CME

ACG Clinical Guideline: Alcoholic Liver Disease

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Alcoholic liver disease (ALD) comprises a clinical-histologic spectrum including fatty liver, alcoholic hepatitis (AH), and cirrhosis with its complications. Most patients are diagnosed at advanced stages and data on the prevalence and profile of patients with early disease are limited. Diagnosis of ALD requires documentation of chronic heavy alcohol use and exclusion of other causes of liver disease. Prolonged abstinence is the most effective strategy to prevent disease progression. AH presents with rapid onset or worsening of jaundice, and in severe cases may transition to acute on chronic liver failure when the risk for mortality, depending on the number of extra-hepatic organ failures, may be as high as 20–50% at 1 month. Corticosteroids provide short-term survival benefit in about half of treated patients with severe AH and long-term mortality is related to severity of underlying liver disease and is dependent on abstinence from alcohol. General measures in patients hospitalized with ALD include inpatient management of liver disease complications, management of alcohol withdrawal syndrome, surveillance for infections and early effective antibiotic therapy, nutritional supplementation, and treatment of the underlying alcohol-use disorder. Liver transplantation, a definitive treatment option in patients with advanced alcoholic cirrhosis, may also be considered in selected patients with AH cases, who do not respond to medical therapy. There is a clinical unmet need to develop more effective and safer therapies for patients with ALD.

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INTRODUCTION

Alcoholic liver disease (ALD) is one of the main causes of chronic liver disease worldwide and accounts for up to 48% of cirrhosis-associated deaths in the United States (1). Alcohol is also a frequent co-factor in patients with other type of liver disease such as hepatitis C virus (HCV) infection where it accelerates hepatic fibrosis (2). Owing to various susceptibility factors, individuals with long-term heavy alcohol use remain at risk for advanced liver disease with alcoholic steatohepatitis (ASH), cirrhosis, and hepatocellular carcinoma (HCC) (3). Most patients with ALD present for medical care after they have developed jaundice or complications of cirrhosis (4). Identification of ALD in the primary-care setting at an early stage and subsequent behavioral interventions should thus be encouraged. Compared with the recent advances in viral hepatitis, few pharmacological advances have been made in the management of patients with ALD. To date, the most effective therapy to attenuate the clinical course of ALD and even reverse liver damage is prolonged alcohol abstinence (5,6). Given its high prevalence and economic burden, ALD is receiving increasing attention by health authorities, research funding organizations, and the liver academic community. Nevertheless, novel non-invasive tools to diagnose ALD at early stages and promising pharmacological approaches for alcoholic hepatitis (AH) are still needed. Finally, recent studies suggest that early liver transplantation (LT) can be successfully performed in highly selected patients with AH.

The authors were invited by the Board of Trustees and Practice Parameters Committee of the American College of Gastroenterology, to develop this practice guideline document on the management of patients with ALD.

Key concepts on ALD and specific recommendations have been developed for specialists in liver disease, gastroenterologists, and primary care providers, to aid them in the management of ALD patients. Recommendations based on Population Intervention Comparison Outcome format/Grading of Recommendations Assessment, Development, and Evaluation analysis are in **Table 1**. These recommendations and guidelines should be tailored to individual patients and circumstances in routine clinical practice. Key concepts and recommendations based on author expert opinion and review of literature are in **Table 2**.

To develop these guidelines, a search was performed on the Ovid search platform: Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE

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Table 1. Recommendations in the management of alcoholic liver disease

Environmental and genetic determinants
1. Patients with obesity or chronic HCV should avoid consumption of alcohol. (Conditional recommendation, very low level of evidence)
2. Patients with ALD should be advised to abstain from cigarettes. (Conditional recommendation, very low level of evidence)
Diagnosis of alcoholic use disorder
3. Patients who have heavy alcohol use (>3 drinks per day in men and >2 drinks in women) for >5 years) should be counseled that they are at increased risk for alcoholic liver disease. (Strong recommendation, low level of evidence)
Management of alcoholic liver disease
Management of alcohol use disorder
4. In patients with ALD, baclofen is effective in preventing alcohol relapse (Conditional recommendation, low level of evidence)
5. In patients with ALD, brief motivational interventions are effective in reducing alcohol relapse compared with no intervention (Conditional recommendation, very low level of evidence)
Alcoholic hepatitis
Treatment of alcoholic hepatitis
6. Patients with AH should be considered for nutritional supplementation to ensure adequate caloric intake and to correct specific deficits, yet its effects on patient survival has not been proven (Conditional recommendation, very low level of evidence)
7. Patients with severe AH should be treated with corticosteroids if there are no contraindications for their use (Strong recommendation, moderate level of evidence)
8. The existing evidence does not support the use of pentoxifylline for patients with severe AH. (Conditional recommendation, low level of evidence)
Liver transplantation in alcoholic liver disease
9. Liver transplantation may be considered for highly selected patients with severe AH (Strong recommendation, moderate level of evidence)

(R), EBM Reviews Cochrane Central Registry of Controlled Trials, EMBASE, and PsycInfo for the period 1980 through July 2016. A combination of database-specific subject headings (e.g., MEDLINE Liver Diseases and Alcoholic) and text words (Alcohol* (truncated) within three words of liver, or hepat* (truncation) or cirrho* (truncation)) in association with LT (subject's headings plus text words). The results were downloaded from each database into EndNote X7 and duplicates removed. To evaluate the level of evidence and strength of recommendations, we used the Grading of Recommendations Assessment, Development, and Evaluation system, as suggested by the American College of Gastroenterology Practice Parameters Committee. The strength of recommendation is graded as strong or conditional as a consensus among the authors, considering the weight of desirable and undesirable effects of intervention. The level of evidence was determined independently of the authors and designated as high, moderate, low, and very low, considering the confidence in the effect estimate based on current literature.

EPIDEMIOLOGY AND DISEASE BURDEN

Alcohol-use disorder (AUD) is one of the main causes of preventable disease and liver disease-associated mortality in the United States and worldwide. A recent report from the World Health Organization indicates that 3.3 million deaths (6% of all global deaths) are attributable to alcohol use, and that alcohol abuse is a risk factor in about 50% of cases of cirrhosis (1). Approximately 1 in 12 adults have AUD defined as consumption of >3 drinks per day in males and >2 drinks per day in females, or binge drinking (defined by the National Institute of Alcoholism and Alcohol Abuse as >5 drinks in males and >4 drinks in females, consumed over 2 h period) (7). In the United States, one drink is defined as a beverage containing about 14 g of alcohol, which is present in 12 ounces of beer (5% weight/volume) or 5 ounces of wine (8–10% weight/volume), or 1.5 ounces of hard liquor (40–45% weight/volume) (7). Economic costs due to AUD (249 billion USD per year) are increasing. An estimated 88,000 people (~62,000 men and 26,000 women) die from alcohol-related causes annually, making alcohol the fourth leading preventable cause of death in the United States (8). Apart from ALD, accidents or violence are other common causes of death among adult people abusing alcohol. In 2014, alcohol-impaired driving fatalities accounted for 9,967 deaths in the United States (31% of overall driving fatalities) (1).

The association between alcohol and liver-related mortality is strongly supported by data showing a linear relationship between the standard liver death rate and overall alcohol consumption in many countries (9,10). Importantly, drinking patterns such as heavy episodic drinking vs. heavy daily use and the type of alcohol consumed may not independently predict the alcohol-attributable fraction of cirrhosis (11). However, designation of countries by moderate or heavy daily drinking most clearly demonstrates the weight of alcohol on the cirrhosis burden (10). The disease burden of alcohol is rapidly increasing in Asian countries such as China, Korea, and India. There are also regional differences in Europe between Eastern and Western Europe, likely to be due to implementation of policy measures leading to decrease in alcohol use in many areas of Western Europe.

Table 2. Key concepts and statements on the management of alcoholic liver disease

Disease spectrum of alcoholic liver disease
1. Liver function tests and ultrasound examination should be performed among patients with harmful alcohol use and/or alcohol use disorders (AUD)
2. Liver biopsy is not routinely recommended for diagnosis of alcoholic fatty liver disease. However, liver biopsy and non-invasive tools of fibrosis may be considered for diagnosis of steatohepatitis and/or liver fibrosis
Diagnosis of alcoholic use disorder
3. The Alcohol Use Disorders Inventory Test (AUDIT) is a validated tool for identifying patients with alcohol use and dependence
Management of alcoholic liver disease
Management of alcohol use disorder
4. Alcohol consumption is a major determinant of disease progression and long-term outcome of patients with alcoholic liver disease (ALD). Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of ALD
5. Medical treatment of ALD should be ideally performed by multidisciplinary teams including addiction specialists
Management of alcohol withdrawal
6. Alcohol withdrawal syndrome (AWS) should be stratified and managed as per Clinical Institute Withdrawal Assessment for Alcohol protocol (45–49)
7. In patients with severe AWS and ALD, benzodiazepines are the treatment of choice
Alcoholic hepatitis
Diagnosis of alcoholic hepatitis
8. Clinical diagnosis of alcoholic hepatitis (AH) is determined in a patient with rapid development or worsening of jaundice and liver-related complications, with serum total bilirubin >3 mg/dL; ALT and AST elevated >1.5 times the upper limit of normal but <400 U/L with the AST/ALT ratio >1.5; documentation of heavy alcohol use until 8 weeks prior to onset of symptoms; and exclusion of other liver diseases
9. In patients with suspected AH, a transjugular liver biopsy is recommended when the clinical diagnosis is confounded by another liver disease etiology or there is uncertainty on alcohol consumption history
10. Patients with severe AH should preferably be hospitalized for management
Treatment of alcoholic hepatitis
11. Severe AH is identified by Maddrey's discriminant function score >32 or MELD score >20
12. Systemic inflammatory response syndrome (SIRS) at admission predisposes to acute kidney injury and multi-organ failure, which are associated with a poor prognosis. Physicians should take appropriate measures to prevent renal injury, such as avoidance of nephrotoxic drugs, judicious use of diuretics, and low threshold for expanding circulating blood volume with albumin or saline infusions
13. Infections are common in AH patients and comprehensive infectious screen is recommended as part of routine work-up of these patients. The development of bacterial infections during hospitalization is associated with poor prognosis
14. Response to treatment with corticosteroids should be determined at 7 days using the Lille score. Treatment should be discontinued among non-responders to therapy, defined as those with a Lille score >0.45
15. Patients non-responsive to corticosteroids, ineligible for early LT, and with multiple organ failures, may be considered for palliative therapy
Liver transplantation in alcoholic liver disease
Liver transplantation for alcoholic cirrhosis
16. Physicians should consider LT while formulating a management plan for patients with end-stage ALD
17. The decision on LT evaluation should not be based solely on minimum 6 months of alcohol abstinence, and other criteria should be taken into consideration
18. Patients too sick to complete rehabilitation therapy may be considered for transplantation via exception pathway dependent on individual center policy and the patient's profile. These patients can complete rehabilitation therapy after transplantation
19. Transplant recipients should be screened at each visit for use of alcohol and other substances especially tobacco and cannabis. Among recidivists, alcohol use should be quantified to identify harmful use
20. Immunosuppression should be optimized to use lowest possible dose needed to prevent graft rejection. Use of sirolimus or everolimus may be considered over other immunosuppression drugs

Effective alcohol policy measures have been shown to reduce alcohol mortality, including ALD-related mortality (10,12). Cost effective measures include increase in taxes on sales of alcohol drinks, minimum sale price for alcohol, raising the legal age for buying alcohol, low level interventions from clinicians, ban on drinking in public places and on use of alcohol as gifts or in advertisements, and stricter legal action for driving under influence of alcohol. These measures have been implemented primarily in Europe and have resulted in reducing the disease burden and consumption of alcohol. In the United States, strict alcohol policy

environments, especially alcohol taxes, were associated with lower alcoholic cirrhosis mortality rates (12).

Alcohol abuse or alcohol dependence is not synonymous with clinically important ALD, as only about 10–20% of chronic heavy drinkers develop severe forms such as AH or cirrhosis (13). According to the National Institute of Alcoholism and Alcohol Abuse Surveillance Report on mortality in 2013, cirrhosis was the 12th leading cause of death in the United States, with about half of cirrhosis-related deaths being due to alcohol (8). The crude death rate from cirrhosis due to any etiology was 12.0 deaths per 100,000 population, whereas the rate from alcohol-related cirrhosis was 5.7, representing an increase of 3.4% and 1.8% from 2012, respectively (1). The WHO aims to reduce the death rate from ALD to below 3.2/100,000 population (1). These figures become more relevant considering that ALD receives only about 5% of the research attention in the field of hepatology (14).

