed 6 months after discontinuation of alcohol in order to obtain an accurate assessment of disease severity.

Determining Prognosis

Several scoring systems have been developed to classify the severity of a patient's AH and guide treatment choices. Although clinical features such as ascites and jaundice can be helpful, laboratory parameters have been proven to be more predictive of outcomes in patients with AH.[17] Scoring systems such as Maddrey Discriminant Function (DF), Model for End-Stage Liver Disease (MELD), ABIC (age, serum bilirubin, international normalized ratio, creatinine) score, and Glasgow Alcoholic Hepatitis Score (GAHS) use these laboratory parameters to predict short-term mortality with great accuracy and help guide treatment decisions for patients with severe disease.[17] The DF was first published in 1978 and is currently used to guide initiation of corticosteroids in patients with severe AH. Short-term mortality for patients with DF less than 32, or nonsevere disease, is 10%, compared with 30% to 60% for patients with severe disease and DF greater than 32.[39] As a result, corticosteroids are typically initiated in patients with DF greater than 32, as this patient population is deemed to receive the greatest potential benefit from treatment.[39,40]

The GAHS, although only validated in the United Kingdom, helps select patients with severe AH who may benefit most from corticosteroid use. This scoring system incorporates age with leukocyte count, serum urea, bilirubin, and prothrombin time, and an overall score of 9 or greater is associated with poor prognosis. Patients with both DF greater than 32 and GAHS greater than 9 treated with corticosteroids had improved survival at 28 and 84 days, whereas patients with DF less than 32 and GAHS less than 9 had no survival benefit after treatment with corticosteroids.[41]

The Lille score was created to assess response to corticosteroid treatment. Using age, albumin, prothrombin time, and bilirubin on day 0 of treatment, and change in bilirubin at day 7 of treatment, a Lille score of less than 0.45 has been associated with 15% mortality at 6 months compared with 75% mortality for patients with a score of 0.45 or greater.[5] Therefore, a score of 0.45 or greater on day 7 of treatment indicates a lack of response to corticosteroids and should be used to guide cessation of treatment.[23,42] A retrospective study of a multinational cohort of patients with severe AH found that the use of the Lille score at day 4 is as accurate as day 7 in predicting response to corticosteroids as well as 28- and 90-day mortality.[43] Use of this score at an earlier time point can avoid prolonged, futile use of corticosteroids.

Although not used to guide treatment, the ABIC score can help make more nuanced survival prediction and has the additional benefit of use over different time points in patients with AH. Low-risk patients with ABIC scores of less than 6.71 are associated with a 90-day mortality of 0% compared with 75% in high-risk patients with scores of greater than 9.0.[44] Similarly, the MELD score, which was initially developed to predict mortality within 3 months of surgery in patients with transjugular intrahepatic portosystemic shunts, has been more commonly used as an independent predictor of patient survival. However, in a retrospective cohort study, Dunn and colleagues demonstrated that a MELD score of at least 20 had a sensitivity and specificity of 0.75 in predicting 90-day mortality in patients with AH.[45]

In addition to laboratory parameters, histologic grading can be helpful in cases in which biopsies were

performed. The Alcoholic Hepatitis Histologic Score provides a liver tissue–based AH prediction model that includes degree of fibrosis, degree of neutrophil infiltration, type of bilirubin stasis, and presence of megamitochondria.[46] Although this score provides an accurate prediction of 90-day mortality in low-, moderate-, and high-risk patients, significant interobserver variability and requirement of an invasive liver biopsy limits the utility of this scoring system.[47]

Despite the multitude of scores that are available, the AASLD only recommends using the DF and MELD score to guide initiation of corticosteroids.[5] Subsequently, if corticosteroids are initiated, the Lille score should be used to identify patients at risk of early nonresponse.

Treatment of Alcohol-Related Liver Disease

Treatment of Alcohol-Associated Hepatitis

Glucocorticoids have been the most-studied treatment in AH. The STOPAH trial randomized 1103 patients with severe AH in Europe between 2011 and 2014 to receive prednisolone 40 mg daily, pentoxifylline 400 mg 3 times daily, the combination of prednisolone and pentoxifylline, or placebo.[48] Overall, the study did not find a statistically significant survival benefit at 28 days in patients receiving corticosteroids compared with patients receiving placebo (17% in the placebo-placebo group, 14% in the prednisolone-placebo group, 19% in the pentoxifylline-placebo group, and 13% in the prednisolone-pentoxifylline group). However, on a post hoc multivariate analysis, corticosteroids were associated with improved 28-day survival (odds ratio, 0.61; *P*=.015), but not at 90 days or 1 year. The findings of this trial, in combination with other meta-analyses, provide moderate support for use of prednisolone but not pentoxifylline.

As mentioned earlier, if corticosteroids are used, the Lille score should be employed to identify patients who have a lower probability of benefit from extending treatment for more than 7 days. Additionally, patients should be carefully evaluated prior to initiation of corticosteroids, with close attention to development or presence of infection. Of note, in the STOPAH trial, serious infections occurred in 13% of the patients treated with prednisolone vs 7% of patients who did not receive prednisolone (*P*=.002).[48] Also, patients with acute kidney injury and gastrointestinal bleeding have been excluded from many clinical trials in AH, and therefore evidence of corticosteroids in patients with these illnesses is lacking overall. The AASLD recommends that if acute kidney injury resolves and gastrointestinal bleeding is controlled, prednisolone can be given safely.[5]

