# Current Management of Alcohol-Associated Liver Disease

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**Abstract:** Alcohol consumption is a major risk factor for various diseases worldwide and is one of the most common causes of chronic liver disease. Alcohol use has risen over the past 30 years and is forecast to continue to rise. Concurrently, there has been an increased incidence of alcohol-associated liver disease (ALD). Alcohol use, regardless of the amount, leads to years of health loss across populations when considering the strong association between alcohol consumption and overall disease burden. Given the rising incidence of ALD and associated mortality, it is imperative to study the underlying factors driving these trends. This article summarizes the diagnosis and management of ALD, with a focus on various screening and prognostic tools and treatments for alcohol-associated hepatitis.

Keywords
Alcohol-associated liver disease, alcoholic hepatitis, alcohol-associated hepatitis, alcoholic cirrhosis, cirrhosis, liver transplantation

Alcohol consumption is a major risk factor for various diseases globally and is linked to more than 200 acute and chronic disease processes.[1,2] It is also one of the most common causes of chronic liver disease. From 1990 to 2017, the annual adult-per-capita consumption increased by 0.6 liters and is forecast to reach 7.6 liters by 2030.[3] Alcohol use is expected to continue to rise, predominantly in middle- and upper-income countries such as India, China, and the United States.[4]

Concurrently with the rise of alcohol use has been an increased incidence of alcohol-associated liver disease (ALD). Due to improved screening, treatment availability, and public health interventions, there has been a decline in other causes of acquired chronic liver diseases, such as chronic hepatitis C virus infection, which used to be one of the most common reasons for liver transplants globally. A meta-analysis of patients on the liver transplant waiting list revealed that the number of patients with ALD is increasing while the number of patients with chronic hepatitis C virus infection is decreasing.[5]

ALD presents as a broad spectrum of disorders, from fatty liver or steatosis (with or without steatohepatitis) to severe forms of liver

**Table 1.** *DSM-5* Criteria for Alcohol Use Disorder[22,a]

| |
|---|
| 1. Have you ever drunk more or for longer than you intended? |
| 2. More than once, have you wanted or tried to cut down or stop drinking, but could not? |
| 3. Have you spent a lot of time drinking or being sick/recovering from the aftereffects of drinking? |
| 4. Have you ever experienced a craving (ie, a strong need or urge) to drink? |
| 5. Have you found that drinking, or being sick from drinking, often interfered with taking care of your home or family, or caused problems with your job or at school? |
| 6. Have you continued to drink even though it was causing problems with your family or friends? |
| 7. Have you given up or cut back on activities that were important or interesting to you in order to drink? |
| 8. More than once, have you gotten into situations while or after drinking that increased your chances of getting hurt (eg, driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)? |
| 9. Have you continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Have you continued to drink after having a memory blackout? |
| 10. Have you had to drink much more than you once did to get the effect you want, or found that your usual number of drinks had much less effect than before? |
| 11. Have you found that when the effects of alcohol were wearing off, you had withdrawal symptoms (eg, trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating)? Have you sensed things that were not present? |

*DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition.

[a]The severity of alcohol use disorder is characterized based on the number of criteria met, with mild being 2-3 criteria, moderate being 4-5 criteria, and severe being ≥6 criteria.

injury, including alcohol-associated hepatitis (AH), cirrhosis, and hepatocellular carcinoma.[6] ALD is thought to be responsible for nearly half of liver-related mortalities globally.[7] According to the 2018 global status report of alcohol published by the World Health Organization, AH and liver cirrhosis are associated with a particularly high rate of mortality, reaching up to 50% in severe acute AH.[8] As such, the global disease burden for ALD is soaring. In 2016, approximately 21.5 million years of life were lost due to ALD (measured as disability-adjusted life years).[9] These years were lost primarily due to premature death as opposed to disability. Death related to liver cirrhosis is projected to triple by the end of 2030, driven largely by the increasing prevalence of ALD and nonalcoholic fatty liver disease.[9] The overall number of hospitalizations and overall inpatient costs of individuals with a primary or secondary ALD have also increased over the last 10 to 15 years; there were 249,884 AH-related hospitalizations in 2002 compared to 326,403 in 2010.[10] Individuals with ALD usually present with a more serious illness and are admitted more frequently for liver-related issues.[10]

Given the rising incidence of ALD and associated mortality, it is imperative to identify the underlying factors driving these trends, beginning with behaviors related to alcohol use. This article focuses primarily on how to approach the diagnosis and management of ALD, and includes a discussion of various screening and prognostic tools and a review of pharmacologic therapy, nutritional therapy, and liver transplantation (LT) for AH.