ENVIRONMENTAL AND GENETIC DETERMINANTS

Recommendations

1. Patients with obesity or chronic HCV should avoid consumption of alcohol. (Conditional recommendation, very low level of evidence)
2. Patients with ALD should be advised to abstain from cigarettes. (Conditional recommendation, very low level of evidence)

As only about 10–20% of individuals with chronic heavy alcohol use develop advanced liver disease and cirrhosis, other disease modifiers and cofactors, such as behavioral, environmental, and genetic factors, possibly have a role. There is a clear dose relationship between the amount of alcohol intake and the likelihood of developing ALD; yet, extensive individual variability exists. Females are at risk for ALD at a lower daily intake of alcohol, probably due to higher body fat component and lower gastric alcohol dehydrogenase activity (15). The impact of drinking patterns (i.e., binge drinking and drinking outside meals) and the type of beverage (wine vs. beer vs. liquors) is not well known and deserves large epidemiological studies. The general assumption that binge drinking favors the development of AH has not been proven in recent studies (11). Obesity is one of most important environmental risk factor determining the risk of cirrhosis in heavy drinkers (16). Heavy drinkers who are overweight for at least 10 years have a twofold risk of developing cirrhosis. Interestingly, several studies indicate that caffeine intake protects against cirrhosis in heavy drinkers (17). The coexistence of chronic hepatitis B or HCV infection leads to an acceleration of liver injury, with more frequent and faster development of cirrhosis and its complications including HCC (2). Iron accumulation, which is a common finding in advanced ALD, has also been associated with hepatic fibrosis in ALD and increased mortality in alcoholic cirrhosis (18,19). Cigarette smoking is common among alcoholic patients. It exacerbates the effects of alcohol in inducing severe ALD and favors development of HCC among patients with alcoholic cirrhosis (3,20). Once alcoholic cirrhosis develops, the risk for hepatic decompensation increases, especially among patients who continue to drink. In a Danish population-based study, which included 446 patients with alcoholic cirrhosis, the risk of developing ascites, variceal bleeding, or hepatic encephalopathy was ~25% after 1 year and 50% after 5 years (21). With abstinence, the expected 5-year transplant-free survival rate following development of hepatic decompensation is 60% vs. 30% for those who continued to drink alcohol (22).

Genetic factors influence the susceptibility for advanced ALD. Monozygotic twins have a higher concordance rate for alcohol-related cirrhosis than dizygotic twins (23). Genetic factors may influence susceptibility to alcohol consumption or predisposition to development of ALD among those with AUD. Genes influencing the susceptibility for alcoholism include modifiers of neurotransmission such as γ-amino butyric acid and modifiers of alcohol metabolism such as alcoholic dehydrogenase and acetaldehyde dehydrogenase enzymes (24). The polymorphisms in these genes may be involved in an individual's susceptibility to alcoholism, with wide allelic variation between different ethnic groups, but their role in the progression of ALD remains controversial. The second group of genes modifies the natural history of ALD through different mechanisms. Small candidate gene studies initially suggested a role for polymorphisms in genes encoding inflammatory mediators, endotoxin response and oxidative stress. However, larger studies including a recent genome-wide association study revealed that patatinlike phospholipase domain containing protein 3, may be the main genetic determinant of risk for and severity of ALD (25,26). Phospholipase domain containing protein 3 is closely related with lipid metabolism and is also a risk factor for non-alcoholic fatty liver disease and HCC (26). The allele that negatively impacts disease progression (i.e., rs738409) is more frequent within the Hispanic population, which is particularly sensitive to fatty liver diseases (25).

DISEASE SPECTRUM OF ALCOHOLIC LIVER DISEASE

ALD comprises a broad spectrum of diseases ranging from asymptomatic or early ALD (defined as fatty liver or alcoholic steatosis), to ASH and advanced ALD, (defined as AH, cirrhosis and its complications such as ascites, portal hypertension-related bleeding, hepatic encephalopathy, and HCC) (**Figure 1**). The clinical course of ALD is influenced by alcohol abstinence (5,6). Patients can regain a compensated status after initial hepatic decompensation if they stop drinking. Notably, some patients rapidly gain weight after they stop drinking, increasing their risk for developing non-alcoholic fatty liver disease. As there is no specific biomarker for the diagnosis of ALD, diagnosis requires excluding other liver diseases in a patient with heavy alcohol use.

Early alcoholic liver disease

Key concepts and statements

1. Liver function tests and ultrasound examination should be performed among patients with harmful alcohol use and/or AUD.

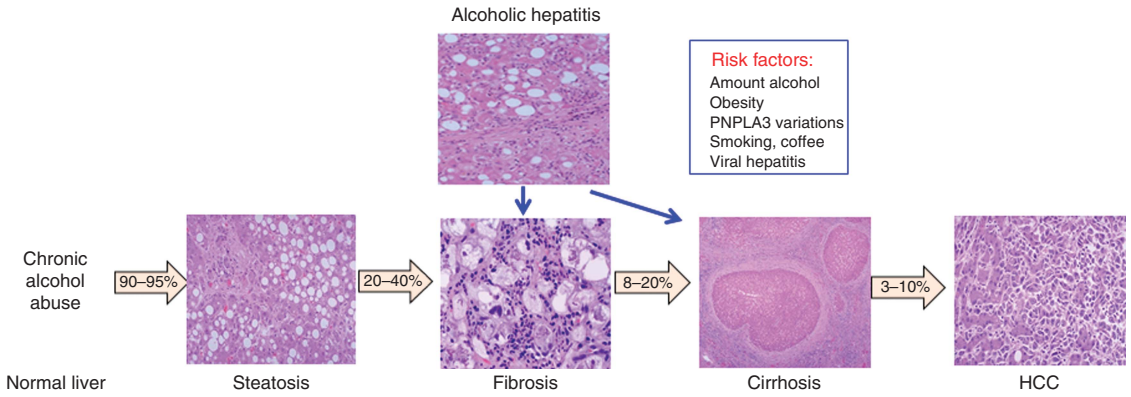

Figure 1. Disease spectrum of alcoholic liver disease.

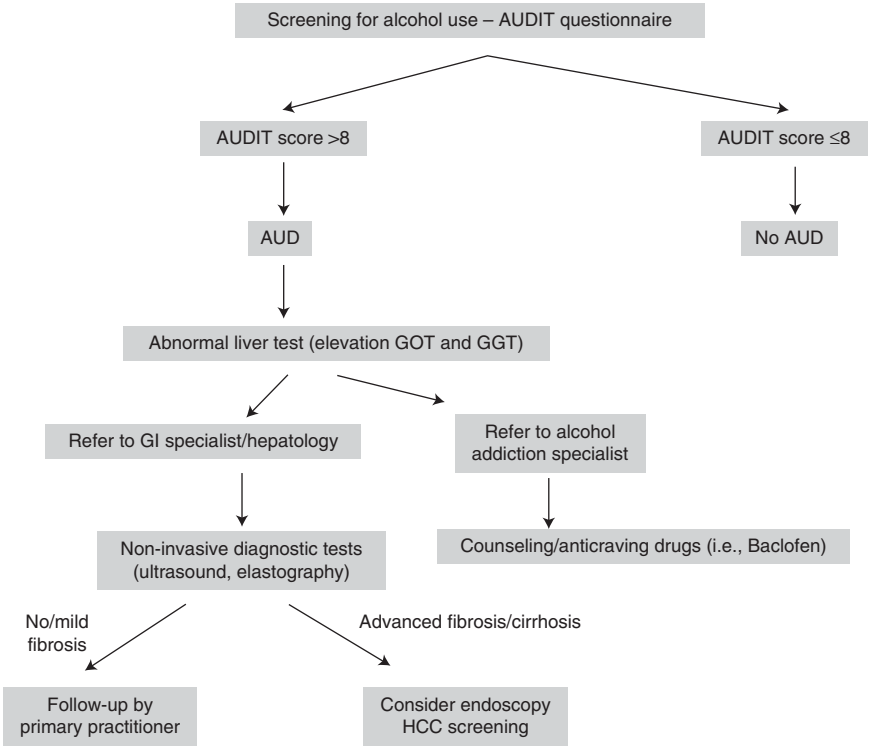

Figure 2. Algorithm for diagnosis of alcohol use disorder (AUD) using AUDIT tool and on management of early alcoholic liver disease (ALD).

2. Liver biopsy is not routinely recommended for diagnosis of alcoholic fatty liver disease. However, liver biopsy and non-invasive tools of fibrosis may be considered for diagnosis of steatohepatitis and/or liver fibrosis.

Alcoholic fatty liver disease is diagnosed in a patient with AUD with hepatic steatosis on ultrasound and/or elevation in liver enzymes (aspartate aminotransferase (AST)>alanine aminotransferase (ALT)), serum bilirubin<3 mg/dL, and the absence of other causes of liver disease. Alcoholic fatty liver or simple steatosis, which is usually macro vesicular develops in ~90% of heavy drinkers and may be seen within 2 weeks of heavy and regular alcohol ingestion. Hepatic steatosis resolves rapidly following complete abstinence (27). The majority of patients with simple alcoholic steatosis are asymptomatic, but nausea, anorexia, and vomiting may be present (28). The impact of simple alcoholic steatosis is not well known and is probably a benign condition.

With continued excessive alcohol ingestion, approximately one-third of patients with steatosis have histological evidence of hepatic inflammation (sometimes termed ASH) (29). ASH, a term sometimes used to describe the histological features in AH, is diagnosed in patients with fatty liver disease when hepatic

inflammation/damage or fibrosis is present on liver biopsy (**Figure 2**). Unfortunately, about half of the patients with seemingly early disease may already have advanced fibrosis or cirrhosis on liver biopsy (5). Of interest, patients with alcohol withdrawal syndrome (AWS) may have a higher prevalence of inflammation on liver biopsy than do patients without withdrawal syndrome (29).

Physical examination of patients with alcoholic fatty liver usually demonstrates only mildly tender hepatomegaly which rapidly resolves with abstinence. AST and ALT elevations are minimal (with AST typically greater than ALT) and γ-glutamyl transpeptidase may be elevated, but the serum bilirubin and International Normalized Ratio (INR) are typically normal. The diagnosis of hepatic steatosis is based on imaging (ultrasound or magnetic resonance) and a liver biopsy is not routinely required nor recommended for diagnosis.

A proportion of patients with evidence of steatohepatitis on liver biopsy develop hepatic fibrosis (20–40%) and cirrhosis (8–20%). The risk of cirrhosis is increased in patients with steatohepatitis on biopsy as compared with patients with simple steatosis. It is important to emphasize that currently steatohepatitis can be diagnosed only on liver biopsy; there are no signs, symptoms, or biochemical tests that allow the confident diagnosis of steatohepatitis. In fact, one-third of patients with asymptomatic forms of ASH have significant liver fibrosis and the presence of advanced fibrosis determines the long-term outcome. There are few programs for early detection of ASH in primary-care centers and addiction centers. Therefore, the prevalence of ASH and fibrosis among patients with AUD is not well known. Although awaiting further studies, the use of non-invasive tests of fibrosis (i.e., serum markers or elastography) may be useful in patients with AUD and abnormal liver tests.

Alcoholic hepatitis and cirrhosis

The true prevalence of AH is not well known, as its presence is commonly overlooked in patients with decompensated ALD. In one study, using the National Inpatient database, AH contributed to 0.8% of all hospitalizations in the United States, with ~325,000 hospital admissions in 2010 (30). The clinical picture of AH is characterized by jaundice and is associated with risk for liver-related complications. AH can occur in any stage of liver disease and up to 80% of patients with severe AH (model for end-stage disease (MELD) score >20 and/or discriminant function (DF) ≥32) may have underlying cirrhosis. The population burden of alcoholic cirrhosis is underestimated and not clearly known, and the odds of alcoholic cirrhosis are higher in patients who have been hospitalized for alcoholism related problems (31). Patients with severe AH are hospitalized for treatment and, in addition, can have complications of cirrhosis and sepsis.

DIAGNOSIS OF ALCOHOLIC-USE DISORDER

Recommendation

3. Patients with heavy alcohol use (>3 drinks per day in men and >2 drinks in women) for >5 years) should be counseled that they are at an increased risk for liver disease. (Strong recommendation, low level of evidence)

Key concept and statement

3. The Alcohol Use Disorders Inventory Test (AUDIT) is a validated tool for identifying patients with alcohol abuse and dependence

Adjudicating alcohol as an etiology of liver disease depends upon diagnosis of AUD and excluding other causes of liver disease. There are no definitive laboratory tests for diagnosis of liver disease related to alcohol use. Compared with non-alcoholic fatty liver disease, those with ALD often present late with advanced liver disease and its complications (4). Data are needed on the role of non-invasive tools such as transient elastography among patients presenting with early ALD, such as fatty liver or minor derangement in transaminases.

Detailed history on alcohol consumption to identify AUD is important. As patients often underreport alcohol intake, questionnaires can be complemented by information from relatives (if appropriate) or by objective measures (e.g., physical signs of chronic alcohol use), tests suggestive of alcohol abuse (i.e., elevated blood alcohol, γ-glutamyl transpeptidase or urinary ethyl glucuronide elevation), or liver biopsy showing signs of alcohol-induced liver damage. The primary screening tool to detect alcohol abuse and dependence is AUDIT, which has high sensitivity and specificity in clinical settings. AUDIT is a 10-item questionnaire, which has been validated as a clinical tool for the accurate detection of alcohol consumption (32). With a score of 0–40, an AUDIT score of >8 constitutes AUD, or alcohol abuse, and a score of >20 qualifies for diagnosis of alcohol dependence (**Figure 2**). As the completion of AUDIT can be time consuming for both physicians and patients, a shorter version or AUDIT-c has been developed and found to be as accurate as an initial screening test for diagnosing AUD (33). This brief version should be employed in the primary-care setting to identify patients with AUD. When approaching patients with suspected ALD, the provider should also ask the patient for the following: type of alcoholic beverage (i.e., beer, wine, and spirits/liquors), pattern of drinking (i.e., daily, with or without meals, increase during the weekend), the frequency of binge drinking, and date of the last drink. It is also important to identify previous attempts made by the patient to stop drinking (i.e., Alcoholics Anonymous meetings, previous treatment by addiction counselors, alcohol detoxification hospitalizations, etc.).

