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Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases

David W. Crabb,[1] Gene Y. Im ,[2] Gyongyi Szabo,[3] Jessica L. Mellinger,[4] and Michael R. Lucey[5]

Purpose and Scope of the Guidance

Alcohol-associated liver disease (ALD) represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcoholic hepatitis (AH), alcohol-associated cirrhosis (AC), and acute AH presenting as acute-on-chronic liver failure. ALD is a major cause of liver disease worldwide, both on its own and as a co-factor in the progression of chronic viral hepatitis, nonalcoholic fatty liver disease (NAFLD), iron overload, and other liver diseases. ALD develops through several stages, beginning with hepatic steatosis, and, in some individuals, gradually progressing through AH (the histological correlate of which is alcoholic steatohepatitis), culminating in cirrhosis (Fig. 1).[1,2] Progression through these various stages is dependent on continued heavy alcohol use and other risk factors, including female sex, genetic susceptibility, diet, and comorbid liver disease. ALD carries a significant stigma in society. It is increasingly recognized by providers that patients and their families seek to reduce the stigma of ALD, and a change from the term "alcoholic" to "alcohol-associated" will help; thus, alcohol-associated liver disease, alcohol-associated steatohepatitis, and alcohol-associated cirrhosis are suggested, retaining the familiar abbreviations (ALD, ASH, and AC, respectively). Due to longstanding usage, the term "alcoholic hepatitis" will likely persist.

This 2019 ALD Guidance provides a data-supported approach to the prevalence, clinical spectrum, diagnosis, and clinical management of ALD and alcohol use disorders (AUDs). The Guidance was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of published literature on the topics. The quality (level) of the evidence and the strength of each guidance statement are not formally rated. Updates to the 2010 Guideline include an emphasis on AUD definition, screening, and treatment; new alcohol biomarkers; additional genetic and environmental susceptibility factors; a consensus

Abbreviations: ABIC, age, serum bilirubin, international normalized ratio, and serum creatinine; AC, alcoholic cirrhosis; AH, alcoholic hepatitis; AKI, acute kidney injury; ALD, alcoholic liver disease; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Inventory Test; AUROC, area under the receiver operating characteristics curve; BMI, body mass index; CDT, carbohydrate-deficient transferrin; CI, confidence interval; CPT, Child-Pugh-Turcotte; EtG, ethyl glucuronide; EtS, ethyl sulfate; FDA, Food and Drug Administration; GAHS, Glasgow Alcoholic Hepatitis Score; G-CSF, granulocyte-colony stimulating factor; GGT, gamma-glutamyl transferase; GIB, gastrointestinal bleeding; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MDF, Maddrey discriminant function; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; NAC, N-acetylcysteine; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NIAAA, National Institute on Alcohol Abuse and Alcoholism; PEth, phosphatidylethanol; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome; STOPAH, Steroids or Pentoxifylline for Alcoholic Hepatitis; UNOS, United Network for Organ Sharing.

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definition of AH, and review of recent studies of corticosteroids and guidance on the role of transplantation in the management of AH.

Prevalence and Burden of Alcohol-Associated Liver Disease

Alcohol-associated liver disease includes a variety of clinical disorders: steatosis, ASH, AH of varying degrees of severity, AC, and AC complicated by hepatocellular carcinoma (HCC). ALD comprises a substantial portion of the overall cirrhosis burden, both in the United States and worldwide, and is responsible for rising rates of liver-related mortality in the United States, especially among younger patients.[3-5] In the United States, mortality due to all ALD was estimated at 5.5 per 100,000 in 2012; the relative contribution of ALD to all cirrhosis mortality is predicted to increase as the proportion of deaths due to hepatitis C virus (HCV) cirrhosis declines.[3,6] More recently, AC mortality was shown to have increased from 2008 to 2016, particularly among patients ages 25-34 years old.[4] Cirrhotic and noncirrhotic ALD prevalence has been estimated at approximately 2% in the general US population, whereas AC in the US Veterans' population was estimated at 327 per 100,000 enrollees.[7,8] In privately insured US patients, AC has been estimated at approximately 100 per 100,000 enrollees, and, overall, rates are projected to rise over time.[3,9] Worldwide, AC deaths account for about 10% of all alcohol-attributable deaths, and nearly half of those deaths are due to liver disease, resulting in the loss of 22.2 million disability-adjusted life years annually.[10,11] In the United States, ALD competes with chronic HCV as the leading indication for liver transplantation (LT).[12] Medical costs are high for AC, driven in part by the higher number of admissions for these patients.[9,13] In addition, deaths related to alcohol use are frequently underestimated due to the stigma of alcohol use and lack of candor in reporting.[10,14] In women, AC prevalence may be increasing at a faster rate than in men, mirroring the rise in alcohol use in women in the United States.[9]

The incidence of AH has been difficult to estimate, as diagnostic accuracy of administrative coding is less reliable for AH.[15,16] The incidence of AH varies worldwide. In the United States, admissions for AH were found to have increased to 0.83% of all admissions for 2010.[13] In Denmark, the incidence of AH for the period 1999-2008 rose from 37 to 46 per million persons per year in men and 24 to 34 per million persons per year for women.[17] A similar study in Finland reported increased incidence rates for AH from 37 to 65 cases per million persons per year for men and from 13 to 27 cases per million persons per year for women.[18] In both of these cases, estimates were based on diagnostic coding, which may be less accurate and highlights the difficulty in estimating the burden of AH.

Accurate assessment of the full spectrum of ALD prevalence is challenging, particularly given the difficulty with identifying earlier, asymptomatic stages of ALD, such as ASH or moderate AH, challenges that may be overcome with broader use of noninvasive steatosis and fibrosis assessment tools and increased awareness for the need to diagnose early-stage disease. Many studies underestimate the true prevalence and burden by counting as ALD only those patients *without*

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ARTICLE INFORMATION:

From the [1]Indiana University School of Medicine, Indianapolis, IN; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]University of Massachusetts Medical School, Worcester, MA; [4]University of Michigan Hospitals & Health Centers, Ann Arbor, MI; [5]University of Wisconsin School of Medicine, Madison, WI.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

David W. Crabb, M.D.
Indiana University School of Medicine
720 Eskenazi Avenue
Fifth Third Bank Building, Fifth Floor
Indianapolis, IN 46202-5112
E-mail: dcrabb@iupui.edu