## Alcohol Use

Excessive alcohol use or alcohol abuse has been renamed alcohol use disorder (AUD). AUD is the most common cause of ALD, and includes binge drinking, heavy drinking, and any alcohol use by pregnant women or anyone younger than 21 years of age. The National Institute on Alcohol Abuse and Alcoholism and the Centers for Disease Control and Prevention (CDC) define binge drinking as consuming 4 or more drinks on 1 occasion for women and 5 or more drinks on 1 occasion for men, whereas heavy drinking is defined as consuming 8 or more drinks per week for women and 15 or more drinks per week for men.[11,12] Patients with AH typically have a history of daily heavy alcohol use for more than 20 years.[13]

Previous studies have shown a dose-dependent relationship between alcohol use and ALD. In 1996, Becker and colleagues demonstrated that the relative risk of developing ALD significantly increased by consuming 7 to 13 alcohol-containing beverages per week for women and 14 to 27 alcohol-containing beverages per

**Table 2.** Questions Asked in the Alcohol Use Disorders Identification Test–Consumption[25]

| | |
|---|---|
| How often did you have a drink containing alcohol in the past year? | Never: 0 points<br>Monthly or less: 1 point<br>2-4 times/month: 2 points<br>2-3 times/week: 3 points<br>≥4 times/week: 4 points |
| How many drinks containing alcohol did you have on a typical day when you were drinking in the past year? | 1-2 drinks: 0 points<br>3-4 drinks: 1 point<br>5-6 drinks: 2 points<br>7-9 drinks: 3 points<br>≥10 drinks: 4 points |
| How often did you have ≥6 drinks on 1 occasion in the past year? | Never: 0 points<br>Less than monthly: 1 point<br>Monthly: 2 points<br>Weekly: 3 points<br>Daily or almost daily: 4 points |
| **Total score** | **≥4 in men: positive**<br>**≥3 in women: positive** |

week for men.[14] It was once postulated that moderate consumption of alcohol was cardioprotective, although recent research has shown nonsignificant or no protective effects of drinking alcohol on all-cause mortality or cardiovascular outcomes.[15] Alcohol use, regardless of the amount, leads to years of health loss across populations when considering the strong association between alcohol consumption and overall disease burden.[16] Based on dietary guidelines published by the US Department of Health and Human Services, women should consume no more than 1 alcohol-containing drink in a single day, and men should consume no more than 2 drinks in a single day.[17] These recommendations were endorsed by the CDC as a measure to reduce alcohol-related morbidity.[18]

The frequency of alcohol consumption also affects the degree of liver disease and associated mortality. Studies conducted in Denmark[19] and Japan[20] have shown that given the same amount of overall alcohol exposure in volume, daily drinking was associated with a higher risk of alcohol-associated cirrhosis and higher all-cause mortality. Thus, it is recommended to incorporate liver holidays, or days without any alcohol consumption, to avoid continuous damage to the liver.

## Screening and Diagnosis of Alcohol Use Disorder

It is imperative that excessive alcohol use be identified early in patients at increased risk for ALD. There is a strong correlation between AUD and ALD.[21] According to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, as published by the American Psychiatric Association in 2013, AUD is defined as maladaptive behavior characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences.[22] AUD is diagnosed when a patient meets at least 2 out of 11 criteria for at least 12 months, and is further characterized as mild, moderate, or severe based on the number of criteria met (Table 1).[22] Along with identifying AUD, clinicians must be able to recognize risky and hazardous alcohol use.