As the self-reported alcohol use is often inaccurate, the use of alcohol biomarkers can be useful to diagnose alcohol consumption. Of the biochemical tests, mean corpuscular volume, aminotransferases, and γ-glutamyl transferase are sensitive tests, but lack specificity in patients with cirrhosis (34). Carbohydrate-deficient transferrin combined with γ-glutamyl transferase has sensitivity of about 75–90%. However, the levels of carbohydrate-deficient transferrin may be confounded with increasing disease severity and active smoking (35). Newer biomarkers using metabolites of alcohol such as ethyl glucuronide can reveal alcohol use up to 3–4 days after the last alcohol drink (36). However, due to its high sensitivity, it can yield false-positive results with exposure to alcohol containing medications and hand sanitizers containing small amounts of ethanol (37). Measurement of ethyl

glucuronide in hair samples can detect alcohol use for a longer period of up to 1 month (38). Urine ethyl glucuronide and phosphatidyl ethanol are commercially available for use in routine clinical practice (36).

Screening of psychosocial conditions

It is important to identify concomitant psychosomatic disorders in individuals with AUD, as simultaneous treatment of these disorders is crucial in maintaining abstinence. Individuals with AUD have high prevalence of anxiety, affective disorders, psychosis, and posttraumatic stress disorder. In other situations, patients use excessive drinking to cope with untreated chronic pain, or sleeping disorders. They may also have a history of sexual abuse, violence, social isolation, and history of driving while impaired. Patients with AUD have a higher risk of developing other addictions, including nicotine, opioids, and benzodiazepines; polysubstance users are difficult to manage and should be systematically referred to specialized treatment. Two of the commonly overlooked issues in a busy clinic practice of physicians are masked depression and anxiety disorder in these individuals, and these factors increase the risk for relapse to alcohol use and failure of counseling or detoxification therapy sessions. A simple screening tool for assessing for underlying depression is a Patient Health Questionnaire (PHQ)-2 questionnaire, which includes two questions (each scored from 0–3 depending on severity) for symptoms over the last 2 weeks for: (a) little interest or pleasure in doing things? and (b) feeling down, depressed, or hopeless? A similar questionnaire for generalized anxiety disorder or Generalized Anxiety Disorder (GAD) includes two questions (each scored from 0 to 3) for symptoms over the last 2 weeks for: (a) feeling nervous, anxious, or edgy? and (b) not being able to stop or control worrying (39)? On each of these tools, a score of 3 or more constitutes a positive response and need for further intervention.

MANAGEMENT OF ALCOHOLIC LIVER DISEASE

Patients with ALD are suffering from two different disorders, namely AUD and liver disease. Hence, the treatment should involve integrated management targeting both the disorders.

Management of alcohol-use disorder

Recommendations

4. In patients with ALD, baclofen is effective in preventing alcohol relapse (Conditional recommendation, low level of evidence)
5. In patients with ALD, brief motivational interventions are effective in reducing alcohol relapse compared with no intervention (Conditional recommendation, very low level of evidence)

Key concepts and statements

4. Alcohol consumption is a major determinant of disease progression and long-term outcome of patients with ALD. Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of ALD.
5. Medical treatment of ALD should be ideally performed by multidisciplinary teams including alcohol addiction specialists.

Therapies for treatment of AUD aim at achieving complete alcohol abstinence with use of pharmacological therapy and behavioral therapy with motivational interviewing. Patients actively drinking are at a high risk of severe AWS during inpatient alcohol detoxification. Obstacles to completing addiction therapies include the following: lack of specialized care, refusal by the patient, lack of insurance coverage, patient too sick to attend therapy sessions, and transportation (40). Recognizing these obstacles will help the clinician to address these with the patient as basis of providing optimal management.

Pharmacological therapies. Many pharmacological agents have been used for treatment of AUD including disulfiram, acamprosate, gabapentin, naltrexone, topiramate, sertraline, and baclofen (41). Of these, only baclofen, a γ-amino butyric acid-B receptor agonist has been found to be safe in patients with ALD and cirrhosis. Its efficacy is shown with increase in abstinence rates (42). Baclofen can be started in a dose of 5 mg three times a day and the dose can be increased at a 3–5 days interval based on patient tolerance to a maximum dose of 15 mg three times a day. Considering its excellent safety profile, even among patients with advanced liver disease and AH, patients on baclofen therapy can be monitored by hepatologists or addiction specialists.

Non-pharmacological therapies. The other major approach to induce or to maintain alcohol abstinence in patients with ALD is behavioral interventions such as motivational enhancement therapy, cognitive behavioral therapy, motivational interviewing, supportive therapy, and psychoeducation (43). Motivational interviewing, the most commonly used intervention, is a technique that aims to be both non-judgmental and non-confrontational. It attempts to increase a patient's awareness of the potential problems caused, consequences experienced, and risks faced because of excessive alcohol use. Essential components of a motivational approach are an empathic attitude and a collaborative approach that respects the patients' autonomy (40,44). A brief intervention should have at least the components defined in the five "A" model: ask about use, advice to quit or reduce, assess willingness, assist to quit or reduce and arrange follow-up. Cognitive behavior therapy is a structured goal-directed form of psychotherapy in which patients learn how their thought processes contribute to their behavior.

Psychologic interventions can be difficult in patients with hepatic encephalopathy, cognitive impairment, or poor performance status (40). Moreover, patients with end-stage liver disease have frequent hospitalizations that preclude attendance at psychosocial interventions. No psychosocial intervention has been consistently shown to be successful in maintaining abstinence in patients with ALD. Rather, an integrated therapy with cognitive behavioral therapy and medical care appear to reduce recidivism. There is a clear need for clinical trials combining psychosocial and pharmacological interventions in ALD patients with AUD.

Management of alcohol withdrawal

Key concepts and statements

6. AWS should be stratified and managed as per Clinical Institute Withdrawal Assessment for Alcohol protocol (45–49).
7. In patients with severe AWS and ALD, benzodiazepines are the treatment of choice.

AWS is a common condition affecting alcohol-dependent patients who abruptly discontinue or markedly decrease alcohol consumption. Light or moderate AWS usually develops within 6–24 h after the last drink and symptoms may include nausea/vomiting, hypertension, tachycardia, tremors, hyperreflexia, irritability, anxiety, and headache. These symptoms may progress to more severe forms of AWS, characterized by delirium tremens, generalized seizures, coma, and even cardiac arrest and death. Older patients are at greater risk for delirium tremens.

Patients with moderate or severe alcohol withdrawal should be closely monitored in an intensive care unit (ICU), where vital signs, volume status, and neurological function are monitored on a regular basis. Severity scores for AWS such as the Clinical Institute Withdrawal Assessment for Alcohol score are useful in the management of patients, although they have not been validated in patients with severe ALD and a symptom-triggered approach is preferred (45,46).

Benzodiazepines are the most commonly used drugs to treat AWS. Long-acting benzodiazepines (e.g., diazepam and chlordiazepoxide) predominantly protect against seizures and delirium; short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function. Patients with AWS and concomitant hepatic encephalopathy should be treated for both the conditions. Of note, high-dose benzodiazepines may precipitate and worsen hepatic encephalopathy; thus, careful monitoring and titration is critical for optimal outcomes. Given the side effects of benzodiazepines in patients with advanced liver disease and the potential for abuse in an addictive population, other drugs such as baclofen, clonidine, gabapentin, and topiramate have been proposed to treat AWS in patients with ALD including alcoholic cirrhosis. However, the efficacy and safety of these substances in patients with AH is unknown and therefore prospective studies are required. A promising approach is to use baclofen to prevent and treat moderate AWS first, and continue the medication to prevent alcohol relapse.

Management of liver disease

Alcoholic cirrhosis. It is important to assess the nutritional status of ALD patients as malnutrition is often present in these patients (see section on nutritional supplementation for details). Patients with alcoholic cirrhosis should be screened for varices with upper gastrointestinal endoscopy (50). These patients are also at an increased risk of developing HCC, with a life-time risk of about 3–10% and an annual risk of about 1%. Obesity and cigarette smoking are risk factors for HCC in patients with alcoholic cirrhosis. Patients with alcoholic cirrhosis should undergo screening with ultrasound examination with or without α-fetoprotein testing every 6 months for HCC (51). Immunization against hepatitis A and B, pneumococcal pneumonia and influenza is also recommended (Center for Disease Control and Prevention link on vaccinations).

Patients with decompensated cirrhosis are managed as for any patient with cirrhosis as described below.

Ascites. A diagnostic paracentesis is warranted to rule out spontaneous bacterial peritonitis. A therapeutic paracentesis is carried out as required for symptom relief of tense ascites. Management of ascites and hepatorenal syndrome should follow established guidelines. In addition to antibiotics, albumin 1.5 g/kg is recommended on day 1 and 1 g/kg on day 3 in the presence of spontaneous bacterial peritonitis (52).

Hepatic encephalopathy. This is managed as per prevailing guidelines and includes lactulose and rifaximin therapy, as well as control of infection. Cerebral damage, malnutrition, and infections among patients with alcohol-related cirrhosis and continued alcohol use may lower the threshold in development of hepatic encephalopathy. However, other causes of altered mental status should be screened for, especially among patients who present with atypical neuro-psychiatric features that warrant questioning the diagnosis of hepatic encephalopathy or AWS. For example, seizures, focal neurological deficits, severe headache, and encephalopathy refractory to all measures should point towards an alternate cause for altered consciousness such as stroke, subdural hematoma, drug overdose, meningitis, and fungal infections of the central nervous system. A drug screen is recommended and in selected patients imaging of the head and cerebral spinal fluid studies may be required (53).

Variceal bleeding. Management of the acute variceal bleeding episode involves pharmacological therapy with available vasoactive agents (terlipressin or octreotide), antibiotics, and endoscopic therapy. Endoscopy should ideally be carried out at least 30 min after initiation of vasoactive therapy (54).

ALCOHOLIC HEPATITIS

Diagnosis of alcoholic hepatitis

Key concepts and statements

8. Clinical diagnosis of AH is determined in a patient with rapid development or worsening of jaundice and liver-related complications, with serum total bilirubin >3 mg/dL; ALT and AST elevated >1.5 times the upper limit of normal but <400 U/L with the AST/ALT ratio >1.5; documentation of persistent heavy alcohol use until 8 weeks before onset of symptoms; and exclusion of other liver diseases
9. In patients with suspected AH, a transjugular liver biopsy is recommended when the clinical diagnosis is confounded by another liver disease etiology or there is uncertainty on alcohol consumption history
10. Patients with severe AH should preferably be hospitalized for management

Table 3. Proposed definitions and subtypes of alcoholic hepatitis

Definite alcoholic hepatitis: Histological confirmation of features of alcoholic hepatitis.
Probable alcoholic hepatitis: Clinical diagnosis based on (a) heavy alcohol use for >5 years, (b) active alcohol use until 4 weeks prior to presentation, (c) sudden onset or worsening of jaundice, (d) AST/ALT ratio >1.5:1 with levels <400 IU/L, and (e) absence of other causes of liver disease.
Possible alcoholic hepatitis: Clinical diagnosis uncertain due to another confounding etiology of liver disease or unclear history on alcohol consumption.

History. Clinical features of AH include non-specific constitutional symptoms such as fatigue but may also include symptoms attributable to advanced liver disease. The history of alcohol use needs to be carefully documented including the date of last drink. Collateral information from relatives about drinking patterns is often required to confirm the history on alcohol consumption. Suspicion for AH should be high in a patient with recent onset or worsening of jaundice in the setting of chronic heavy alcohol use, which has been active until at least 8 weeks before presentation. History should also include previous admissions for AH, type, duration and amount of alcohol intake, previous alcohol counseling and/or detoxification attempts, recent cocaine and other drug use, potential hepatotoxic drugs, gastrointestinal bleeding, duration of jaundice, and possible source of infection including urinary, pulmonary, cutaneous, and abdominal.

Physical examination. Many physical examination signs overlap with alcoholic cirrhosis reflecting portal hypertension and complications of cirrhosis. Malnutrition of variable degree and sarcopenia is present in most patients with AH. Signs of chronic alcohol intake (e.g., Dupuytren contracture, rhinophyma, etc.), signs of chronic liver disease (spider angioma, palmar erythema, and jaundice), signs of portal hypertension (splenomegaly, ascites, and hepatic encephalopathy), and of alcohol withdrawal (tremors, tachycardia, agitation, seizures in severe AWS, or delirium tremens) may be present (55). Features of systemic inflammatory response syndrome (SIRS) may be present in these patients even in the absence of infection (56). SIRS criteria include the presence of ≥2 of the following: heart rate >100 beats per minute, temperature >38 °C or <36 °C, respiratory rate >12 breaths per minute, and white blood cell count >12,000 or <4,000 mm.

In addition to SIRS criteria, tender hepatomegaly and occasionally, hepatic bruit may be present. A very careful search should be made for a source for potential infection or sepsis, including skin examination for signs of cellulitis and infection around venous lines.