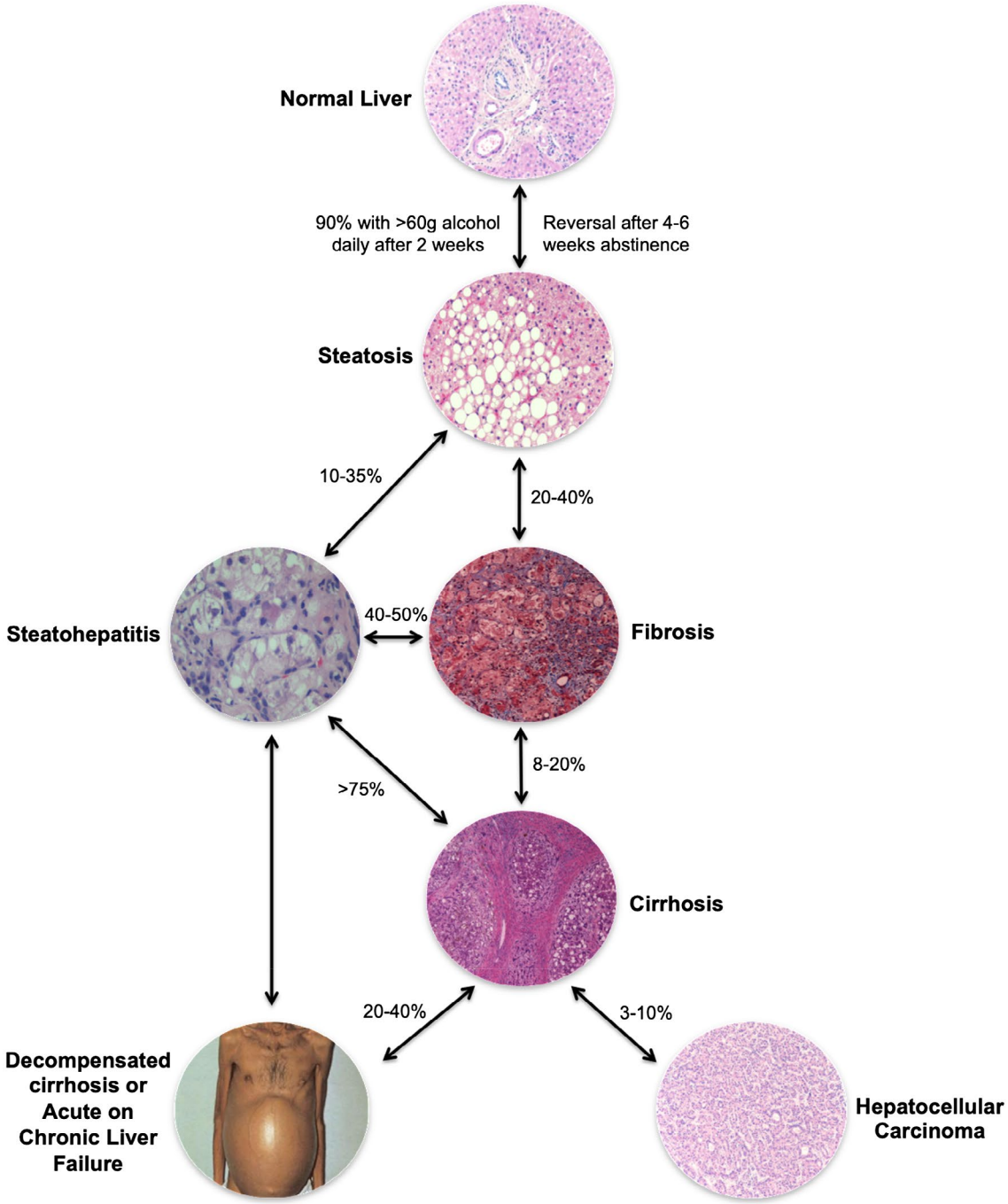


FIG. 1. Natural history of alcohol-associated liver disease. Images courtesy of Dr. M. Isabel Fiel.

additional liver diseases such as HCV, in spite of the fact that concomitant ALD rates are as high as 61% in some patients with other liver diseases, in particular nonalcoholic steatohepatitis (NASH), HCV, and hemochromatosis.[14,19] These factors may result in as much as a 2-fold underestimate for ALD-related mortality.[11]

Diagnosis of Alcohol Use Disorders

Since publication of the Diagnostic and Statistical Manual (Fifth Edition), the former categories of

alcohol abuse and dependence have been replaced by the term "alcohol use disorder," characterized as mild, moderate, or severe based on the accumulation of negative consequences and symptoms (Table 1).[20] Alcohol use is common in the United States, with many people drinking moderate amounts without significant consequences.[21] However, more severe forms of AUD, defined by escalating alcohol consumption despite attempts to cut back, negative personal consequences, and the appearance of alcohol craving, are also on the rise.[21] Rates of AUD and high-risk drinking have risen dramatically, with the prevalence of AUD in two nationally representative surveys of US adults increasing by 50% between 2001 and 2013, with even greater increases reported among women, minorities, and those of lower socioeconomic status.[22] The type of alcohol consumed and the prevalence of binge drinking (five or more drinks occurring monthly or more often) changed over the same time period (2000-2013) with substantial increases observed for consumption of distilled spirits (+11.5%), wine (+7.7%), and binge drinking.[22] Worldwide, alcohol consumption varies geographically, with the highest rates of reported per capita alcohol consumption occurring in northern and eastern European countries and Russia.[14]

SCREENING, BRIEF INTERVENTION, AND REFERRAL TO TREATMENT

The public health approach to the problem of alcohol use is termed "screening, brief intervention, and referral to treatment." This process begins with screening for and assessing the level of alcohol use. Discussion of alcohol use can be off-putting for patients, who may feel stigmatized or judged.[23] As such, a nonjudgmental, open, and accepting interview style can help maintain therapeutic alliance, and limit underreporting and denial of AUDs.[24] The symptoms of AUD and ALD may not be readily apparent, particularly in early stages of ALD. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has published a brief guide for clinicians to help assess alcohol use (including more severe AUDs), provide brief intervention, pharmacotherapy, and refer more severe cases to treatment.[25] Of note, NIAAA guidelines for limits on drinking apply to general populations rather than patients with ALD (i.e., there is no known safe level of alcohol consumption for patients with ALD). Similarly, the US Preventive Services Task Force (USPSTF) has recently published its recommendations regarding "Unhealthy Alcohol Use in Adolescents and Adults: Screening and Behavioral

TABLE 1. Diagnostic Criteria for Alcohol Use Disorder

Your Experience in the Past Year	
1. Alcohol is often taken in larger amounts or over a longer period than intended.	The presence of at least 2 of these symptoms indicates an AUD: • **Mild:** 2-3 symptoms • **Moderate:** 4-5 symptoms • **Severe:** 6 or more symptoms
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.	
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.	
4. Craving, or a strong desire or urge to use alcohol.	
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.	
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.	
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.	
8. Recurrent alcohol use in situations in which it is physically hazardous.	
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.	
10. Tolerance, defined as either of the following: A Need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or B Markedly diminished effect with continued use of the same amount of alcohol.	
11. Withdrawal, as manifested by either of the following: A The characteristic alcohol withdrawal syndrome; or B Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.	