According to the US Preventive Services Task Force (USPSTF), screening for unhealthy alcohol use accompanied by a brief intervention should be routine protocol in the primary care setting.[23] Time constraints are often a barrier to widescale screening of patients for alcohol use, making comprehensive surveys, such as the Alcohol Use Disorders Identification Test (AUDIT),[24] difficult to administer. Therefore, the USPSTF determined that 1- to 3-item screening tools are ideal for assessing unhealthy alcohol use in adults 18 years of age or older.[23] These tools include the abbreviated Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) and the Single Alcohol Screening Question (SASQ).[25,26]

AUDIT-C has 3 questions regarding the frequency of alcohol use, typical amount of alcohol use, and occasions of heavy use, each with 5 answer choices with point values ranging from 0 to 4 (Table 2). Bush and colleagues demonstrated that AUDIT-C had a higher area under the receiver operating characteristic (ROC) curve (0.89)

**Table 3.** Scoring Systems to Measure the Severity of Alcohol-Associated Hepatitis

| | |
|---|---|
| **Modified discriminant function** | |
| 4.6 × (prothrombin time – control time) + serum bilirubin | Score >32: severe |
| **Model for End-Stage Liver Disease score** | |
| 3.78 × Ln(serum bilirubin) + 11.2 × Ln(INR) + 9.57 × Ln(serum creatinine) + 6.43 | Range, 6-40<br>Score >21: increased severity |
| **ABIC score** | |
| (age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8) | <6.71: low risk<br>6.71-9.00: intermediate risk<br>>9.00: high risk |
| **Glasgow alcoholic hepatitis score** | |
| Age:<br><50 years: 1 point<br>≥50 years: 2 points<br>BUN:<br><14 mg/dL: 1 point<br>>14 mg/dL: 2 points<br>Peripheral blood leukocyte count:<br><15 $10^3$/μL: 1 point<br>>15 $10^3$/μL: 2 points<br>Serum bilirubin:<br><7.3 mg/dL: 1 point<br>7.3-14.6 mg/dL: 2 points<br>>14.6 mg/dL: 3 points<br>Prothrombin time:<br><1.5: 1 point<br>1.5-2.0: 2 points<br>>2.0: 3 points | <9: 87% survival at 28 days<br>≥9: 46% survival at 28 days |

ABIC, age, serum bilirubin, INR, and serum creatinine; BUN, blood urea nitrogen; INR, international normalized ratio; Ln, natural logarithm.

than the full AUDIT questionnaire, which is composed of 10 questions.[24] Bradley and colleagues later validated the superior performance of AUDIT-C in their study of a female Veterans Affairs patient population; they found that the sensitivity and specificity of the gender-specific AUDIT-C were 0.81 and 0.85, respectively.[25]

The SASQ asks when was the last time a patient had more than 4 drinks (for women) or 5 (for men) in 1 day (a standard drink in the United States contains 14 g of ethanol).[26] A response of more than 1 is considered positive. Williams and colleagues demonstrated that the SASQ had a sensitivity and specificity of 0.86 each in identifying excessive alcohol use and AUD. The authors also found that the questionnaire had an area under the ROC curve of 0.9.[26]

## Severity of Alcohol-Associated Hepatitis

Given the spectrum of ALD and the high risk of adverse outcomes related to ALD, several tools have been developed over the last 40 years to help classify the severity of AH. One of the earliest tools developed to assess the severity of AH was the Maddrey discriminant function (DF) score. In a randomized, double-blind treatment trial published in 1978, Maddrey and colleagues showed that prednisolone reduced early mortality and subsequent cirrhosis in survivors of acute AH.[27] Early mortality was most significantly associated with prolonged prothrombin time and elevated serum bilirubin, which formed the DF formula (4.6 × prothrombin time [sec] + serum bilirubin [mg/dL]).[27] In 1989, Carithers and colleagues proposed a modified discriminant function (mDF) using the formula 4.6 × (prothrombin time – control time) + serum bilirubin, with a mDF score greater than 32 considered to be severe AH (Table 3).[28] In a randomized, double-blind, multicenter trial, AH patients with a mDF score greater than 32 and/or encephalopathy received prednisolone therapy. The 28-day mortality of the treatment group was 6% vs 35% in the control group.[28] Rahimi and colleagues compared

various prognostic models for AH and determined that the prognostic performance of mDF in predicting mortality was accurate only 66.6% of the time.[29] Despite its limitations, mDF has been used as an inclusion criterion in most modern therapeutic trials for AH.