Further studies with concomitant corticosteroids and N-acetylcysteine treatment have shown lower mortality at 1 month (8% vs 24%; *P*=.006) and decreased rate of death owing to hepatorenal syndrome (9% vs 22%; *P*=.02) but no significant difference in mortality at 3 months (22% vs 34%; *P*=.06) or 6 months (27% vs 38%; *P*=.07).[49] Further studies, including a meta-analysis of 22 randomized controlled trials, have supported the addition of N-acetylcysteine to corticosteroids for reducing short-term mortality only.[50] Therefore, corticosteroids and N-acetylcysteine should be considered for use in patients with AH, although the combination treatment requires further validation.[5]

As the understanding of the pathophysiology of AH evolves, novel therapies based on mechanisms of injury are under consideration. 25-hydroxycholesterol 3-sulfate (larsucosterol), an epigenetic regulator, is currently under evaluation as a promising therapy for AH.[17] Reduction of inflammation mediated by the innate immune response via interleukin-1 receptor blockers has also been evaluated and showed promising results. Given the potential role of gut dysbiosis and translocation of bacterial products in patients with AH, probiotics and fecal microbiota transplantation are under evaluation as possible therapeutic options. In a small study of patients with AH, short-term supplementation of *Lactobacillus plantarum* and *Bifidobacterium bifidum* improved levels of AST, ALT, GGT, lactate dehydrogenase, and bilirubin.[51] Additionally, small studies have shown efficacy of fecal microbiota transplantation in AH, although concerns regarding possible infections continue to limit its use.[17,51,52] Lastly, stimulation of liver regeneration with granulocyte colony-stimulating factor is also currently being explored. In a pilot study of granulocyte colony-stimulating factor plus standard of care, including pentoxifylline, results demonstrated improved survival of 78.3% compared with 30.4% (*P*=.01) in patients treated with standard of care alone at 90 days.[17,53]

Liver Transplant

The evolution and perception of liver transplant (LT) in patients with ALD has dramatically changed during the past several years. At the 1997 consensus conference of the AASLD and American Society of Transplantation, waiting 6 months prior to listing for transplant (the 6-month rule) was justified, as experts believed this allowed ample time to evaluate a patient's commitment to alcohol abstinence as well as assess liver recovery and potentially negate the need for LT.[5,54] As a result, more than 85% of LT programs and 43% of third-party payers in the United States began requiring 6 months of abstinence before transplantation.[55-57] However, several studies have shown that, despite adherence to the 6-month rule, this approach did not reliably predict relapse posttransplant. In a study of 91 patients with AC, risk of relapse was predicted using

the High-Risk Alcoholism Relapse (HRAR) scale.[58] This scale can be used to predict relapse risk independent of duration of sobriety (based on number of years of heavy drinking, usual daily number of alcoholic beverages, and number of previous treatments), making it a useful tool to evaluate the validity of the 6-month rule. Yates and colleagues noted that, although relapse risk rates declined with increasing duration of sobriety, relapse risks were overall low even in patients with no period of alcohol abstinence in the low-risk HRAR group. In patients with high-risk HRAR scores, even 6 months of abstinence did not predict lack of relapse.[57,58]

Furthermore, patients with severe AH who do not respond to medical therapy have mortality rates as high as 70% at 6 months. The 6-month rule therefore placed these patients at a disadvantage.[42] Then in 2011, Mathurin and colleagues published findings of a seminal study of early LT (before 6 months of alcohol abstinence) from 7 centers in France and Belgium.[59] Patients were required to meet strict criteria, which included no prior episodes of AH, Lille score of 0.45 or higher, supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence. Survival was compared between patients who underwent early LT and matched patients who did not. In 26 patients, the cumulative 6-month survival rate was higher among patients who received early LT than among patients who did not (77±8% vs 23±8%; P<.001). This benefit of early LT was maintained through 2 years of follow-up (HR, 6.08; P=.004).

These findings were confirmed by a retrospective study of AH by the American Consortium of Early Liver Transplantation, which is comprised of 12 centers from 8 United Network for Organ Sharing regions. Among 147 patients with severe AH and no prior diagnosis of liver disease who received LT before 6 months of alcohol abstinence, the cumulative patient survival after LT was 94% at 1 year (95% CI, 89%-97%) and 84% at 3 years (95% CI, 75%-90%). The cumulative incidence of sustained alcohol use was 10% at 1 year (95% CI, 6%-18%) and 17% at 3 years (95% CI, 10%-27%) after LT.[60] Ultimately, these findings support the selective use of LT as a treatment option for severe AH, but future studies are still needed to optimize outcomes for patients with severe AH undergoing LT.

One major challenge regarding LT in AH is predicting alcohol relapse posttransplant. Several assessment scores have been proposed, including the Stanford Integrated Psychosocial Assessment for Transplant, Alcohol Relapse Risk Assessment, and Sustained Alcohol Use Post-LT score. However, given the complexity of AUD, evaluation by a multidisciplinary team is essential because no single score or measure can reliably predict the risk of relapse posttransplant.

Conclusion

With the rising prevalence of AUD and ALD, clinicians must understand the validated screening tools available as well as diagnostic and treatment options. Although current research has elucidated multiple mechanisms of pathogenesis, novel therapies are still under review for treatment of ALD and AH. Currently, initiation of corticosteroids remains the mainstay treatment for AH, but this option is available to a narrow patient population and has limited efficacy. For patients with severe AH refractory to medical therapy, many centers have developed protocols for LT. Although LT has proven to be an effective treatment for select patients, identification of patients at high risk for post-LT alcohol relapse is an area of ongoing research. Treatment of AUD and AH remains an unmet medical need, and better treatment options for afflicted patients are awaited.

Disclosures

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