Counseling Interventions." The summary statement recommended screening for unhealthy alcohol use in primary care settings in adults 18 years or older, including pregnant women, and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use.[26]

Efforts to uncover harmful alcohol use are aided by the use of structured, validated screening tools. The NIAAA recommends a one-question initial screen: "How many times in the past year have you had 5 or more drinks in a day (for men) or 4 or more drinks in a day (for women)?" This is the NIAAA definition of binge drinking (five drinks in men; four in women over 2 hours). If the patient reports even a single episode, performing the Alcohol Use Disorders Inventory Test (AUDIT) is recommended.[27] The AUDIT is used widely and is recommended by the USPSTF. Its original form included 10 questions on consumption (Q1-Q3), dependence symptoms (Q4-Q6), and any alcohol-associated problems (Q7-Q10), with a score greater than 8 being predictive of harmful or hazardous alcohol use, and scores greater than 20 suggestive of alcohol dependence (now termed moderate/severe AUD).[27,28] Questions 1-3 are often used alone (the "AUDIT-C") as a more efficient means of screening for problem alcohol use, but this shorter form does not provide information on more severe alcohol use problems.[29] The AUDIT-C is brief, convenient, and performs better than the CAGE and other questionnaires in identifying alcohol misuse.[30] AUDIT-C scores of at least 4-5 may indicate harmful alcohol use. These screening tests do not provide a diagnosis of AUD, but rather point to the need for a formal assessment. The NIAAA Clinicians' Guide outlines brief intervention and referral to treatment for the general public; space limitations prevent a more thorough discussion of brief interventions.[31]

Screening in general medicine and specialty clinics has been shown to help identify patients with ALD early, and by coupling this with a discussion of the implications for liver disease, may be motivational for alcohol reduction.[32] Mandatory alcohol use screening of inpatients and in the emergency department effectively identifies heavy users, assists ALD diagnosis, and improves connection to treatment of AUD.[33] Importantly, use of screening tools such as AUDIT has been shown to improve detection as well as the ability to predict long-term clinical outcomes, including hospitalization for alcohol-associated diagnoses.[34,35]

BIOMARKERS OF ALCOHOL USE

Biomarkers of alcohol use refer to moieties in urine, blood, or hair, which identify metabolites or surrogates of alcohol use and provide an estimated timeframe of recent drinking. The American Society of Addiction Medicine and American Psychiatric Association suggest the use of alcohol biomarkers as an aid to diagnosis, to support recovery, and as catalysts for discussion with the patient, rather than as tools to "catch" or punish patients.[36,37] Principles of use include discussing biomarker use with patients *before* testing, to maintain therapeutic alliance and improve alcohol use disclosure. Each of the alcohol biomarkers described subsequently has limitations. They should not be used on their own to confirm or refute alcohol use, but should be combined with other lab testing (including other alcohol biomarkers), physical exam, and the clinical interview.

Liver-related enzymes, bilirubin, or gamma-glutamyl transferase (GGT) or evidence of macrocytic anemia may suggest alcohol use, but on their own are inadequate to establish alcohol use in ALD.[38,39] GGT is an enzyme found in the cell membranes of several body tissues, including liver and spleen. Although it is frequently elevated in heavy drinking and has greater sensitivity than AST, it is not specific for alcohol use.[40] Carbohydrate-deficient transferrin (CDT) is generated as a result of alcohol inhibition of transferrin glycosylation. Typically reported as the percentage of CDT (%CDT) per total transferrin, to account for differences in total transferrin levels, CDT has a half-life of 2-3 weeks.[41] The utility of CDT is limited by its low sensitivity of 25%-50% in several studies and by false-positive results arising in patients with severe liver disease in the absence of alcohol use.[42-44] However, posttransplant use of %CDT appears to be more accurate, likely due to improved liver function.[45,46]

A small (about 0.1%) amount of alcohol is metabolized by uridine diphosphoglucuronate–glucuronosyltransferase and uridine diphosphoglucuronate–sulfotransferase, producing ethyl glucuronide (EtG) and ethyl sulfate (EtS).[47] Both are excreted in the urine, but are also found in blood and hair. Although false positives and false negatives have been

reported, sensitivity and specificity of urinary EtG for detection of alcohol use were 89% and 99%, respectively, among patients with ALD before and after LT.[48] Other studies in patients with mixed etiology of liver disease, including cirrhosis, found sensitivities of 76% and 82% for drinking within 3 days of the test for EtG and EtS, respectively, with higher specificities of 93% and 86%, respectively.[49] Urinary EtG and EtS detection times can also be prolonged in renal failure, resulting in a longer window of positive results after alcohol ingestion in patients with kidney disease.

Phosphatidylethanol (PEth) is a phospholipid formed by the reaction of phosphatidylcholine with ethanol catalyzed by phospholipase D in the erythrocyte cell membrane.[50] PEth has a half-life of approximately 10-14 days, although this can be longer with more chronic, repeated heavy alcohol consumption and does not appear to be influenced by age, body mass index (BMI), sex, kidney disease, or liver disease.[51-57] Women may have higher PEth levels for a given amount of alcohol consumption compared with men.[58] Although there are interindividual variations in PEth metabolism, PEth has been validated in a study of chronic liver disease patients who had not undergone LT at a cutoff of 80 ng/mL for four drinks per day or more with a sensitivity of 91% (95% confidence interval [CI], 82%-100%) and specificity of 77% (95% CI, 70%-83%).[59] Another study of PEth use in patients with ALD before and after LT revealed a sensitivity of 100% (CI, 79%-100%) and specificity of 96% (CI, 91%-99%) for a cutoff of over 20 ng/mL.[50] The performance of the current best biomarkers for alcohol use are given in Tables 2 and 3.

Guidance Statements

- **All patients receiving care in primary care and gastroenterology/hepatology outpatient clinics, emergency departments, and inpatient admissions should be screened routinely for alcohol use using validated questionnaires.**
- **Brief intervention, pharmacotherapy, and referral to treatment should be offered to patients engaged in hazardous drinking (AUDIT-C ≥4, AUDIT >8, binge drinkers).**
- **Alcohol biomarkers can be used to aid in diagnosis and support recovery. Urine and hair ethyl glucuronide, urine ethyl sulfate, and PEth are not affected by liver disease, and therefore are preferable.**

Treatment of Alcohol Use Disorders

Because abstinence is the single most important factor in improving survival from ALD, multidisciplinary management with addiction specialists and referral to treatment for AUD, particularly in patients with moderate to severe AUDs or clinically evident ALD, is mandatory. We present a review of different types of treatment, with a focus on treatments that have been studied in patients with ALD. Many

TABLE 2. Performance of Biomarkers of Alcohol Use in Alcoholic Liver Disease. Detection Time, Cutoff Values, and Performance of Individual Tests