The Model for End-Stage Liver Disease (MELD) is a scoring system developed to predict mortality within 3 months of surgery in patients who have undergone a transjugular intrahepatic portosystemic shunt procedure,[30] and was validated as an independent predictor of patient survival in candidates for LT.[31] MELD score has been used to assess disease severity in patients with AH (Table 3). In 2005, Dunn and colleagues showed that MELD was comparable to mDF in predicting 30- and 90-day mortality in patients with AH. In this study, a MELD score of 21 had a sensitivity and a specificity of 0.75 in predicting 90-day mortality.[32] Of note, the MELD threshold for initiating corticosteroids and other therapies has not been established.

In 2008, Dominguez and colleagues developed a new prognostic scoring system that comprises age, serum bilirubin, international normalized ratio (INR), and serum creatinine, known as the ABIC score, using the following formula: (age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8) (Table 3). Using Kaplan-Meier analysis with cutoff values of 6.71 and 9.00, the ABIC score identified patients with AH who have a low risk (100% survival), intermediate risk (70% survival), and high risk (25% survival) of death at 90 days. The sensitivity and specificity were 1.0 and 0.5, respectively, for the cutoff of 6.71, and 0.70 and 0.33, respectively, for the cutoff of 9.00.[33]

The Glasgow alcoholic hepatitis score (GAHS) is a scoring system for AH developed in 2005 by Forrest and colleagues using 5 variables: age, blood urea nitrogen, peripheral blood leukocyte count, serum bilirubin, and prothrombin time, expressed as a ratio of the control value.[34] Scores range from 5 to 12, with patients separated into those with less than 9 or at least 9 points. The survival at 28 days in patients with AH with a day 1 GAHS of less than 9 was 87% compared to 46% in patients with a GAHS of 9 or greater (Table 3). The sensitivity and specificity of a 90-day outcome for GAHS assessment on admission were 0.67 and 0.78, respectively.[34]

## Treatment for Alcohol-Associated Hepatitis

The mainstay of management for acute AH is alcohol abstinence and managing any secondary complications related to cirrhosis or acute liver injury. These complications include coagulopathy, encephalopathy, renal failure, and infections, and may require admission to an intensive care unit (ICU). All patients with severe AH should have blood, urine, and ascites culture tests regardless of fever.[35] Monitoring for alcohol withdrawal is also important. Only a few medical therapies exist for AH, and even fewer have shown significant benefit. Management of chronic ALD is similar to that of other chronic liver diseases, with a focus on alcohol abstinence.

### *Pharmacologic Therapy*

The STOPAH trial, conducted in the United Kingdom in 2015, was a multicenter, prospective, double-blind, randomized, controlled study evaluating pentoxifylline and prednisolone for the treatment of AH.[36] The trial included 1103 patients with severe AH based on clinical diagnosis with a mDF score of at least 32. Treatment with prednisolone was associated with a decreased 28-day mortality compared to placebo (odds ratio [OR], 0.72), but this was not statistically significant (*P*=.06). Prednisolone did not demonstrate change in mortality at 90 days and 1 year. Use of pentoxifylline did not improve survival.[36] Although prednisolone can be considered for short-term mortality benefit, its long-term benefit is unknown. The use of prednisolone should be weighed against the risk of infection and other adverse events from glucocorticoids.