Laboratory abnormalities. Specific laboratory abnormalities to diagnose AH include bilirubin >3 mg/dL; AST >50 but <400 IU/L, with AST/ALT ratio of >1.5. The severity of liver disease should also be documented by measuring the serum bilirubin, creatinine, INR, albumin, and electrolytes to calculate the MELD score, MELD sodium score, and Maddrey discriminate function scores (see section on prognosis and disease severity). As these patients have high risk for infection, diligent infectious work up should be performed including ascitic fluid cell counts with cultures in patients with ascites, urine microscopic examination and cultures, chest X-ray, blood, and sputum cultures as clinically indicated. As SIRS features along with rapidly increasing jaundice may mimic cholangitis, it is prudent to exclude biliary obstruction.

Liver biopsy. One area of controversy is the need for a liver biopsy to confirm the diagnosis of AH. In a recent NIH-sponsored consensus meeting of investigators, it was proposed to define AH as definite, probable, or possible based on clinical features, presence of confounding serology for other liver disease etiology, and liver histology (57) (**Table 3** and **Figure 3**). Definite AH was categorized as a compatible clinical diagnosis along with liver biopsy confirming the existence of criteria of AH; probable AH was defined as classic clinical syndrome, as defined above in the absence of confounding serology for another disease; possible AH was defined as clinically suspicious for AH, presence of confounding factors such as ischemic hepatitis, possible drug-induced liver injury, serology positive for another liver disease etiology, or uncertain alcohol use. It was proposed that patients with possible AH should undergo liver biopsy to confirm the diagnosis, especially if specific pharmacologic interventions are proposed. On the other hand, the diagnosis of probable AH may be associated with only a low rate of histologic misclassification and therefore biopsy may not be essential in this population.

Characteristic histological findings of AH include macro vesicular steatosis, lobular infiltration of neutrophils with hepatocyte damage (Mallory–Denk bodies and/or ballooning), bilirubin stasis and liver fibrosis, which is typically described as peri cellular and sinusoidal ("chicken wire" appearance) (58) (**Figure 4**). These features are indistinguishable from non-ASH and the alcohol–non-ALD index (including body mass index, gender, AST, ALT, and mean cell volume of the red blood cells or mean corpuscular volume) can be helpful to distinguish the two in cases of unclear alcohol consumption (59). The majority of AH patients have underlying macronodular cirrhosis, which is not easily distinguishable from other forms of cirrhosis. When cirrhosis is established, steatosis may be less prominent. On electron microscopic examination, megamitochondria may be observed. If liver biopsy is performed for diagnosis of AH, the findings may also have prognostic value. For example, one recent study showed that presence of severe fibrosis, megamitochondria, degree of neutrophil infiltration, and cholestasis could predict prognosis in patients with AH (60).

Prognostic scores and natural history

Many scoring systems have been developed to predict severity of AH. The Maddrey Discriminant Function is the most time tested and validated scoring system, with severe AH defined by Maddrey Discriminant Function ≥32 (61). Retrospective and prospective analysis of this score indicates that Maddrey Discriminant Function ≥32 predicts a mortality rate of ~20–50% over 30 days (62). Most clinical trials for AH have used this score based on its use in the original corticosteroid trials. A number of other scoring

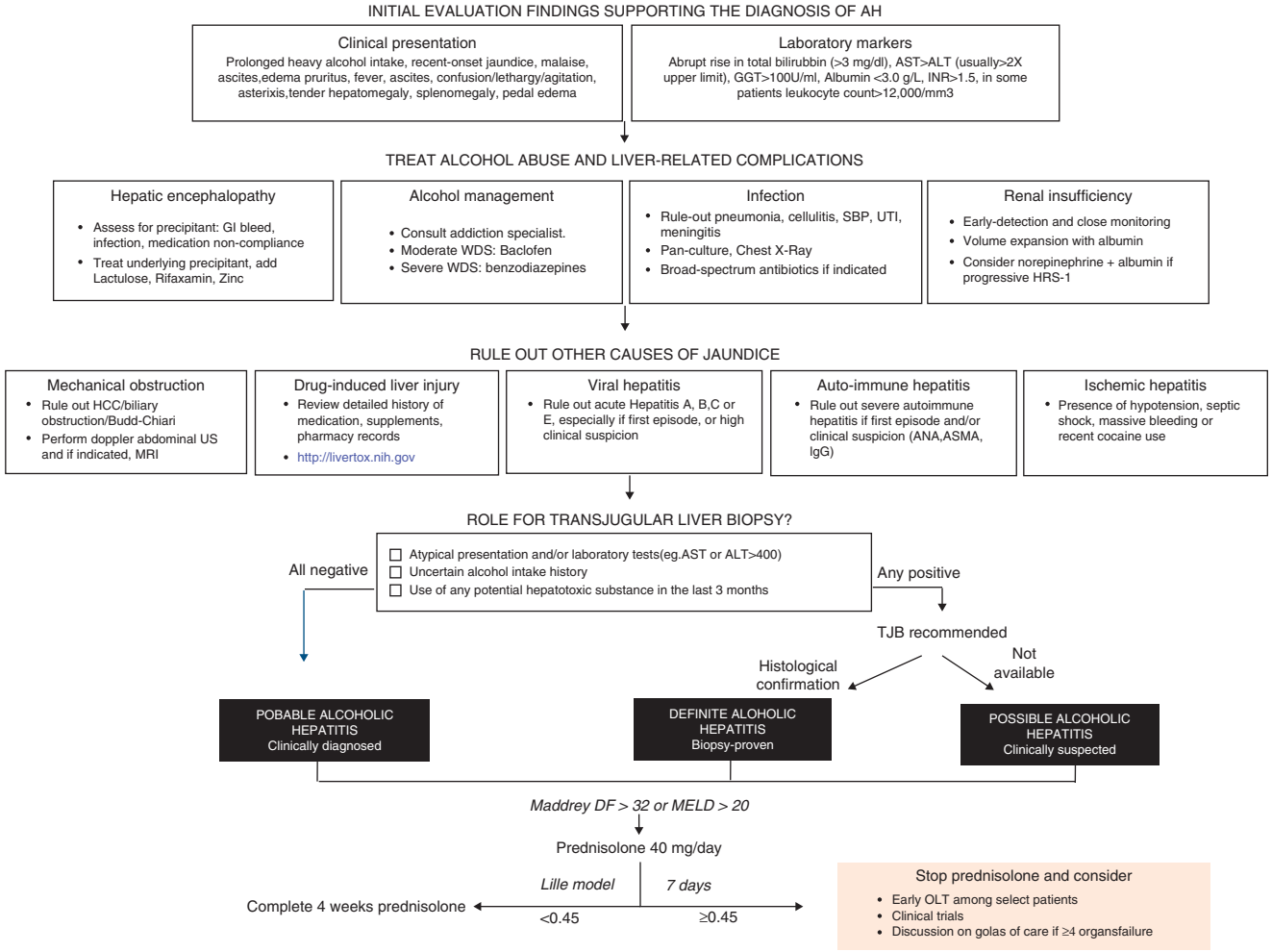

Figure 3. Approach towards the diagnosis and management of alcoholic hepatitis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio.

systems have also been validated and generally performed similar to the Maddrey score, including the MELD score, Age Bilirubin INR Creatinine (ABIC) score, and the Glasgow scale (62). The MELD score is being increasingly used to assess severity of AH given its better accuracy, worldwide use in organ allocation, INR as standard in reporting prothrombin time, and incorporation of renal function and serum creatinine, which is a major determinant of outcomes in AH patients. A MELD score >20 has been proposed as defining severe AH with an ~20% mortality (63). Lille score (a continuous score with a scale from 0 to 1) at 4–7 days of corticosteroids therapy can be used to assess the response to corticosteroids (Lille score <0.45) (64). Most of these scores by themselves do not predict prognosis accurately after 90 days and are most predictive at 30 days. A number of other variables influence prognosis after 30–90 days, most notably the ability to maintain abstinence from alcohol or not (5,6). Recent studies have shown that combination use of MELD at baseline and Lille score at day 7 has best discrimination and calibration for 2-month and 6-month mortality (65). In addition, serum lipopolysaccharide levels, SIRS criteria, and other serum markers may also serve as biomarkers of mortality (56).

Treatment of alcoholic hepatitis

General measures and supportive treatment: provided to all AH patients irrespective of disease severity.

Recommendation

6. Patients with AH should be considered for nutritional supplementation to ensure adequate caloric intake and to correct specific deficits, yet its effects on patient survival has not been proven (Conditional recommendation, very low level of evidence)

Key concepts and statements

11. Severe AH is identified by Maddrey's discriminant function score >32 or MELD score >20
12. SIRS syndrome at admission predisposes to acute kidney injury and multi-organ failure, which are associated with a poor prognosis. Physicians should take appropriate measures to prevent renal injury, such as avoidance of nephrotoxic drugs, judicious use of diuretics, and low threshold for expanding circulating blood volume with albumin or saline infusions

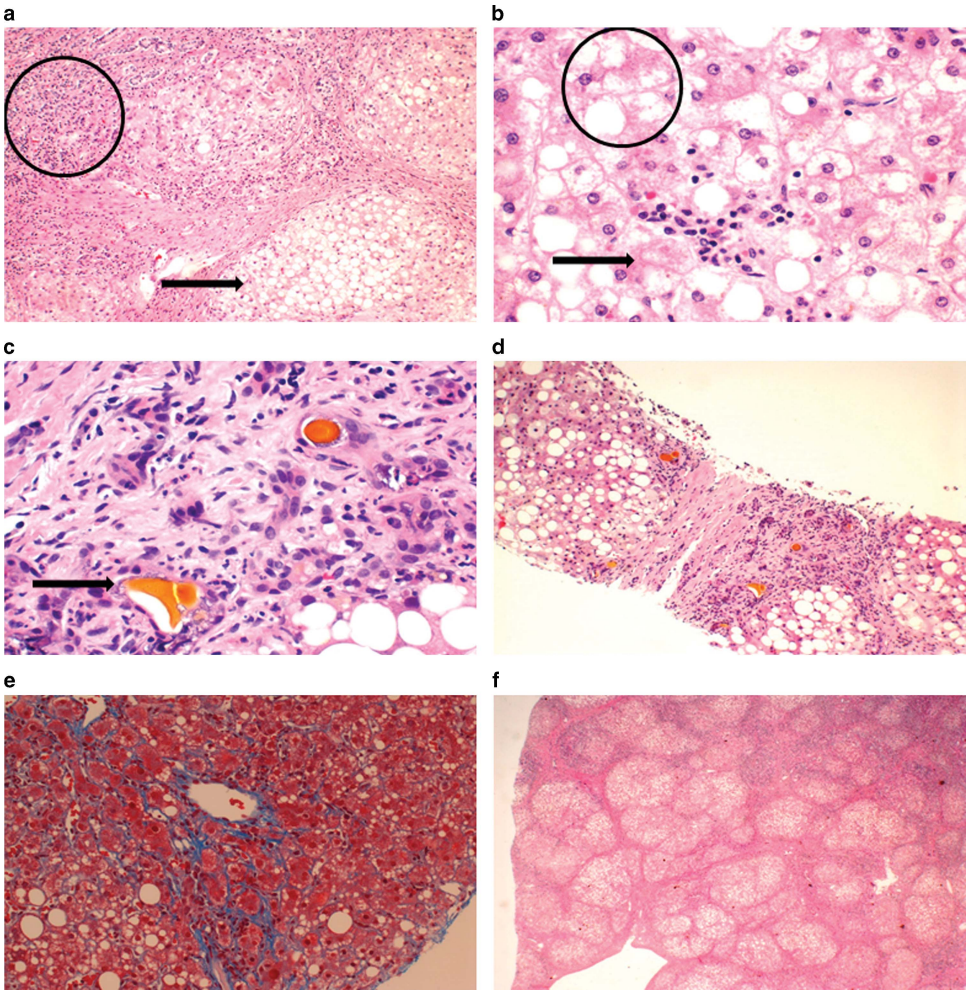

Figure 4. Histologic features of alcoholic hepatitis and Alcoholic Hepatitis Histologic Score. (**a**) Circle represents lobular inflammation and arrow represents steatosis, (**b**) circle and arrow represent cell ballooning, (**c**) arrow represents cholestasis with bile canalicular and hepatocyte plugging, (**d**) steatosis and fibrosis, (**e**) chicken wire and pericellular fibrosis, (**f**) cirrhosis.

13. Infections are common in AH patients and a comprehensive infectious screen is recommended as part of routine work-up of these patients. The development of bacterial infections during hospitalization is associated with poor prognosis

Patients hospitalized with severe AH often have history of active heavy alcohol use and present with manifestations of the SIRS (56). Sepsis and malnutrition are common among this population (4). Ascites, variceal bleeding, and hepatic encephalopathy may also be present. In-patient management should therefore focus on alcohol withdrawal, nutritional supplementation, infections and sepsis, complications of cirrhosis and portal hypertension, and specific treatment of AH. Patients may also develop acute on chronic liver failure, which manifests with hepatic and extrahepatic organ failure requiring intensive care (see below).