Test	Source	Detection Time	Cutoff Values	Sensitivity	Specificity	PPV	NPV	Clinical Use
CDT/%CDT*	Blood	2-3 weeks	1.7%-2.6%	21%-50%	50%-100%	64%-100%	86%-93%	Lower sensitivity and specificity
EtG	Urine	3 days	500 ng/mL	76%-89%	93%-99%	81%-90%	91%-99%	False positives and greater patient awareness of testing
EtG	Hair	Months	30 pg/mg	81%-100%	83%-98%	68%-95%	86%-100%	Costly, requires significant hair sample, limited availability
EtS	Urine	3 days	75 ng/mL	82%	86%	70%	93%	Often used to confirm + EtG
PEth	Blood	2-3 weeks	20 ng/mL	97%-100%	66%-96%	85%	100%	More costly than urine EtG

*Not all studies used the preferred disialotransferrin glycoform that best correlates with alcohol intake. Some studies conducted on post-transplant patients show better performance than pretransplant patients.
Abbreviations: NPV, negative predictive value; and PPV, positive predictive value.

TABLE 3. Performance of Biomarkers of Alcohol Use in Alcoholic Liver Disease. Direct Comparison of Test Performance Characteristics in Patients with Alcoholic Liver Disease Before and After Liver Transplantation

	Sensitivity	Specificity	PPV	NPV
Andresen-Streichert[42]				
%CDT	21% (6-45)	100% (96-100)	100% (39-100)	—
Urine EtG	71% (41-91)	98% (94-100)	90% (58-99)	95% (89-98)
Hair EtG	84% (54-98)	92% (82-97)	68% (41-89)	96% (88-99)
PEth	100% (79-100)	96% (91-99)	85% (62-96)	100% (96-100)
Staufer[43]				
%CDT	25%	98%	64%	93%
Urine EtG	89%	99%	89%	99%

Abbreviations: NPV, negative predictive value; and PPV, positive predictive value.

patients, however, will be reluctant to see a professional mental health provider. For patients who are ambivalent about alcohol cessation, motivational interviewing has been shown to help patients change behaviors, including alcohol use.[60] A new online resource developed by NIAAA is now available to help people and their families recognize AUD and find high-quality care through an easily accessible and user-friendly web-based system, the NIAAA Alcohol Treatment Navigator.[61]

PSYCHOSOCIAL AND BEHAVIORAL APPROACHES TO ALCOHOL USE DISORDER TREATMENT IN PATIENTS WITH ALD

There are a wide variety of alcohol use disorder treatments available to patients, although relatively few have been studied in patients with ALD. Major categories of treatment include inpatient alcohol rehabilitation, group therapies, individual therapy, family/couples counseling, and mutual aid societies (such as Alcoholics Anonymous). Within counseling sessions, various modalities of treatment are available that target different mechanisms of behavior change. These include cognitive-behavior therapy (CBT), motivational interviewing, motivational enhancement therapy (MET), contingency management, 12-step facilitation, network therapy, and couples/family counseling.[24]

Psychosocial treatment has been studied in a limited fashion in ALD. A recent systematic review of treatment trials in ALD found that integrating AUD treatment providers alongside medical providers in clinic produced better abstinence rates than usual care, which typically means a referral to a treatment provider outside the liver center.[62]

Types of AUD treatment evaluated in both randomized and observational trials include CBT, MET, psycho-education, and motivational interviewing, with modalities combined in varying ways in each trial. Five randomized controlled trials (RCTs) were reported, three of which enrolled patients with AC exclusively and only one of which showed statistically significant benefit with an integrated intervention combining alcohol use disorder treatment with medical care.[63-65] Other observational studies evaluated psychosocial interventions for patients with HCV and AUD and showed modest improvement in abstinence with integrated care, again producing improved outcomes.[66-69] However, there are few data to show that one treatment modality is consistently superior to another across all categories of populations.[70] Based on these findings, integrated, multidisciplinary care remains the best option for management of advanced ALD and AUD, although it may not be practical in all resource settings.[71]

RELAPSE PREVENTION MEDICATIONS

Pharmacotherapy for AUDs includes both Food and Drug Administration (FDA) and non-FDA approved medications provided in Table 4. There are three FDA-approved medications: disulfiram, naltrexone, and acamprosate. The number needed to treat to prevent return to any drinking is estimated

TABLE 4. Relapse Prevention Medications in Alcoholic Liver Disease

Medication	Dosing	Metabolism (M) and Excretion (E)	Mechanism of Action	ALD Considerations
Naltrexone*	50 mg/d orally or 380 mg monthly sq	M: Hepatic E: Mostly renal, fecal 2%-3%	Opioid receptor antagonist	Not studied in patients with ALD Hepatotoxicity concerns
Acamprosate*	666 mg tid	M: None E: Renal	NMDA receptor antagonist	Not studied in patients with ALD No reported instances of hepatotoxicity
Gabapentin	600-1,800 mg/d	M: None E: Renal 75%, fecal 25%	Modulates GABA activity through action at presynaptic calcium channels	Not studied in patients with ALD Monitor closely for renal dysfunction and worsening mental status/sedation
Baclofen	30-60 mg/d	M: Hepatic, limited E: Renal	GABA-B receptor agonist	Single RCT in patients with ALD showed benefit
Topiramate	75-400 mg/d	M: Not extensively metabolized E: Renal	GABA action augmentation, glutamate antagonism	Not studied in patients with ALD

Note: Adapted from Winder et al.[237]
*FDA-approved for AUD treatment. Disulfiram is not included on this list because it is not recommended for use in patients with ALD.
Abbreviations: GABA, gamma-aminobutyric acid; NMDA, *N*-methyl-D-aspartate; sq, subcutaneous; and tid, 3 times per day.

to be approximately 12 for acamprosate and 20 for naltrexone. Disulfiram and naltrexone undergo hepatic metabolism and can cause liver damage, whereas acamprosate has no hepatic metabolism. Of note, none of these medications have been studied in patients with AH and AC. In addition, there are several medications with some benefit in relapse prevention that have not been FDA-approved for AUD treatment. These agents include gabapentin, baclofen, topiramate, ondansetron, and varenicline.[72-75] Baclofen, a gamma-aminobutyric acid–B (GABA-B) receptor agonist, is the only AUD pharmacotherapy that has been tested in an RCT in patients with AC with AUD as well as in two small, uncontrolled observational studies.[71,76,77] In a randomized trial consisting of patients with both compensated and decompensated AC, a 12-week course of baclofen (10 mg three times daily) resulted in improved rates of total alcohol abstinence and decreased relapse compared with the control during 1 year of observation while exhibiting an acceptable safety profile.[71,78] Notably, patients with hepatic encephalopathy were excluded from this trial, as baclofen may impair mentation, a side effect that may be exacerbated in more advanced liver disease. Based on limited data, and in the absence of an RCT demonstrating efficacy, acamprosate does not appear to be toxic to the liver and is probably safe.