The antioxidant N-acetylcysteine has been studied in combination with glucocorticoids in a multicenter, randomized, controlled trial.[37] A total of 174 patients with severe AH were randomized to receive either prednisolone alone or in combination with N-acetylcysteine. Prednisolone in combination with N-acetylcysteine had improved survival at 1 month (hazard ratio [HR], 0.58; *P*=.006) but not at 6 months (HR, 0.62; *P*=.07). At 6 months, the use of prednisolone with N-acetylcysteine as compared to prednisolone alone had a decreased rate of hepatorenal syndrome (OR, 0.41; *P*=.02) as well as decreased mortality from hepatorenal syndrome (OR, 2.79; *P*=.02).[37] Although there appears to be benefit in regard to hepatorenal syndrome and short-term survival, further studies are needed to recommend this regimen for the long-term treatment for acute AH.

The use of beta-blockers was associated with worsening renal function among patients with severe AH. Serste and colleagues retrospectively studied 139 patients with severe AH, 48 of whom received a nonselective beta-blocker.[38] There was no difference in transplant-free mortality at approximately 6 months (56.8% in the beta-blocker group vs 46.7% in the group without; *P*=.25). However, the incidence of acute renal injury was significantly increased at approximately 6 months (89.6% in the beta-blocker group vs 50.4% in the group without; *P*=.0001). Therefore, use of beta-blockers in the treatment of severe AH is not recommended.[38]

### *Nutritional Therapy*

Patients with ALD are frequently malnourished, and the degree of malnutrition has been associated with increased morbidity and mortality among patients with AH. Malnutrition and sarcopenia, which is a loss of muscle and/or fat mass, are defined by loss of body weight, strength, protein levels (albumin, prealbumin), and nutrient deficiencies. Guidelines from the European Society for Clinical Nutrition and Metabolism recommend that nutritional therapy be provided to patients with severe AH to improve patient overall survival.[39] Oral nutritional therapy, such as oral protein supplements, is a preferred method for patients with severe AH who do not meet their daily caloric requirement via their meals. Enteral nutrition, such as nasogastric or nasojejunal feeding, is recommended for patients with AH who have swallowing difficulties or nausea and/or vomiting. Parenteral nutrition is recommended for profoundly malnourished patients with severe AH who have unprotected airways due to encephalopathy or who are not candidates for oral nutritional therapy or enteral nutrition therapies.[39]

Factors contributing to poor nutrition include the amount and duration of alcohol use, reduced oral intake, hypermetabolism, direct effects of alcohol on skeletal muscle metabolism, slowed gut motility, and malabsorption.[40] In acute AH, hepatocellular dysfunction, end-organ failure, and impaired metabolism of macronutrients all play an additional role resulting in malnutrition. Micronutrient deficiencies, including zinc; folate; thiamine; pyridoxine; and vitamins A, B12, D, and E, are common among patients with AH due to poor dietary habits and impaired absorption. Thiamine should be administered early and prior to glucose administration to prevent Wernicke encephalopathy and Korsakoff psychosis. Supplementation of branched-chain amino acids (BCAAs) has been studied previously, but evidence does not support better outcomes when they are used in acute liver failure. There are no randomized trials on BCAAs in severe AH, and available data only involve intravenous BCAAs, which did not reveal a mortality benefit.[41]

Zinc deficiency is common in patients with ALD and AH. There is no zinc storage in the human body, and daily intake of zinc from nutrition is vital. Zinc is an essential trace element with anti-inflammatory and antioxidant properties. Zinc homeostasis is regulated by the liver, and zinc deficiency can lead to abnormalities in metabolism, hepatic steatosis, and hepatic encephalopathy. Zinc supplementation in malnourished patients with severe AH is recommended to improve clinical outcomes.[42]

Quantification of the amount of caloric or protein intake in malnourished patients with severe AH is not clear. A randomized, controlled trial of ICU patients with severe AH to evaluate the addition of intensive enteral nutrition (1500-3000 kcal/day depending on body weight) to glucocorticoids did not show improvement in survival.[43] This study was limited by nearly half of the patients in the study arm prematurely removing their feeding tube. However, patients consuming less than 21.5 kcal/kg/day had a significantly higher mortality at 6 months ($P$<.0001), indicating the importance of adequate caloric intake.[43] Preventing prolonged fasting with daytime and late-evening snacks also helps reduce sarcopenia.[44]