Nutrition and fluid replacement. Malnutrition and sarcopenia are common among hospitalized AH patients with negative impact on outcome (66–68). Many randomized controlled studies have shown improvement in nutritional status, but with controversial data on survival benefit with enteral supplementation (69–73) or parenteral supplementation. Although enteral supplementation in severe AH did not show survival benefit in a recently reported randomized study, there were more deaths with daily caloric intake of <21.5 kcal/kg per day compared with higher intake of calories. The enteral route due to its low cost, safety, and lower risk for infections is the preferred route. Feeding tube can be safely placed in the presence of esophageal varices without active bleeding or who have not undergone recent endoscopic variceal banding (74). Patients with severe AH need daily protein intake of 1.2 to 1.5 g/kg and caloric intake of 35 Kcal/kg. Zinc and other trace elements may need to be replaced. Thiamine and B complex vitamins need to be replaced. Albumin is preferred to crystalloid for volume replacement.

Intensive care. The patient may require transfer to the ICU in the presence of extrahepatic organ failure. Indications for transfer to the ICU include stage III or stage IV hepatic encephalopathy and the need for ventilation, respiratory failure, hemodynamic instability, and septic shock. Scoring systems to predict mortality in ICU patients include the SOFA score (75) and the CLIF SOFA

Table 4. Specific pharmacological therapies for management of alcoholic hepatitis

A) Therapies with proven efficacy
1. Corticosteroids
2. Nutritional supplementation
B) Therapies with potential efficacy
1. Pentoxifylline
2. *N*-acetyl cysteine
3. Granulocyte colony stimulating factor
C) Therapies with no efficacy
1. Tumor necrosis factor-α inhibitors
2. Antioxidant cocktail and vitamin E
3. Hepatic mitogens: insulin and glucagon, anabolic steroids
4. Propylthiouracil

score (76). The North American Consortium for Study of End Stage Liver Disease-Acute on Chronic Liver Failure (NACSELD ACLF) score is the easiest to use—patients with two or more extra-hepatic organ failures, second infections, and higher MELD score are at greatest risk of mortality (77).

Sepsis surveillance should be performed and broad-spectrum antibiotics should be administered before transfer to the ICU, or within one hour of admission. The choice of antibiotics depends on prevailing local antimicrobial resistance patterns. Piperacillin-tazobactam is generally the preferred drug used for sepsis, although vancomycin and meropenem may be considered in patients with penicillin hypersensitivity. As sepsis is difficult to diagnose in this group and about 40– 50% of patients may be culture negative, there should be a low threshold for diagnosis of infection and initiation of antibiotic therapy. Diagnosis of infections in patients with AH and cirrhosis should be performed using standardized definitions and guidelines (78). It is important to differentiate community acquired infections from nosocomial infections (onset after 48 h of admission to hospital) or healthcare-associated infections (within first 48 h of admission in patients with hospitalization within past 6 months, clinic visit within past 30 days, or those residing in nursing homes), as the empiric antibiotics for nosocomial or healthcare-associated infections should cover broadly for multidrug resistant bacteria, and in select high-risk cases for atypical organisms and fungal infections.

Ulcer prophylaxis is recommended using proton pump inhibitors. Both proton pump inhibitors and H2 antagonists increase the risk of infections such as aspiration pneumonia and clostridium difficile, but decrease the risk of chemical pneumonitis and gastrointestinal bleeding. Proton pump inhibitors are superior to H2 antagonists for the prevention of gastrointestinal bleeding. Glucose control is targeted to levels <200 mg/dL and transfusion is required with the hemoglobin target of 7–8 g/dL.

Organ failure scores are used to determine severity of acute on chronic liver failure. Patients with renal failure and acute kidney injury should receive diligent care with the aim to identify and reverse precipitating factors and improve renal function. Renal replacement therapy is recommended in the presence of acute kidney injury in the presence of sepsis-associated acute tubular necrosis, or if the cause of acute kidney injury is unclear. In the presence of hepatorenal syndrome, a therapeutic trial of renal replacement therapy may be considered in patients who are potential liver transplant candidates. Patients requiring pulmonary support should receive low tidal volume to avoid lung injury. Vasoconstrictors and pressor may be needed to maintain mean blood pressure of >65 mm Hg.

Specific pharmacologic therapies. Pharmacological therapies examined for AH patients are listed in **Table 4**.

Recommendations

7. Patients with severe AH should be treated with corticosteroids if there are no contraindications for their use (Strong recommendation, moderate level of evidence)
8. The existing evidence does not support the use of pentoxifylline for patients with severe AH. (Conditional recommendation, low level of evidence)

Key concepts and statements

14. Response to treatment with corticosteroids should be determined at 7 days using the Lille score. Treatment should be discontinued among non-responders to therapy, defined as those with a Lille score >0.45
15. Patients non-responsive to corticosteroids, ineligible for early LT, and with multiple organ failures may be considered for palliative therapy.

Corticosteroids. As the first randomized controlled study to assess efficacy of corticosteroids in the treatment of AH in 1971 (79), a total of 14 randomized studies (12 against placebo, 1 against enteral supplementation, and 1 against antioxidant cocktail) have reported conflicting data, likely to be due to variations on inclusion/exclusion criteria and the use of liver biopsy for confirming the diagnosis of AH (61,79–90). In a pooled analysis, using individual patient data from the five largest randomized controlled studies (85–88,91), corticosteroids provided survival benefit at 28 days (80% vs. 66%, $P<0.0001$) in half of the patients (92). The largest randomized placebo controlled multicenter study from the United Kingdom (the STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH) study) on 1,103 severe AH patients showed only a trend for mortality benefit at 28 days with prednisolone, compared with patients receiving placebo (13.8% vs. 18%, $P=0.056$). A meta-analysis of randomized studies (including the STOPAH study) showed that corticosteroids were effective in reducing short-term mortality by 46%.

Prednisolone is preferred over prednisone, as the latter requires conversion to prednisolone, which may be impaired in patients with impaired liver synthetic function. Moreover, prednisone did not improve patient survival in a randomized clinical trial (89). Prednisolone is used in a dose of 40 mg per day for a total duration of 4 weeks. Methylprednisolone 32 mg per day by intravenous route is used for patient unable to take oral medications. There are no studies examining different doses

and durations of corticosteroid therapy. Response to therapy is determined at 1 week of therapy using the Lille score. About 50–60% of patients do not respond to steroids (Lille score>0.45) and these patients do not derive further benefit from continuing steroids (**Figure 3**) (64). Recently, the Lille score at day 4 of corticosteroid therapy has been shown to be as accurate as day 7 Lille score in predicting the outcome and response to treatment, although this observation needs further validation studies (93). Unpredictable response to corticosteroids combined with fear of adverse effects, especially risk of infections limit the use of these drugs in routine clinical practice, with only 25–45% providers using them as reported in two different surveys (94,95). There is a clear unmet need for development of safer effective pharmacological options for management of AH patients and for biomarkers to predict response to corticosteroids at the time of presentation (96–98).

Active hepatitis B virus infection and active tuberculosis are contraindications for use of corticosteroids (99). Although HCV infection may potentially worsen the outcome of AH patients (30,100–102), there are no data on whether 4 weeks of corticosteroid therapy will increase HCV replication or that HCV infection worsens the response to corticosteroids. Active infection or sepsis, uncontrolled diabetes mellitus, and gastrointestinal bleeding remain relative contraindications to the use of corticosteroids. In these situations, corticosteroids can be used once the contraindication has been reversed with appropriate therapy. For example, use of corticosteroids after adequate control of infection has been reported to provide similar benefit as in uninfected patients (103). However, development of infections remains a concern among patients treated with corticosteroids, as these drugs compromise the immune status of an individual, putting them at risk for infections (104). In pooled data from 12 randomized studies comparing corticosteroids and placebo, infections during treatment occurred in about 20%, with steroid use associated with risk of fungal infections (105). In one study comprising patients with high bacterial DNA levels (>18.5 pg/mL) enrolling in the STOPAH study, the use of prophylactic antibiotics improved patient survival in corticosteroids treated patients (106). There remains an unmet need to determine accurate biomarkers with a potential for earlier diagnosis of infections, and randomized studies exploring benefit of antibiotics used as prophylaxis or as adjuvant to corticosteroids among patients with AH at high risk for development of infections (56).

Pentoxifylline. A phosphodiesterase inhibitor, pentoxifylline inhibits tumor necrosis factor-α activity, one of the major cytokines speculated in the pathogenesis of AH (107,108). As the first seminal study on the benefit of pentoxifylline used as 400 mg 3 times a day (109), many other randomized studies have failed to show survival benefit in severe AH patients (110–113). However, pentoxifylline has consistently shown benefit in reducing the risk of renal injury and deaths from hepatorenal syndrome (109,114). Although pentoxifylline is known to inhibit tumor necrosis factor, levels of tumor necrosis factor did not change with pentoxifylline (PTX) in the reported seminal study (109). Pentoxifylline compared with corticosteroids showed benefit in one study (115) and no difference in another study (116). Pentoxifylline was not effective when examined as salvage option for steroid non-responders, (117) or as an adjuvant therapy to corticosteroids (118,119). In a meta-analysis of 10 randomized studies, pentoxifylline failed to show survival benefit at 1 month, but was effective in reducing the occurrence of hepatorenal syndrome by 53% (120). The exact mechanism of renal protection with pentoxifylline remains unclear. The STOPAH study showed no survival benefit with pentoxifylline (90). In a network meta-analysis of 22 studies including the STOPAH study, there was low-quality evidence for benefit of pentoxifylline in reducing the short-term mortality at 28 days by 30% (121). It is possible that subgroups of patients (i.e., kidney failure) with AH may benefit from pentoxifylline, but this needs to be examined prospectively.

Tumor necrosis factor-α inhibitors. Based on pre-clinical efficacy and beneficial effects in open label pilot studies (122–125), trials examining infliximab and etanercept in the management of severe AH had to be terminated prematurely due to higher number of deaths in the treatment arm, with most deaths due to infections (126,127). The mechanisms of these findings are speculated to be due to blocking the beneficial effects of tumor necrosis factor on hepatic regeneration (128).

Antioxidants. Oxidative stress is a major player in the pathogenesis of ALD and AH (129). Antioxidant cocktails and vitamin E examined earlier have not shown beneficial effects in the management of severe AH (88,130,131). N-acetylcysteine infusion showed improved survival at 1 month, when used as an adjuvant to prednisolone in a multicenter randomized controlled study (132). There was no survival advantage with *N*-acetylcysteine at 3 or 6 months from presentation. A network meta-analysis comparing various pharmacological agents showed moderate quality evidence that combination of prednisolone and *N*-acetylcysteine provides best survival benefit at 28 days with 85% risk reduction of death from AH (121). However, more data on the efficacy of *N*-acetylcysteine in severe AH patients are needed before recommending its routine use in practice.

Miscellaneous drugs. Hepatic regenerative capacity supported by bone marrow-derived stem cells and hepatic progenitor cells is a major determinant of the outcome of patient with AH (133,134). However, drugs targeting this pathway including insulin and glucagon (135,136), anabolic steroid, oxandrolone (137), and propylthiouracil (138,139) failed to demonstrate a mortality benefit. Recently, the use of growth factors with granulocyte colony stimulating factor and erythropoietin have shown encouraging data in improving liver disease, reducing infectious complications, and patient survival (140,141). Molecular adsorbent recycling system safely improves liver disease, renal function, and portal hypertension, without any significant improvement in survival (142). Fecal transplantation has also been tested in eight subjects with contraindications to steroid therapy with encouraging results in a preliminary analyses (143). Patients with ≥4 failed organs being treated in ICU, who are not candidates for LT, are unlikely to survive beyond 3–6 months. Continuing further intensive treatment in these patients may be futile (**Figure 3**) (144).

LIVER TRANSPLANTATION IN ALCOHOLIC LIVER DISEASE

Liver transplantation for alcoholic cirrhosis

Key concepts and statements

16. Physicians should consider LT while formulating a management plan for patients with end-stage ALD
17. The decision on LT evaluation should not be based solely on minimum 6 months of alcohol abstinence, and other criteria should be taken into consideration
18. Patients too sick to complete rehabilitation therapy may be considered for transplantation via exception pathway dependent on individual center policy and the patient's profile. These patients should complete rehabilitation therapy after transplantation
19. Transplant recipients should be screened at each visit for use of alcohol and other substances especially tobacco and cannabis. Among recidivists, alcohol use should be quantified to identify harmful use
20. Immunosuppression should be optimized to use the lowest possible dose needed to prevent graft rejection. Use of sirolimus or everolimus may be considered over other immunosuppression drugs

LT is a definitive therapy for patients with cirrhosis and end-stage liver disease. Alcoholic cirrhosis is the third most common indication for LT after hepatitis C and non-alcoholic fatty liver disease. LT for alcohol related cirrhosis accounts for about 15% of all liver transplants in the United States and about 20% in Europe (145–147). Similarly, of all the LT performed, about 10% and 6% are performed for HCV-infected drinkers in the United States and Europe, respectively (145–147).

Referral for LT. Access to LT involves three steps: referral to a LT center, formal evaluation and listing, and finally receipt of LT. Although, barriers to receiving LT exist at every step, physicians may have bias against referral of patients with alcoholic cirrhosis for formal LT evaluation (148). Subjective variables like patient age, physician empathy on alcoholism as a disease and not behavior, geographical area, race, amount and duration of alcohol use, and adherence to treatment are some of the barriers for referral of patients, who otherwise may be potential LT candidates (148–150). Studies are needed to provide a basis for deriving guidelines using objective parameters on referral of these patients to a LT center. While evaluating an ALD patient for LT, specific issues as outlined below need to be considered.