Guidance Statements

- **Referral to AUD treatment professionals is recommended for patients with advanced ALD and/or AUD, to ensure access to the full range of AUD treatment options.**
- **Multidisciplinary, integrated management of ALD and AUD is recommended and improves rates of alcohol abstinence among patients with ALD.**
- **Based on limited data, the use of acamprosate or baclofen can be considered for the treatment of AUD in patients with ALD.**

Pathophysiology and Risk Factors for Alcohol-Associated Liver Disease

Given the widespread levels of heavy alcohol use worldwide, it is clear that a minority of heavy drinkers develop significant liver disease. The injurious effect of alcohol on the liver is not linearly dose-dependent, but there is a threshold beyond which the risk for serious liver disease increases with increasing levels of consumption.[79] According to the "Dietary Guidelines for Americans 2015-2020,"

US Department of Health and Human Services and US Department of Agriculture, the upper limit of safe drinking appears to be one standard drink per day for women and two standard drinks for men.[80] Furthermore, the NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL, and that typically occurs after four drinks for women and five drinks for men, in about 2 hours.[81] The Substance Abuse and Mental Health Services Administration, which conducts the annual National Survey on Drug Use and Health, uses an almost identical definition while adding "on at least 1 day in the past month."[82] By NIAAA definition, a standard drink contains 14 g alcohol (equivalent to 12 oz. beer [5% alcohol], 8-9 oz. malt liquor, 5 oz. table wine, or 1.5 oz. distilled spirits). A simplification would be to adopt the European standard that one standard measure of any form of alcohol is constituted by 10 g. The upper threshold of safe consumption continues to be reviewed, with a recent analysis suggesting that alcohol use should be limited to one drink per day for men and women, or even that any drinking may have adverse health consequences.[83,84]

The pathophysiology of ALD is complex. Heavy alcohol use results in accumulation of fat through effects on the redox state of the liver and on a number of transcription factors that regulate pathways involved in fatty acid synthesis (increased) and oxidation (decreased). In some individuals, changes in gut permeability lead to increased portal vein endotoxin, activation of the innate immune response, and liver cell inflammation, injury, apoptosis and necrosis, and fibrosis through cytokine and oxidative stress cascades. These cascades involve interactions among the resident macrophages (Kupffer cells), myofibroblasts, endothelial cells, and hepatocytes.[85] Interruption of these pathways has resulted in improvement in liver injury, and these results help explain current therapy with anti-inflammatory and anti-oxidant agents. There are ongoing trials examining anti-cytokine and gut-directed therapies.

Table 5 lists the factors that influence the risk of alcohol-associated liver injury.[86-91] Women have a greater risk of liver injury compared with men for any level of drinking.[88] Wine consumption was less likely to be associated with cirrhosis than other beverages.[89] Daily drinking conferred greater risk of ALD, and smoking independently increases the risk for cirrhosis.[90,91] A meta-analysis of studies of alcohol consumption and cirrhosis risk confirmed increased risk for women.[83] There is evidence that binge drinking increases the risk of ALD.[92] Coffee consumption protects against cirrhosis of many causes, including ALD as well as AH.[93-97]

TABLE 5. Factors Affecting the Risk of Alcoholic Liver Disease

Implicated in increasing the risk of alcohol-associated liver injury
- Alcohol dose above threshold of 1 drink/day (women), 2 drinks/day (men)
- Pattern of consumption: daily drinking; drinking while fasting, binge drinking
- Smoking cigarettes
- Women compared with men
- Genetics*: *PNPLA3, TM6SF2, MBOAT7, HSD17B13*
- Increased BMI
- Presence of comorbid conditions: chronic viral hepatitis, hemochromatosis, NAFLD, NASH

Implicated in ameliorating the risk of alcohol-associated liver injury
- Coffee consumption

Equivocal data regarding effect on the risk of alcohol-associated liver injury
- Type of alcohol consumed
- Moderate alcohol use in patients with high BMI

*Typically in studies of genetic predisposition, one allele of a risk gene will be associated with increased risk compared with the alternate allele; thus, each of these genes are listed as being implicated in increasing risk.

Studies of monozygotic versus dizygotic twins suggest a heritability of about 50% for AUD, and subsequent genome-wide studies show this to be a complex polygenic disorder.[98,99] Polymorphisms in the alcohol-metabolizing genes alcohol dehydrogenase 2 (*ADH2*) and aldehyde dehydrogenase 2 (*ALDH2*) have been strongly linked to risk of AUDs, but not with risk of liver disease.[100] Polymorphisms in the gene for the alcohol oxidizing enzyme, cytochrome P450 Family 2 Subfamily E Member 1 (*CYP2E1*), confer a minor risk for ALD.[101] Studies of racial and ethnic predisposition have shown that Hispanics are at substantially increased risk of developing ASH, NASH and cirrhosis, and of developing AH compared with non-Hispanic whites and African Americans.[102,103]

Genetic variants have been associated with differential risk of ALD. Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) polymorphism has been associated with risk of AC and AH, as have polymorphisms in the transmembrane 6 superfamily member 2 (*TM6SF2*), and membrane bound O-acyltransferase domain-containing

7 (*MBOAT7*) genes.[104-107] *PNPLA3* and *TM6SF2* polymorphisms are also associated with increased risk of HCC in ALD.[108,109] Most recently, Abul-Husn et al. described a polymorphism related to a hepatic lipid droplet protein hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), the presence of which confers protection against the progression from steatosis to steatohepatitis in alcohol-associated and non-alcohol-associated chronic liver disease.[110]

Co-existent heavy alcohol use by patients with certain other liver diseases promotes the development of advanced fibrosis and cirrhosis. The most common are NAFLD, HCV, and hemochromatosis. Even moderate alcohol use in NAFLD may worsen fibrosis and risk of HCC.[111] Conversely, the different elements of the metabolic syndrome were found to be important risk factors for alcohol-associated liver injury.[112] The interaction between alcohol use and progression of HCV disease is well-established: A recent French study showed that the patients with concomitant AUDs had greatly increased risk of liver complications, need for transplantation, and liver-related death.[113] Alcohol use (above 60 g/day) was also associated with a markedly increased risk of cirrhosis in patients with hemochromatosis.[114]

Guidance Statements

- **Patients without liver disease should be educated about safe levels of alcohol use for men (no more than two standard drinks per 24 hours) and women (no more than one standard drink per 24 hours).**
- **Patients with ALD or other liver diseases, in particular NAFLD, NASH, viral hepatitis, and hemochromatosis, should be counseled that there is no safe level of drinking, and that they should abstain.**