### *Liver Transplantation*

LT for ALD has become increasingly common due to the rise in incidence of ALD. ALD is now the most common reason for LT in the United States, replacing hepatitis C virus infection.[45] A large national cohort study evaluated all liver transplants from the United Network for Organ Sharing (UNOS) database between 2002 and 2016.[46] In 2002, the proportion of liver transplants for ALD was 24.2%, which increased to 27.2% in 2010 and to 36.7% in 2016. Overall patient survival at 5 years after LT was 79% among patients with ALD vs 80% with nonalcohol-related liver diseases, whereas overall patient survival at 10 years after LT was 63% among patients with ALD and 68% among patients with nonalcohol-related liver diseases ($P$=.01). However, in a multivariable analysis, there was no significant difference in overall patient survival and graft survival between both groups. Posttransplant death was strongly associated with donor risk index and mechanical ventilation at the time of transplant, and late death after transplant was most commonly caused by cancer and infection. Relapse of alcohol use was the strongest risk factor for graft failure 5 years posttransplant.[46]

Early LT for severe, acute AH is also increasingly common, with more transplant centers performing the procedure without the requirement of the so-called 6-month sobriety rule. Given the high mortality of severe AH, especially when there is no response to medical therapy, LT is the only option for survival when the patient is deemed suitable for LT. One of the first prospective studies on early LT among patients with severe AH who did not respond to medical therapy was conducted in 2011.[47] Mathurin and colleagues demonstrated a superior 6-month patient survival of 77% in 26 patients with severe AH who underwent LT compared to a 6-month patient survival of 23% in matched controls who did not undergo LT ($P$<.001). Only 3 of the patients in the LT arm had alcohol relapse starting after 2 years posttransplant.[47] In a single-center, retrospective study from 2012 to 2015, Im and colleagues demonstrated 6-month patient survival of 89% for early LT