Evaluation for comorbidities. Alcohol consumed on a long-term basis can damage other body organs such as the cardiovascular system (cardiomyopathy, hypertension, and chronic kidney disease), gastrointestinal system (chronic pancreatitis, diarrhea, malnutrition, and vitamin deficiencies), nervous system (Wernicke's encephalopathy, seizures, dementia, and peripheral neuropathy), hematological system (macrocytosis and multifactorial anemia), musculoskeletal system (sarcopenia, deconditioning, and osteoporosis), and psychological system (psychiatric comorbidities and use of cigarette smoking and recreational drugs) (151–154). In one epidemiological study, either alcohol abuse or smoking was associated with a nearly two-fold increased risk for chronic kidney disease and this risk was about fivefold when both factors were present (154). Presence of any of these comorbidities in ALD patients should be assessed before transplantation since they can negatively impact posttransplant outcomes (150,151).

Evaluation for risk of recidivism. Relapse to alcohol use after LT (recidivism) is an important concern in any transplant recipient who had AUD before transplantation (155). Most transplant centers require minimum of 6 months of abstinence before considering LT evaluation (150). However, data on minimum 6 months of abstinence as a predictor of recidivism remain conflicting. Other predictors include younger age, social support, psychiatric comorbidities, polysubstance abuse, duration and amount of alcohol use, family history of alcoholism, and failed rehabilitation attempts (156,157). Many transplant centers utilize the Psychosocial Assessment of Candidacy for Transplantation scale to evaluate patients to stratify patients to low, intermediate and high risk for recidivism (34). Patients at high risk for recidivism are particularly advised to go through therapy for alcoholism prior to LT (158). Patients waiting on the transplant list should be monitored for alcohol consumption at every clinic visit, as about 17–30% of these patients may relapse to alcohol use (159,160).

Involvement of addiction specialists and incorporation of an addiction unit within the LT center is useful in reducing frequency of drinking and recidivism compared to referring these patients to an outside center for addiction therapy (161). However, the patient's degree of illness and transportation issues may be significant limiting factors in these patients' ability to complete therapy sessions (40).

Posttransplant outcomes. Patient survival rates after LT for alcoholic cirrhosis at 1, 3, 5, and 10 years after LT are reported to be 84–89%, 78–83%, 73–79%, and 58–73%, respectively, which are better compared with transplants for HCV cirrhosis or for HCC, and similar to other indications for LT (145,147). These excellent results are associated with improved feeling of physical and mental health, environment at home and at work, sexual relationship, and relationships within family and friends (162–164). Although transplant recipients experience an improved quality of life within the first year, this tends to decline over long-term with perception of poorer physical health (165). Many transplant recipients resume employment and return to work, either full or part time.

It is important to emphasize that LT cures the liver disease, but not the underlying AUD (150). Prevalence of recidivism varies from 10 to 60% across different studies due to variations on definition of recidivism (any or harmful alcohol use) and on follow-up time after LT. In a pooled data from 50 studies on LT for alcoholic cirrhosis, annual incidence of recidivism was 5.7% and 2.5% for any alcohol use and for harmful use, respectively (166). Recidivism is most likely to be reported after 2 years of LT with the majority of recidivists reporting intermittent use of alcohol (155,167). Patients with harmful use of alcohol after LT have 10-year survival rates 45–71%, compared with 75–93% among abstinent patients or those with occasional slips (168–171). Self-reported alcohol use is often unreliable (159,172), and biomarkers of alcohol consumption can help in identifying patients with ongoing alcohol consumption (please refer to the section on 'Diagnosis of AUD').

The limited data comparing outcomes of patients receiving LT for liver disease due to combined ALD and HCV infection with LT for alcoholic cirrhosis have shown conflicting findings, likely due to variations on HCV treatment before LT and on data source (registry based vs. single-center chart review) (173–175). Whether outcomes of transplant recipients of HCV infected drinkers will improve with the advent of newer potent and safer anti-HCV therapy, remains a testable hypothesis, yet to be answered.

Causes of posttransplant morbidity and mortality. Important causes of patient morbidity and mortality among transplant recipients for alcoholic cirrhosis are development of *de-novo* malignancy or cardiovascular complications. Compared with the general population, the risk of development of *de-novo* malignancy is about two- to threefold higher among transplant recipients for alcoholic cirrhosis, contributing to 20–40% of all deaths (176,177) especially malignancies of the head and neck, pharynx, esophagus, and lung (176–179).

The risk for aero-digestive cancers is higher among transplant recipients with a history of smoking prior to LT and who continue to smoke after LT (179,180). The risk of malignancy may be also related to dose and type of immunosuppression. Compared with other immune-suppressing drugs, malignancy risk is lower with agents targeting mammalian target of rapamycin inhibitors such as sirolimus an everolimus, given their anti-tumor effects (181,182).

Recurrent alcoholic cirrhosis is reported in about 5% of all LT performed for alcoholic cirrhosis, with cumulative probability of 33–54% at 10 years after LT among recidivists (183,184). Survival of patients with recurrent cirrhosis is about 41 and 21% at 10 and 15 years after LT respectively, compared to similar survival rates of about 70 and 50% among abstainers (183). Immunosuppression should be maintained at the lowest safe levels as with all patients who undergo a liver transplant; it is unclear whether everolimus or sirolimus are superior to calcineurin inhibitors among patients transplanted for alcoholic cirrhosis (185).

Liver transplantation for alcoholic hepatitis

Recommendation

9. LT may be considered for highly selected patients with severe AH (Strong recommendation, moderate level of evidence)

To minimize the risk of recidivism, most transplant centers require a minimum of 6 months of abstinence before considering LT for a patient with ALD. However, patients with severe AH not

Table 5. Areas of prospects and clinical translational research

A. Epidemiology and prevention
1. Population based studies on prevalence of early spectrum of alcoholic liver disease and steatohepatitis
2. Cost-effective measures to reduce alcohol consumption
3. Collaborative studies with addiction service with long-term outcome as end
4. Reliable and accurate models to predict recidivism
5. Studies on efficacy and safety of baclofen and other drugs for alcohol abstinence in patients with alcoholic hepatitis
6. Biomarkers for clinical use for predicting alcohol consumption
7. Studies to identify genetic factors predicting response to abstinence
B. Pharmacological therapies
1. Developing animal models simulating human AH phenotype
2. Studies on mechanism and benefits of pentoxifylline in AH patients with renal failure
3. Non-invasive accurate biomarkers for predicting response to corticosteroids
4. Safer and effective targets and for treatment of alcoholic hepatitis
5. Drugs for improving the long-term outcome with improvement in fibrosis
6. Studies on treatment of hepatitis C in patients with alcoholic hepatitis
7. Guidelines on treatment of alcoholic hepatitis in patients with hepatitis C
C. Liver transplantation
1. Multicenter prospective data on liver transplantation in alcoholic hepatitis
2. Criteria for patient selection for liver transplantation in alcoholic hepatitis
3. Immunosuppression and antibiotic prophylaxis in peri-transplantation period
4. Biomarkers for early diagnosis of infections in patients with AH
5. Protocol for malignancy surveillance before and after transplantation
6. Genetic factors to predict recurrent disease in graft among recidivists
7. Strategies to overcome barriers to liver transplantation in alcoholic hepatitis

responding to medical therapy cannot afford to meet this requirement given their short-term mortality at 1 month from presentation as high as 50% (96). The lack of effective rescue medical therapies for non-responders to prednisolone provides the rationale for considering early LT.

In a case controlled study, Mathurin *et al.* (186) transplanted highly selected patients with severe AH, who were non-responsive to corticosteroids and had a favorable psychosocial profile. Patients receiving early LT for AH were compared with an historical cohort managed medically. Survival at 6 months of patients with early LT was dramatically improved (77% vs. 23%) (186). Most of this benefit was achieved within first month, confirming the utility of early LT in salvaging select AH patients who do not respond to corticosteroids. Further, recidivism was only reported in a minority of patients with salvage LT (<15%) (186). The recidivism rate reported in this study was similar to historical data on self-reported annual recidivism rate in LT recipients for alcoholic cirrhosis (166). In another study on analysis of national transplant database in the United States, patients receiving LT for listing diagnosis of AH compared with matched LT recipients for alcoholic cirrhosis had similar liver graft and patient survival at 5 years follow-up (187). Data are also emerging from other centers reporting similar benefits of early LT in select severe AH patients (188–190). As patients with AH are neither listed for urgent LT nor receive exception points, live donor LT is being performed in many Asian countries. Limited data on outcomes of living donor LT in AH patients are similar compared with LT using deceased donors (191). In light of these emerging data, early LT as a definitive therapy is gaining momentum and acceptance within the transplant community, as well as the general public (190,192). LT for AH can salvage these sick AH patients at risk of death in their most productive life and consumes only 1.5–3% of the donor pool (186,188,190).

Despite these encouraging data, there remain barriers at every level to use this treatment modality for AH. For example, in a recently reported survey, LT center directors in the US reported center protocol, socio-cultural issues, organ shortage, and insurance approval as barriers to LT in AH (190). In this survey, there was agreement among the transplant centers on excellent psychosocial support and non-response to corticosteroids as criteria for patient selection. However, only 50% of LT centers were using all the five criteria proposed in the study by Mathurin *et al.* (190). Further, 1-year survival of 77% as reported in the prospective study is inferior to historic survival of over 90% after LT for alcoholic cirrhosis, with majority of deaths being due to invasive fungal infections (145,186). Patients with severe AH are prone to fungal infections, especially those who are non-responders to corticosteroids (105,193). Prospective multicenter studies are needed as basis for deriving guidelines for selection of AH patients for LT, antibiotic protocol for infection prevention in the perioperative period, and immunosuppression protocol on long-term follow-up of these patients.

CONCLUSIONS AND PROSPECTS

Alcohol use constitutes a huge economic and population burden in the United States and worldwide. Despite the known hepatotoxic effect of alcohol use, the field lacks availability of effective safe pharmacotherapies for management of ALD patients. With growing interest of the research community and increasing funding from National Institute of Alcoholism and Alcohol Abuse and other organizations, the future holds promise for overcoming some of these urgent unmet clinical needs in this field (**Table 5**).

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CONFLICT OF INTEREST

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REFERENCES

1. Yoon Y-H, Chen CM. Surveillance Report #105. Liver cirrhosis mortality in the United States: national, state, and regional trends, 2000-2013. 2016 (cited 19 April 2017). Available at https://pubs.niaaa.nih.gov/publications/surveillance105/Cirr13.htm
2. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825–32.
3. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology 2004;127:S87–S96.
4. Orntoft NW, Sandahl TD, Jepsen P *et al.* Short-term and long-term causes of death in patients with alcoholic hepatitis in Denmark. Clin Gastroenterol Hepatol 2014;12:1739–44 e1.
5. Lackner C, Spindelboeck W, Haybaeck J *et al.* Histological parameters and alcohol abstinence determine long-term prognosis in patients with alcoholic liver disease. J Hepatol 2017;66:610–8.
6. Louvet A, Labreuche J, Artru F *et al.* Main drivers of outcome differ between short and long-term in severe alcoholic hepatitis: a prospective study. Hepatology 2017;66:1464–73.
7. Alcohol Facts and Statistics. In: Alcoholism NIoAAa, editor. 2017.
8. Yoon YH, CC . Liver cirrhosis mortality in the United States: National, State, and Regional trends, 2000–2013. In: Alcoholism NIoAAa, editor 2016.
9. Stein E, Cruz-Lemini M, Altamirano J *et al.* Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol 2016;65:998–1005.
10. Sheron N. Alcohol and liver disease in Europe--simple measures have the potential to prevent tens of thousands of premature deaths. J Hepatol 2016;64:957–67.
11. Askgaard G, Gronbaek M, Kjaer MS *et al.* Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. J Hepatol 2015;62:1061–7.
12. Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. 2004 (cited 20 April 2017). Available at https://pubs.niaaa.nih.gov/publications/arh27-3/209-219.htm

13. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 2011;141:1572–85.
14. Ndugga N, Lightbourne TG, Javaherian K *et al.* Disparities between research attention and burden in liver diseases: implications on uneven advances in pharmacological therapies in Europe and the USA. BMJ Open 2017;7:e013620.
15. Frezza M, di Padova C, Pozzato G *et al.* High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med 1990;322:95–9.
16. Hart CL, Morrison DS, Batty GD *et al.* Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. BMJ 2010;340:c1240.
17. Goh GB, Chow WC, Wang R *et al.* Coffee, alcohol and other beverages in relation to cirrhosis mortality: the Singapore Chinese Health Study. Hepatology 2014;60:661–9.
18. Nahon P, Sutton A, Rufat P *et al.* Liver iron, HFE gene mutations, and hepatocellular carcinoma occurrence in patients with cirrhosis. Gastroenterology 2008;134:102–10.
19. Nahon P, Nuraldeen R, Rufat P *et al.* In alcoholic cirrhosis, low-serum hepcidin levels associate with poor long-term survival. Liver Int 2016;36:185–8.
20. Yuan JM, Ross RK, Wang XL *et al.* Morbidity and mortality in relation to cigarette smoking in Shanghai, China. A prospective male cohort study. JAMA 1996;275:1646–50.
21. Jepsen P, Ott P, Andersen PK *et al.* Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51:1675–82.
22. Pares A, Caballeria J, Bruguera M *et al.* Histological course of alcoholic hepatitis. Influence of abstinence, sex and extent of hepatic damage. J Hepatol 1986;2:33–42
23. Hrubec Z, Omenn GS. Evidence of genetic predisposition to alcoholic cirrhosis and psychosis: twin concordances for alcoholism and its biological end points by zygosity among male veterans. Alcohol Clin Exp Res 1981;5:207–15.
24. Whitfield JB. Meta-analysis of the effects of alcohol dehydrogenase genotype on alcohol dependence and alcoholic liver disease. Alcohol Alcohol 1997;32:613–9.
25. Salameh H, Raff E, Erwin A *et al.* pnpla3 gene polymorphism is associated with predisposition to and severity of alcoholic liver disease. Am J Gastroenterol 2015;110:846–56.
26. Ali M, Yopp A, Gopal P *et al.* A variant in PNPLA3 associated with fibrosis progression but not hepatocellular carcinoma in patients with hepatitis C virus infection. Clin Gastroenterol Hepatol 2016;14:295–300.
27. Lane BP, Lieber CS. Ultrastructural alterations in human hepatocytes following ingestion of ethanol with adequate diets. Am J Pathol 1966;49:593–603.
28. Rubin E, Lieber CS. Alcohol-induced hepatic injury in nonalcoholic volunteers. N Engl J Med 1968;278:869–76.
29. Barrio E, Tome S, Rodriguez I *et al.* Liver disease in heavy drinkers with and without alcohol withdrawal syndrome. Alcohol Clin Exp Res 2004;28:131–6.
30. Singal AK, Kuo YF, Anand BS. Hepatitis C virus infection in alcoholic hepatitis: prevalence patterns and impact on in-hospital mortality. Eur J Gastroenterol Hepatol 2012;24:1178–84.
31. Askgaard G, Leon DA, Kjaer MS *et al.* Risk for alcoholic liver cirrhosis after an initial hospital contact with alcohol problems: a nationwide prospective cohort study. Hepatology 2017;65:929–37.
32. Saunders JB, Aasland OG, Babor TF *et al.* Development of the alcohol use disorders identification test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 1993;88:791–804.
33. Bradley KA, DeBenedetti AF, Volk RJ *et al.* AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res 2007;31:1208–17.
34. Singal AK, Chaha KS, Rasheed K *et al.* Liver transplantation in alcoholic liver disease current status and controversies. World J Gastroenterol 2013;19:5953–63.
35. Fleming MF, Anton RF, Spies CD. A review of genetic, biological, pharmacological, and clinical factors that affect carbohydrate-deficient transferrin levels. Alcohol Clin Exp Res 2004;28:1347–55.
36. Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: recent advances and future research opportunities. Alcohol Clin Exp Res 2010;34:955–67.
37. Staufer K, Andresen H, Vettorazzi E *et al.* Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. Hepatology 2011;54:1640–9.
38. Sterneck M, Yegles M, Rothkirch von G *et al.* Determination of ethyl glucuronide in hair improves evaluation of long-term alcohol abstention in liver transplant candidates. Liver Int 2014;34:469–76.
39. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. J Psychosom Res 1997;42:17–41.
40. Weinrieb RM, Van Horn DH, Lynch KG *et al.* A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver Transpl 2011;17:539–47.
41. Jonas DE, Amick HR, Feltner C *et al.* Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 2014;311:1889–900.
42. Addolorato G, Leggio L, Ferrulli A *et al.* Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007;370:1915–22.
43. Leggio L, Lee MR. Treatment of alcohol use disorder in patients with alcoholic liver disease. Am J Med 2017;130:124–34.
44. Foxcroft DR, Coombes L, Wood S *et al.* Motivational interviewing for alcohol misuse in young adults. Cochrane Database Syst Rev 2014, CD007025.
45. Sullivan JT, Sykora K, Schneiderman J *et al.* Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 1989;84:1353–7.
46. Mayo-Smith MF, Beecher LH, Fischer TL *et al.* Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004;164:1405–12.
47. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 1997;278:144–51.
48. Amato L, Minozzi S, Vecchi S *et al.* Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev 2010, CD005063.
49. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database Syst Rev 2011, CD008537.
50. Garcia-Tsao G, Abraldes JG, Berzigotti A *et al.* Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310–35.
51. Heimbach J, Kulik LM, Finn R *et al.* AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2017; e-pub ahead of print, 28 January 2017.
52. Runyon BA. Committee APG. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49:2087–107.
53. Drenth JP, Montagnese S. First evidence-based guidelines for the diagnosis and management of hepatic encephalopathy: a welcome development. J Hepatol 2015;62:1457.
54. Garcia-Tsao G, Sanyal AJ, Grace ND *et al.* Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–38.
55. Basra G, Basra S, Parupudi S. Symptoms and signs of acute alcoholic hepatitis. World J Hepatol 2011;3:118–20.
56. Michelena J, Altamirano J, Abraldes JG *et al.* Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. Hepatology 2015;62:762–72.
57. Crabb DW, Bataller R, Chalasani NP *et al.* Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology 2016;150:785–90.
58. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009;360:2758–69.
59. Dunn W, Angulo P, Sanderson S *et al.* Utility of a new model to diagnose an alcohol basis for steatohepatitis. Gastroenterology 2006;131:1057–63.
60. Altamirano J, Miquel R, Katoonizadeh A *et al.* A histologic scoring system for prognosis of patients with alcoholic hepatitis. Gastroenterology 2014;146:1231–9.e1-6
61. Maddrey WC, Boitnott JK, Bedine MS *et al.* Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193–9.
62. Gholam PM. Prognosis and prognostic scoring models for alcoholic liver disease and acute alcoholic hepatitis. Clin Liver Dis 2016;20:491–7.
63. Dunn W, Jamil LH, Brown LS *et al.* MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology 2005;41:353–8.
64. Louvet A, Naveau S, Abdelnour M *et al.* The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45:1348–54.

65. Louvet A, Labreuche J, Artru F *et al.* Combining data from liver disease scoring systems better predicts outcomes of patients with alcoholic hepatitis. Gastroenterology 2015;149:398–406 e8.quiz e16-7.
66. Mendenhall CL, Anderson S, Weesner RE *et al.* Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med 1984;76:211–22.
67. Mendenhall C, Roselle GA, Gartside P *et al.* Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995;19:635–41.
68. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. Clin Liver Dis 2012;16:805–26.
69. Calvey H, Davis M, Williams R. Controlled trial of nutritional supplementation, with and without branched chain amino acid enrichment, in treatment of acute alcoholic hepatitis. J Hepatol 1985;1:141–51.
70. Mendenhall C, Bongiovanni G, Goldberg S *et al.* VA Cooperative Study on Alcoholic Hepatitis. III: Changes in protein-calorie malnutrition associated with 30 days of hospitalization with and without enteral nutritional therapy. J Parenter Enteral Nutr 1985;9:590–6.
71. Mendenhall CL, Moritz TE, Roselle GA *et al.* A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. Hepatology 1993;17:564–76.
72. Moreno C, Langlet P, Hittelet A *et al.* Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: a randomized multicenter controlled trial. J Hepatol 2010;53:1117–22.
73. Moreno C, Deltenre P, Senterre C *et al.* Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. Gastroenterology 2016;150:903–910 e8.
74. de Ledinghen V, Beau P, Mannant PR *et al.* Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study. Dig Dis Sci 1997;42:536–41.
75. Piano S, Bartoletti M, Tonon M *et al.* Assessment of Sepsis-3 criteria and quick SOFA in patients with cirrhosis and bacterial infections. Gut 2017; e-pub ahead of print, 31 August 2017.
76. Moreau R, Jalan R, Gines P *et al.* Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426–37.1437 e1-9
77. Bajaj JS, O'Leary JG, Reddy KR *et al.* Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology 2014;60:250–6.
78. Nadim MK, Durand F, Kellum JA *et al.* Management of the critically ill patient with cirrhosis: a multidisciplinary perspective. J Hepatol 2016;64:717–35.
79. Helman RA, Temko MH, Nye SW *et al.* Alcoholic hepatitis. Natural history and evaluation of prednisolone therapy. Ann Intern Med 1971;74:311–21.
80. Blitzer BL, Mutchnick MG, Joshi PH *et al.* Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double-blind randomized study. Am J Dig Dis 1977;22:477–84.
81. Lesesne HR, Bozymski EM, Fallon HJ. Treatment of alcoholic hepatitis with encephalopathy. Comparison of prednisolone with caloric supplements. Gastroenterology 1978;74:169–73.
82. Shumaker JB, Resnick RH, Galambos JT *et al.* A controlled trial of 6-methylprednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients. Am J Gastroenterol 1978;69:443–9.
83. Depew W, Boyer T, Omata M *et al.* Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. Gastroenterology 1980;78:524–9.
84. Theodossi A, Eddleston AL, Williams R. Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis. Gut 1982;23:75–9.
85. Carithers RLJr., Herlong HF, Diehl AM *et al.* Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med 1989;110:685–90.
86. Ramond MJ, Poynard T, Rueff B *et al.* A randomized trial of prednisolone in patients with severe alcoholic hepatitis. N Engl J Med 1992;326:507–12.
87. Cabre E, Rodriguez-Iglesias P, Caballeria J *et al.* Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology 2000;32:36–42.
88. Phillips M, Curtis H, Portmann B *et al.* Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. J Hepatol 2006;44:784–90.
89. Campra JL, Hamlin EMJr., Kirshbaum RJ *et al.* Prednisone therapy of acute alcoholic hepatitis. Report of a controlled trial. Ann Intern Med 1973;79:625–31.
90. Thursz MR, Richardson P, Allison M *et al.* Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med 2015;372:1619–28.
91. Mendenhall CL, Anderson S, Garcia-Pont P *et al.* Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. N Engl J Med 1984;311:1464–70.
92. Mathurin P, O'Grady J, Carithers RL *et al.* Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 2011;60:255–60.
93. Garcia-Saenz-de-Sicilia M, Duvoor C, Altamirano J *et al.* A day-4 Lille model predicts response to corticosteroids and mortality in severe alcoholic hepatitis. Am J Gastroenterol 2016.
94. Singal AK, Salameh H, Singal A *et al.* Management practices of hepatitis C virus infected alcoholic hepatitis patients: A survey of physicians. World J Gastrointest Pharmacol Ther 2013;4:16–22.
95. Ahn JMT, Cohen SM. Evaluation and management of alcoholic hepatitis: A survey of current practices. Hepatology 2009, 612A.
96. Singal AK, Kamath PS, Gores GJ *et al.* Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol 2014;12:555–64.quiz e31-2
97. Sanyal AJ, Gao B, Szabo G. Gaps in knowledge and research priorities for alcoholic hepatitis. Gastroenterology 2015;149:4–9.
98. Chacko BK, Kramer PA, Ravi S *et al.* The Bioenergetic Health Index: a new concept in mitochondrial translational research. Clin Sci (Lond) 2014;127:367–73.
99. Singal AK, Walia I, Singal A *et al.* Corticosteroids and pentoxifylline for the treatment of alcoholic hepatitis: current status. World J Hepatol 2011;3:205–10.
100. Singal AK, Sagi S, Kuo YF *et al.* Impact of hepatitis C virus infection on the course and outcome of patients with acute alcoholic hepatitis. Eur J Gastroenterol Hepatol 2011;23:204–9.
101. Punzalan CS, Bukong TN, Szabo G. Alcoholic hepatitis and HCV interactions in the modulation of liver disease. J Viral Hepat 2015;22: 769–76.
102. Shoreibah M, Anand BS, Singal AK. Alcoholic hepatitis and concomitant hepatitis C virus infection. World J Gastroenterol 2014;20:11929–34.
103. Louvet A, Wartel F, Castel H *et al.* Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 2009;137:541–8.
104. Franchimont D. Overview of the actions of glucocorticoids on the immune response: a good model to characterize new pathways of immunosuppression for new treatment strategies. Ann N Y Acad Sci 2004;1024:124–37.
105. Hmoud BS, Patel K, Bataller R *et al.* Corticosteroids and occurrence of and mortality from infections in severe alcoholic hepatitis: a meta-analysis of randomized trials. Liver Int 2015;36:721–8.
106. Vergis N, Atkinson SR, Knapp S *et al.* In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. Gastroenterology 2017;152:1068–1077 e4.
107. Reuter BK, Wallace JL. Phosphodiesterase inhibitors prevent NSAID enteropathy independently of effects on TNF-alpha release. Am J Physiol 1999;277:G847–G854.
108. McClain CJ, Cohen DA. Increased tumor necrosis factor production by monocytes in alcoholic hepatitis. Hepatology 1989;9:349–51.
109. Akriviadis E, Botla R, Briggs W *et al.* Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 2000;119:1637–48.
110. Paladugu H, SP , Dalvi L *et al.* Role of pentoxifylline in treatment of severe alcoholic hepatitis—a randomized controlled trial. J Gastroenterol Hepatol 2006;21:
111. McHutchison JG, RB , Dragueskı JO *et al.* Pentoxifylline may prevent renal impairment (hepatorenal syndrome) in severe acute alcoholic hepatitis. Hepatology 1991;14:96A.
112. Sidhu S, SM , Bhatia K. Pentoxifylline reduces disease severity and prevents renal impairment in severe acute acloholic hepatitis: a double-blind placebo-controleld trial. Hepatology 2006;44:373A.
113. Leebrec D, Thabut D, Oberti F *et al.* Pentoxifylline for treatment of patients with advanced cirrhosis. A randomzied placebo controlled double blind trial. Hepatology 2007;46:A249–A250.
114. Whitfield K, Rambaldi A, Wetterslev J *et al.* Pentoxifylline for alcoholic hepatitis. Cochrane Database Syst Rev 2009, CD007339.
115. De BK, Gangopadhyay S, Dutta D *et al.* Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. World J Gastroenterol 2009;15:1613–9.