Diagnosis and Treatment of Alcohol-Associated Liver Diseases

There is no unique presentation of ALD that can be distinguished with confidence from other forms of liver disease. Alcohol use is often not disclosed by the affected patient, whereas liver injury, whether due to alcohol or other causes, often proceeds silently. Although not all patients with ALD meet the criteria for AUD, failure to recognize AUD remains a significant clinical problem.[115] Providers need to have a high index of suspicion for AUD in patients presenting with nonspecific symptoms and signs given in Table 6.[116]

ALCOHOL-ASSOCIATED STEATOSIS

Patients with alcohol-associated steatosis are usually asymptomatic. A palpably enlarged liver may be found in the absence of jaundice or stigmata of advanced liver disease. Among the common liver enzymes, elevations of aspartate aminotransferase and GGT are the best indicators of recent excessive alcohol consumption.[117,118] Hepatic steatosis is readily identified on sonography, computed tomography, and magnetic resonance imaging (MRI) of the liver.[119] MRI is more accurate for quantifying fat than other radiologic techniques, with the added advantage that MRI can assess fat over the entire volume of the liver.[120] Liver biopsy is rarely needed for the diagnosis of alcohol-associated steatosis. Treatment consists of avoidance of alcohol, with attention to the

TABLE 6. Symptoms and Signs Associated With Alcoholic Liver Disease

Symptoms
- Odor of alcohol on breath*

Nonspecific
- Tiredness
- Abdominal pain
- Day/night reversal (sleepy by day, wakeful at night)
- Peripheral neuropathy
- Weight gain (due to ascites)
- Weight loss (due to loss of proximal muscle mass)
- Confusion (as part of hepatic encephalopathy)
- Loss of sexual drive
- Amenorrhea

Signs
- Skin: Spider angiomata, palmar erythema, leukonychia, ecchymoses
- Eyes: Icteric conjunctivae
- Musculoskeletal: Loss of proximal muscle mass, especially temporal wasting
- Cardiovascular: Systemic hypotension; tachycardia suggests alcohol withdrawal syndrome*
- Abdominal: Ascites, hepatomegaly, splenomegaly, bruits, caput medusa
- Reproductive: Gynecomastia, gonadal atrophy in men
- Neurological:
  - Alcohol withdrawal syndrome*: Fine tremor, psychomotor agitation, transient hallucinations or illusions
  - Hepatic encephalopathy: Coarse flapping tremor (asterixis), altered consciousness
  - Wernicke-Korsakoff syndrome
- Hands: Dupuytren's contracture

*Specific for alcohol; otherwise nonspecific.

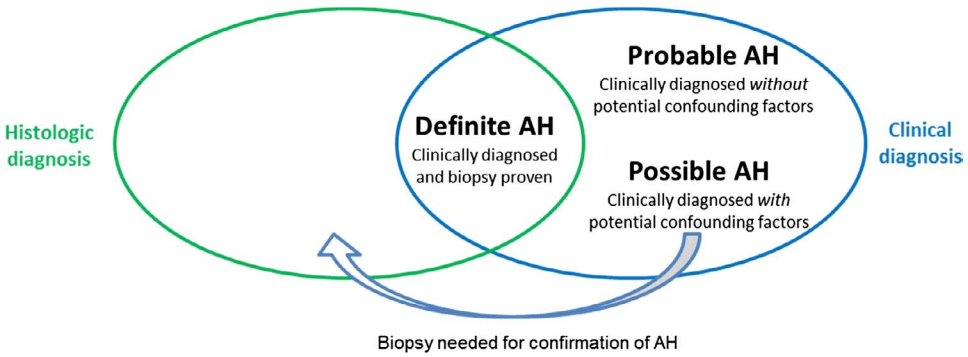
common association with NAFLD; thus, lifestyle measures that address obesity, physical activity, and alcohol use are often needed. Alcohol-associated steatosis is reversible with cessation of alcohol use.

ALCOHOL-ASSOCIATED CIRRHOSIS

Cirrhosis is often diagnosed at the time of decompensation or may be uncovered in the course of evaluating abnormal physical findings or laboratory tests. Signs and symptoms are listed in Table 6. Abdominal imaging may reveal hepatic nodularity or signs of portal hypertension, and transient elastography may provide evidence of increased liver stiffness. AC cannot be differentiated from other causes of cirrhosis except through careful evaluation of drinking history and exclusion of other causes of liver disease. The prognosis of AC is assessed just as other forms of cirrhosis, namely, using the Child-Pugh-Turcotte (CPT) and the Model for End-Stage Liver Disease (MELD or MELD-Na) score. The outcome of AC is crucially influenced by the patient's ability to abstain, both to slow the progression of fibrosis and its consequences, and in anticipation of evaluation for LT. It is important to realize that decompensation of a patient with cirrhosis may reflect the onset of AH, as most patients with AH have already developed AC; thus, an opportunity for treatment may be lost.

ALCOHOLIC HEPATITIS

There is a broad spectrum of clinical presentation of patients with AH who may exhibit few signs or symptoms, or present with liver failure. AH *per se* is a clinical syndrome (criteria are described subsequently and in Fig. 2) with a distinct histopathological correlate, called ASH. The histological features of AH may be present in patients with no symptoms and mild laboratory abnormalities. Its histological features consist of neutrophilic lobular inflammation, degenerative changes in hepatocytes (ballooning and Mallory-Denk bodies), steatosis, and pericellular fibrosis.[121] However, these features are variable in individual cases, and are often co-existent with frank cirrhosis. In addition, liver biopsy cannot distinguish between



Clinical diagnosis of AH

- Onset of jaundice within prior 8 weeks
- Ongoing consumption of >40 (female) or 60 (male) g alcohol/day for ≥6 months, with <60 days of abstinence before the onset of jaundice
- AST >50, AST/ALT >1.5, and both values <400 IU/L
- Serum total bilirubin >3.0 mg/dL

Potential confounding factors

- Possible ischemic hepatitis (e.g., severe upper gastrointestinal bleed, hypotension, or cocaine use within 7 days) or metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency)
- Possible drug-induced liver disease (suspect drug within 30 days of onset of jaundice)
- Uncertain alcohol use assessment (e.g., patient denies excessive alcohol use)
- Presence of atypical laboratory tests (e.g., AST <50 or >400 IU/L, AST/ALT <1.5), ANA >1:160 or SMA >1:80.

FIG. 2. Consensus definitions for alcoholic hepatitis.[123] Abbreviations: AH, alcoholic hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; and SMA, smooth muscle antibody.

ASH and NASH. The role of liver biopsy is therefore to resolve diagnostic dilemmas and to establish consistency regarding AH in patients recruited to clinical trials.[122] However, because uncertainty persists in a fair number of patients, a consensus statement regarding the clinical diagnosis of AH, and when biopsy confirmation of ASH was most valuable, was published in 2016.[123] The statement was intended to improve consistency in diagnosis of AH across research studies and clinical trials, and to guide clinical decision making about the use of potentially toxic medications such as corticosteroids (Fig. 2). It categorizes patients with putative AH into three groups: those with definite biopsy-proven AH, those with probable AH, and those with possible AH who would require biopsy confirmation of histological features of ASH.