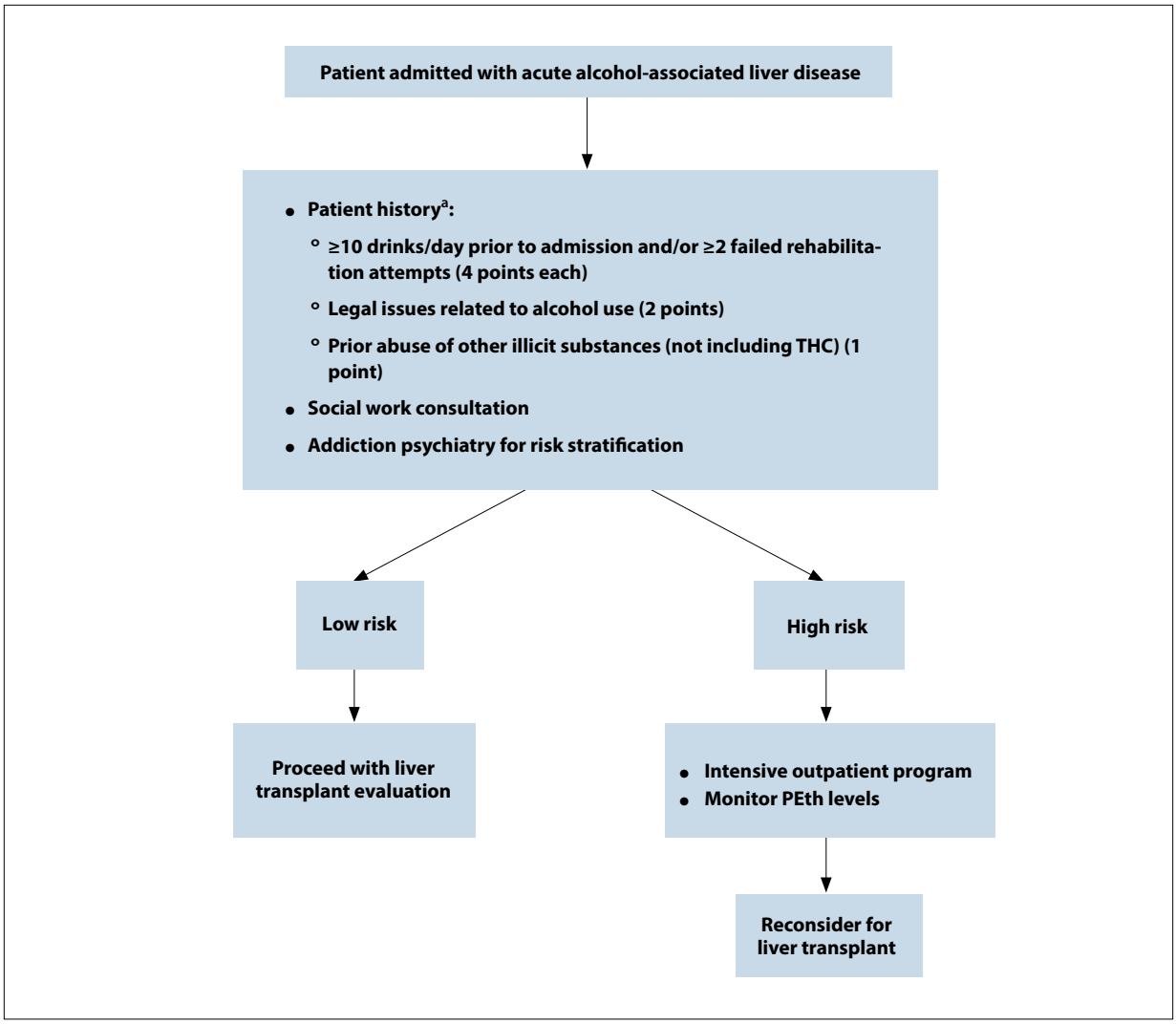


**Figure.** Proposed algorithm for liver transplant evaluation in patients with alcohol-associated liver disease.

PEth, phosphatidylethanol; SALT, Sustained Alcohol Use Post–Liver Transplant; THC, tetrahydrocannabinol.

[a]SALT score adapted from Lee et al.[52] A score of 5 or higher has a 95% negative predictive value of predicting alcohol use posttransplant.

recipients (8/9 patients) vs 11% for matched controls ($P$<.001). After LT, all 8 patients had a median survival of 2 years, and only 1 patient had alcohol relapse.[48] Another case-control study compared 46 patients who underwent LT for severe AH without 6 months of abstinence to 34 patients who underwent LT for alcohol-associated cirrhosis with 6 months of abstinence.[49] Both patient survival and alcohol relapse rates were similar in the 2 groups. In patients without 6 months of abstinence, 1-year post-LT patient survival was 97% and alcohol relapse was 24%, whereas patients with 6 months of abstinence had 1-year post-LT patient survival of 100% and alcohol relapse of 28% ($P$=1.00). The duration of pretransplant sobriety was not predictive of patient survival or relapse after LT.[49]

The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH), which includes 12 transplant centers from 8 UNOS regions, completed a large retrospective review of early transplantation for acute AH from 2006 to 2017.[50] A total of 147 patients received transplants with less than 6 months of abstinence (median, 55 days). Survival at 1- and 3-years posttransplant was 94% and 84%, respectively, which is comparable to survival rates for alcoholic cirrhosis. On follow-up, 40 patients (27%) had any alcohol use, with 15 (10%) having sustained use.[50]

Traditionally, a period of 6 months of abstinence is required prior to consideration for LT for patients with ALD and/or AH. However, this timeline has been challenged, particularly for patients with severe AH. This

6-month rule arose arbitrarily, has not been adopted by UNOS, and came to serve as a predictive measure of relapse after LT. Now, with a better understanding of psychosocial factors, various tools exist to predict future drinking, including the University of Michigan Alcoholism Prognosis Score, Alcohol Relapse Risk Assessment, High-Risk Alcoholism Relapse, and Stanford Integrated Psychosocial Assessment for Transplantation.[51] Most recently, the ACCELERATE-AH conducted a retrospective, multicenter trial in which the survival outcome and alcohol relapse of 134 LT recipients for severe AH were analyzed.[52] The median period of alcohol abstinence before LT was 54 days. After a median of 1.6 years (interquartile range, 0.7-2.8) follow-up post-LT, 74% of patients remained abstinent, 16% had slips only, and 10% had sustained alcohol use. ACCELERATE-AH developed the Sustained Alcohol Use Post–Liver Transplant score, which can be used along with other consultation services to predict alcohol abstinence post-LT (Figure).[52]