116. Park SH, Kim DJ, Kim YS *et al.* Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial. J Hepatol 2014;61:792–8.
117. Louvet A, Diaz E, Dharancy S *et al.* Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. J Hepatol 2008;48:465–70.
118. Sidhu SS, Goyal O, Singla P *et al.* Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). Dig Dis Sci 2012;57:1664–71.
119. Mathurin P, Louvet A, Duhamel A *et al.* Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. JAMA 2013;310:1033–41.
120. Parker R, Armstrong MJ, Corbett C *et al.* Systematic review: pentoxifylline for the treatment of severe alcoholic hepatitis. Aliment Pharmacol Ther 2013;37:845–54.
121. Singh S, Murad MH, Chandar AK *et al.* Comparative effectiveness of pharmacological interventions for severe alcoholic hepatitis: a systematic review and network meta-analysis. Gastroenterology 2015;149:958–70.e12.
122. Iimuro Y, Gallucci RM, Luster MI *et al.* Antibodies to tumor necrosis factor alfa attenuate hepatic necrosis and inflammation caused by chronic exposure to ethanol in the rat. Hepatology 1997;26:1530–7.
123. Tilg H, Jalan R, Kaser A *et al.* Anti-tumor necrosis factor-alpha monoclonal antibody therapy in severe alcoholic hepatitis. J Hepatol 2003;38:419–25.
124. Sharma P, Kumar A, Sharma BC *et al.* Infliximab monotherapy for severe alcoholic hepatitis and predictors of survival: an open label trial. J Hepatol 2009;50:584–91.
125. Menon KV, Stadheim L, Kamath PS *et al.* A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis. Am J Gastroenterol 2004;99:255–60.
126. Naveau S, Chollet-Martin S, Dharancy S *et al.* A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. Hepatology 2004;39:1390–7.
127. Boetticher NC, Peine CJ, Kwo P *et al.* A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology 2008;135:1953–60.
128. Akerman P, Cote P, Yang SQ *et al.* Antibodies to tumor necrosis factor-alpha inhibit liver regeneration after partial hepatectomy. Am J Physiol 1992;263:G579–G585.
129. Loguercio C, Federico A. Oxidative stress in viral and alcoholic hepatitis. Free Radic Biol Med 2003;34:1–10.
130. Stewart S, Prince M, Bassendine M *et al.* A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 2007;47:277–83.
131. Mezey E, Potter JJ, Rennie-Tankersley L *et al.* A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. J Hepatol 2004;40:40–6.
132. Nguyen-Khac E, Thevenot T, Piquet MA *et al.* Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med 2011;365:1781–9.
133. Fang JW, Bird GL, Nakamura T *et al.* Hepatocyte proliferation as an indicator of outcome in acute alcoholic hepatitis. Lancet 1994;343:820–3.
134. Dubuquoy L, Louvet A, Lassailly G *et al.* Progenitor cell expansion and impaired hepatocyte regeneration in explanted livers from alcoholic hepatitis. Gut 2015;64:1949–60.
135. Trinchet JC, Balkau B, Poupon RE *et al.* Treatment of severe alcoholic hepatitis by infusion of insulin and glucagon: a multicenter sequential trial. Hepatology 1992;15:76–81.
136. Bird G, Lau JY, Koskinas J *et al.* Insulin and glucagon infusion in acute alcoholic hepatitis: a prospective randomized controlled trial. Hepatology 1991;14:1097–101.
137. Rambaldi A, Iaquinto G, Gluud C. Anabolic-androgenic steroids for alcoholic liver disease: a Cochrane review. Am J Gastroenterol 2002;97:1674–81.
138. Orrego H, Israel Y. Propylthiouracil treatment for alcoholic hepatitis: the case of the missing thirty. Gastroenterology 1982;83:945–6.
139. Halle P, Pare P, Kaptein E *et al.* Double-blind, controlled trial of propylthiouracil in patients with severe acute alcoholic hepatitis. Gastroenterology 1982;82:925–31.
140. Singh V, Sharma AK, Narasimhan RL *et al.* Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. Am J Gastroenterol 2014;109:1417–23.
141. Kedarisetty CK, Anand L, Bhardwaj A *et al.* Combination of granulocyte colony-stimulating factor and erythropoietin improves outcomes of patients with decompensated cirrhosis. Gastroenterology 2015;148:1362–1370 e7.
142. Banares R, Nevens F, Larsen FS *et al.* Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELIEF trial. Hepatology 2013;57:1153–62.
143. Philips CA, Pande A, Shasthry SM *et al.* Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. Clin Gastroenterol Hepatol 2017;15:600–2.
144. Gustot T, Fernandez J, Garcia E *et al.* Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology 2015;62:243–52.
145. Singal AK, Guturu P, Hmoud B *et al.* Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. Transplantation 2013;95:755–60.
146. Adam R, Karam V, Delvart V *et al.* Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 2012;57:675–88.
147. Burra P, Senzolo M, Adam R *et al.* Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010;10:138–48.
148. Julapalli VR, Kramer JR, El-Serag HB *et al.* Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large Veterans Affairs center. Liver Transpl 2005;11:1370–8.
149. Vidal-Trecan G, Kone V, Pilette C *et al.* Subjective parameters markedly limit the referral of transplantation candidates to liver transplant centres. Liver Int 2016;36:555–62.
150. Martin P, DiMartini A, Feng S *et al.* Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144–65.
151. Gaglio PJJr., Gaglio PJSr. Complications in patients with alcohol-associated liver disease who undergo liver transplantation. Clin Liver Dis 2012;16:865–75.
152. Piano MR. Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology. Chest 2002;121:1638–50.
153. Englesbe MJ, Patel SP, He K *et al.* Sarcopenia and mortality after liver transplantation. J Am Coll Surg 2010;211:271–8.
154. Shankar A, Klein R, Klein BE. The association among smoking, heavy drinking, and chronic kidney disease. Am J Epidemiol 2006;164:263–71.
155. Russ KB, Chen NW, Kamath PS *et al.* Alcohol use after liver transplantation is independent of liver disease etiology. Alcohol Alcohol 2016;6:6.
156. McCallum S, Masterton G. Liver transplantation for alcoholic liver disease: a systematic review of psychosocial selection criteria. Alcohol Alcohol 2006;41:358–63.
157. De Gottardi A, Spahr L, Gelez P *et al.* A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med 2007;167:1183–8.
158. Erim Y, Bottcher M, Schieber K *et al.* Feasibility and acceptability of an alcohol addiction therapy integrated in a transplant center for patients awaiting liver transplantation. Alcohol Alcohol 2016;51:40–6.
159. Carbonneau M, Jensen LA, Bain VG *et al.* Alcohol use while on the liver transplant waiting list: a single-center experience. Liver Transpl 2010;16:91–7.
160. Webzell I, Ball D, Bell J *et al.* Substance use by liver transplant candidates: an anonymous urinalysis study. Liver Transpl 2011;17:1200–4.
161. Addolorato G, Mirijello A, Leggio L *et al.* Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. Alcohol Clin Exp Res 2013;37:1601–8.
162. Pegum N, Connor JP, Feeney GF *et al.* Neuropsychological functioning in patients with alcohol-related liver disease before and after liver transplantation. Transplantation 2011;92:1371–7.
163. Pereira SP, Howard LM, Muiesan P *et al.* Quality of life after liver transplantation for alcoholic liver disease. Liver Transpl 2000;6:762–8.
164. Yang LS, Shan LL, Saxena A *et al.* Liver transplantation: a systematic review of long-term quality of life. Liver Int 2014;34:1298–313.
165. Ruppert K, Kuo S, DiMartini A *et al.* In a 12-year study, sustainability of quality of life benefits after liver transplantation varies with pretransplantation diagnosis. Gastroenterology 2010;139:1619–29.1629 e1-4
166. Dew MA, DiMartini AF, Steel J *et al.* Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008;14:159–72.
167. DiMartini A, Dew MA, Day N *et al.* Trajectories of alcohol consumption following liver transplantation. Am J Transplant 2010;10:2305–12.
168. Jain A, DiMartini A, Kashyap R *et al.* Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. Transplantation 2000;70:1335–42.

169. Faure S, Herrero A, Jung B *et al.* Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. J Hepatol 2012;57:306–12.
170. Cuadrado A, Fabrega E, Casafont F *et al.* Alcohol recidivism impairs long-term patient survival after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2005;11:420–6.
171. Grat M, Lewandowski Z, Grat K *et al.* Negative outcomes after liver transplantation in patients with alcoholic liver disease beyond the fifth post-transplant year. Clin Transplant 2014;28:1112–20.
172. Bajaj JS, Saeian K, Hafeezullah M *et al.* Failure to fully disclose during pre-transplant psychological evaluation in alcoholic liver disease: a driving under the influence corroboration study. Liver Transpl 2008;14: 1632–6.
173. Singal AK, Hmoud BS, Guturu P *et al.* Outcome after liver transplantation for cirrhosis due to alcohol and hepatitis C: comparison to alcoholic cirrhosis and hepatitis C cirrhosis. J Clin Gastroenterol 2013;47: 727–33.
174. Lucey MR, Schaubel DE, Guidinger MK *et al.* Effect of alcoholic liver disease and hepatitis C infection on waiting list and posttransplant mortality and transplant survival benefit. Hepatology 2009;50:400–6.
175. Aguilera V, Berenguer M, Rubin A *et al.* Cirrhosis of mixed etiology (hepatitis C virus and alcohol): Posttransplantation outcome-Comparison with hepatitis C virus-related cirrhosis and alcoholic-related cirrhosis. Liver Transpl 2009;15:79–87
176. Watt KD, Pedersen RA, Kremers WK *et al.* Long-term probability of and mortality from de novo malignancy after liver transplantation. Gastroenterology 2009;137:2010–7.
177. Schrem H, Kurok M, Kaltenborn A *et al.* Incidence and long-term risk of de novo malignancies after liver transplantation with implications for prevention and detection. Liver Transpl 2013;19:1252–61.
178. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. Liver Transpl 2012;18:1277–89.
179. Coordes A, Albers AE, Lenarz M *et al.* Incidence and long-term survival of patients with de novo head and neck carcinoma after liver transplantation. Head Neck 2016;38:707–14.
180. Herrero JI, Pardo F, D'Avola D *et al.* Risk factors of lung, head and neck, esophageal, and kidney and urinary tract carcinomas after liver transplantation: the effect of smoking withdrawal. Liver Transpl 2011;17:402–8.
181. Zhou J, Hu Z, Zhang Q *et al.* Spectrum of de novo cancers and predictors in liver transplantation: analysis of the scientific registry of transplant recipients database. PLoS ONE (Electronic Resource) 2016;11:e0155179.
182. Thimonier E, Guillaud O, Walter T *et al.* Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease. Clin Transplant 2014;28: 1339–48.
183. Dumortier J, Dharancy S, Cannesson A *et al.* Recurrent alcoholic cirrhosis in severe alcoholic relapse after liver transplantation: a frequent and serious complication. Am J Gastroenterol 2015;110:1160–6.quiz 1167
184. Erard-Poinsot D, Guillaud O, Hervieu V *et al.* Severe alcoholic relapse after liver transplantation: What consequences on the graft? A study based on liver biopsies analysis. Liver Transpl 2016;22:773–84.
185. Farges O, Saliba F, Farhamant H *et al.* Incidence of rejection and infection after liver transplantation as a function of the primary disease: possible influence of alcohol and polyclonal immunoglobulins. Hepatology 1996;23:240–8.
186. Mathurin P, Moreno C, Samuel D *et al.* Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365:1790–800.
187. Singal AK, Bashar H, Anand BS *et al.* Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. Hepatology 2012;55:1398–405.
188. Im GY, Kim-Schluger L, Shenoy A *et al.* Early liver transplantation for severe alcoholic hepatitis in the United States-a single-center experience. Am J Transplant 2016;16:841–9.
189. Lee BP, Chen PH, Haugen C *et al.* Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. Ann Surg 2016;8:8.
190. Hasanin M, Dubay DA, McGuire BM *et al.* Liver transplantation for alcoholic hepatitis: a survey of liver transplant centers. Liver Transpl 2015;21:1449–52.
191. Choudhary NS, Kumar N, Saigal S *et al.* Liver transplantation for alcohol-related liver disease. J Clin Exp Hepatol 2016;6:47–53
192. Stroh G, Rosell T, Dong F *et al.* Early liver transplantation for patients with acute alcoholic hepatitis: public views and the effects on organ donation. Am J Transplant 2015;15:1598–604.
193. Gustot T, Maillart E, Bocci M *et al.* Invasive aspergillosis in patients with severe alcoholic hepatitis. J Hepatol 2013;60:267–74.