Noninvasive tests for AH are sorely needed. A study of a panel of serum biomarkers of liver injury and inflammation in patients with AH demonstrated that circulating fragments of cytokeratin-18 (CK-18) and the main constituent of Mallory-Denk bodies, termed M65 and M30, both had an area under the receiver operating characteristic curve (AUROC) of 0.84 to estimate the presence of AH.[124] These data suggest that we may have biomarkers that have diagnostic significance for AH soon. In addition, there may be characteristic "breathprints" in AH.[125] Transient elastography and serum liver fibrosis markers like the enhanced liver fibrosis test and the FibroTest may have a role in assessing fibrosis in compensated ALD, and in following improvement of inflammation with recovery.[126-128] At present, none of these have been adequately validated for routine clinical use in the diagnosis of AH.

Guidance Statements

- **The diagnosis of AH (definite, probable, possible) should be made using the published consensus criteria (Fig. 2).**

ASSESSING PROGNOSIS IN AH

Lab-Based Prognostic Scores

Several validated, lab-based scoring systems can be used to assess the severity and short-term prognosis of AH (Tables 7 and 8). Common elements are shared between the scores, particularly those of the MELD score, and are easily obtained.[129] Providers can use smartphone applications or online calculators like www.lillemodel.com to calculate these scores with careful awareness of the units of measurement being used. These scoring systems perform similarly well in predicting short-term outcome (up to 6 months) in AH. The Maddrey discriminant function (MDF) was derived from the results of an early clinical trial comparing corticosteroids to placebo and later modified to identify patients with AH with high risk of short-term mortality (30%-50% at 28 days) when the MDF was at least 32.[130] (Fig. 3). In contrast, a MDF of less than 32 accurately identifies those with mild/moderate AH, conferring low, but not zero, risk of mortality with supportive care. The additional ability to discriminate between patients achieving a survival benefit from corticosteroids and those who do not, has given the MDF time-tested value in patient care and a universal inclusion criterion in clinical trials of AH. Although not validated outside the United Kingdom, the Glasgow Alcoholic Hepatitis Score (GAHS) has

TABLE 7. Characteristics of Lab-Based Prognostic Scores in Alcoholic Hepatitis

	Bili	PT/INR	Cr/BUN	Age	Alb	WBC	Stratification	Clinical Use
MDF	+	+	-	-	-	-	Severe: ≥32	Initiate corticosteroids
MELD	+	+	+	-	-	-	Severe: ≥21, but a continuous scale	Prognosis only
ABIC	+	+	+	+	-	-	Low: <6.71	Prognosis only
GAHS	+	+	+	+	-	+	Poor prognosis: ≥9	Initiate corticosteroids if ≥9 and MDF ≥32
Lille	+	+	+	+	+	-	≥0.45: Nonresponse <0.45: Response	Day 7 cessation or continuation of corticosteroids

Abbreviations: Alb, serum albumin; Bili, serum total bilirubin; Cr/BUN, creatinine/blood urea nitrogen; PT/INR, prothrombin time/international normalized ratio; and WBC, white blood cell count.

TABLE 8. Advantages and Disadvantages of Lab-Based Prognostic Scores in Alcoholic Hepatitis

	Advantages	Disadvantages
MDF	Decades of experience in AH	False positives can lead to excess corticosteroid treatment
	Key inclusion criterion in most AH trials	
MELD	Extensive experience in hepatology	Uncertain threshold for initiating corticosteroids
ABIC	Three-tiered stratification	Uncertain threshold for initiating corticosteroids and not verified outside of Spain
GAHS	Improves specificity of patients with MDF ≥32 needing corticosteroids	Not verified outside of United Kingdom
Lille	Allows early cessation of corticosteroids	Uncertain decision making with partial response (Lille 0.46-0.56)

been shown to further refine the identification of patients with an MDF of at least 32 who will benefit from corticosteroids (GAHS ≥9), thereby potentially reducing the number needed to treat.[131]

Although the MDF is predictive at 1 month, it is less accurate in the intermediate and long term. The MELD score and the more recently validated age, serum bilirubin, international normalized ratio, and serum creatinine (ABIC) score provide more nuanced survival prediction by emphasizing impaired renal function and can be calculated at different time points.[132,133] When there is renal failure but recovering liver function, these scores may give a falsely poor prognosis. While not assessed specifically in patients with severe AH, among patients on the LT waiting list, the ΔMELD score over time reflects progression of liver disease and conveys important additional prognostic information.[134] An increasing MELD score reflects greater risk of death, whereas a declining MELD score reflects a diminution in risk.

Notably, the threshold for initiating liver-specific treatment like corticosteroids has not been established for ABIC or MELD, although a MELD of at least 20 has been proposed.[132] The Lille score differs as a dynamic score by incorporating the change in bilirubin at 7 days after starting corticosteroids to assess early treatment response and the utility of its continuation for 28 days.[135] Nonresponse defined by the Lille score greater than 0.45 predicts poor prognosis and supports cessation of corticosteroids and consideration of clinical trial enrollment or early LT. Calculating the Lille score after 4 days has also been shown to have similar accuracy, potentially reducing unnecessary exposure to corticosteroids even further, although this approach needs additional validation.[136] Combining static and dynamic models to enhance prediction in AH, Louvet et al. demonstrated that the joint-effect model of MELD plus Lille outperformed other combinations such that for a patient with a MELD score of 21 and Lille score of 0.45 had a 1.9-fold higher risk of death at 2 months than one with a MELD of 21 and Lille of 0.16 (23.7% versus 12.5%).[137] This strategy of combining models improves prediction by incorporating the early change of disease after an intervention and may aid patient care and the design of future clinical trials.

Tissue-Based Prognostic Scores

There are two contemporary liver tissue–based AH prediction models. The Alcoholic Hepatitis Histologic Score (AHHS) was derived and validated in a multicenter, international cohort that includes four histologic parameters: degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria.[138] Although the AHHS predicted low, moderate, and high risk of 90-day mortality with an AUROC of 0.77, there are concerns about the requirement of liver biopsy (within 48 hours) and significant interobserver variability among pathologists, limiting its utility.[139] In a proof-of-principle study to incorporate baseline gene-expression variables in liver tissue with clinical variables, Trepo et al. devised the gene-signature plus MELD (gs-MELD) scoring system.[140] Combining the expression patterns of 123 genes with the MELD score discriminated patients with poor and good 90-day survival with an AUROC of 0.86 and outperformed other models including MELD plus Lille. Although this new score was implemented in an FDA-approved assay platform, it is not yet commercially available for use; further, with liver biopsy done on only a minority of patients with AH, such scores are unlikely to affect practice substantially.