When medical therapy fails, early LT is a promising treatment option for severe AH, with significantly improved survival rates compared to patients who do not undergo LT. Post-LT survival rates of patients with AH are comparable to those seen in patients transplanted for other chronic liver diseases. With close follow-up, risk of alcohol relapse is low. Further work is needed to develop more accurate tools in selecting appropriate candidates for LT in ALD.

## Relapse Recurrence of Alcohol-Associated Liver Disease

Abstinence from alcohol is the primary method of preventing further liver damage or complications post-LT. Most patients with AUD do not receive long-term treatment, which is usually required if LT becomes an option. Both pharmacologic and psychosocial therapies are likely to be of benefit, but there are no randomized, controlled studies investigating the combination of these therapies in patients with chronic liver disease.

### *Pharmacologic Therapies for Relapse Prevention in Patients With Alcohol Use Disorder*

Only 3 medications are approved by the US Food and Drug Administration (FDA) for AUD: disulfiram, naltrexone, and acamprosate.[53-55] Disulfiram is not recommended in patients with underlying liver disease due to the risk of hepatotoxicity. Naltrexone is also associated with hepatotoxicity and is contraindicated in patients with acute liver injury and decompensated cirrhosis; however, it can be used safely in patients with compensated cirrhosis and in patients without liver disease.[56] Further studies are needed in this area. Acamprosate may have a more promising use given its lack of hepatic metabolism, but no long-term studies in liver disease have been conducted.

Other medications for AUD are either not FDA-approved or are not available in the United States. A recent literature review of baclofen, a gamma-aminobutyric acid B receptor agonist with renal clearance, found that baclofen is an effective and safe treatment to lower alcohol cravings for AUD among patients with chronic liver disease. Efficacy was directly correlated with the severity of liver disease, and no added benefit was found for doses greater than 30 mg/day.[57] Nalmefene, an opioid antagonist, is effective in reducing alcohol consumption with no known hepatotoxicity, but is not available in the United States.

### *Psychosocial Therapies for Relapse Prevention in Patients With Alcohol Use Disorder*

A review of psychosocial interventions among patients with chronic liver disease found that a combination of psychotherapy with cognitive behavioral therapy, motivational enhancement therapy, and medical care significantly increases alcohol abstinence.[58] Overall, the combination of therapies including cognitive behavioral therapy, motivational enhancement therapy, psychoeducation, and motivational interviewing appeared to have better alcohol use outcomes than individual interventions. There is a variable rate of adherence to therapy, ranging from 14% to 95%, suggesting that identifying barriers to compliance may increase effectiveness.

Intensive outpatient programs (IOPs) are designed for individuals with substance use disorders who do not need inpatient detoxification or monitoring. IOPs have been found to be as effective as inpatient and residential treatments, with abstinence rates of 50% to 70% on follow-up.[59] An important component of care appears to be longer duration. However, there is wide variation in IOPs, and more standardization is needed in terms of treatment duration, type, intensity, and post-IOP management. Another common resource for assistance is Alcoholics Anonymous (AA), which appears to improve alcohol addiction outcomes. Recently, Kelly and colleagues demonstrated a 42% abstinent rate for AA and 12-step facilitation treatments compared to a 35% abstinent rate for non-AA treatment and 12-step programs.[60]

## Summary

The alcohol consumption rate and the incidence of ALD are increasing. It is vital for clinicians to identify and screen patients who are at risk of AUD, establish the

diagnosis, and implement early interventions to prevent unwanted outcomes. Diagnostic tools, prognostic models, and pharmacologic and nutritional therapies have evolved in the management of AH.

### *Disclosures*

*The authors have no relevant conflicts of interest to disclose.*

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