Acute Kidney Injury in AH

The hemodynamic consequences of portal hypertension that overlap with systemic inflammatory

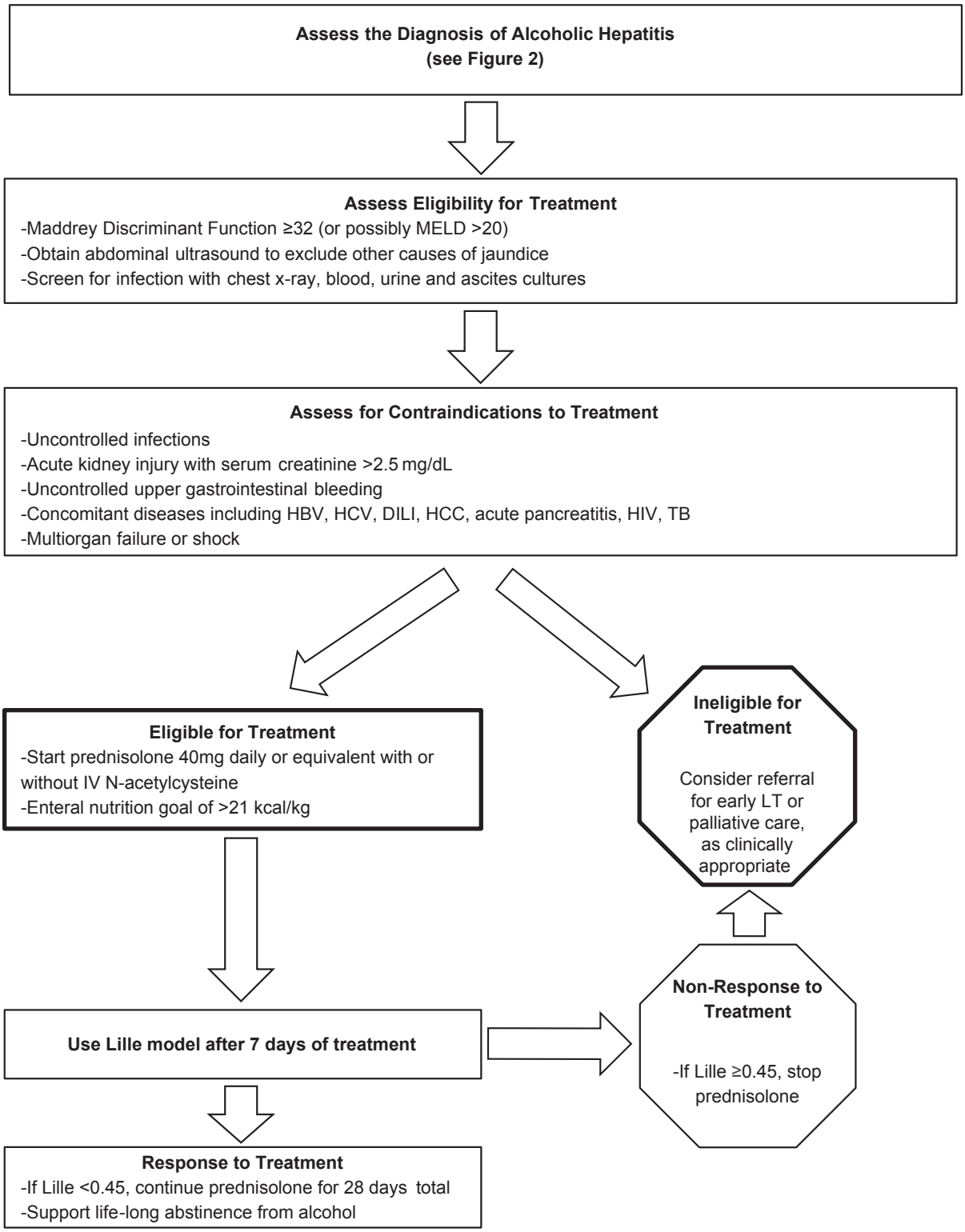


FIG. 3. Assessment of patients with alcoholic hepatitis likely to benefit from treatment with corticosteroids. Abbreviations: DILI, drug-induced liver injury; HBV, hepatitis B virus; HIV, human immunodeficiency virus; and TB, tuberculosis.

response syndrome (SIRS) also place patients with AH at high risk for acute kidney injury (AKI) due to hepatorenal syndrome (HRS).[141,142] The prognostic significance of AKI is reflected in the inclusion of serum creatinine or urea in the AH prognostic scores in Table 7. Strategies to preserve renal function in AH include the avoidance of nephrotoxins like intravenous contrast, aminoglycosides, and nonsteroidal anti-inflammatory drugs, and the cautious use of diuretics. Careful surveillance of AKI allows for early treatment with intravenous albumin and vasoconstrictors.[1] Because SIRS is strongly associated with infection, development of multi-organ failure, and high mortality in AH, multidisciplinary care involving specialists in hepatology, critical care, infectious disease, and nephrology should be provided.[143]

Other Prognostic Factors in AH

The prognostic scores in AH were largely derived and validated in well-defined cohorts receiving corticosteroids. Because a significant proportion of patients with severe AH are ineligible for corticosteroids, these scores may not capture other factors contributing to the protean presentations of severe AH. Infections are common in severe AH with 12%-26% prevalence at the time of admission, with up to half infected at some point while receiving corticosteroids.[144] Infection-related biomarkers like pretreatment serum lipopolysaccharide, bacterial DNA, high-sensitivity C-reactive protein, and procalcitonin are associated with the risk of infection and 90-day mortality.[145] Furthermore, as mentioned previously, the presence of SIRS at admission, with or without infection, predicts multiorgan failure (especially AKI) and early death.[106,143] Although the recovery of liver function in short-term prognosis is paramount and captured by the previously discussed prognostic models, in the long term, abstinence from alcohol is the main driver of outcome in patients with severe AH surviving beyond 6 months.[146-148] Improvement in long-term survival after severe AH should include secondary prevention strategies to promote complete alcohol abstinence.

Moderate AH

To date, little attention has been given to the diagnosis, management, and treatment of patients with AH not meeting these criteria for severe AH. Such patients might be classified as having moderate AH (which would be defined as having a MELD ≤20 or MDF <32). Although there is no well-established therapy for these patients, medical attention should focus on the diagnosis of disease, patient education, referral, and interdisciplinary management of these patients with AUD treatment specialists to achieve alcohol cessation. Given the fact that many patients with chronic alcohol use present to medical providers only at the late stage of cirrhosis, early detection of "subclinical" ALD and prevention of progression to AC should be a management goal in both the primary care setting as well as in hepatology referrals. Future studies are needed to explore the natural history of moderate AH with regard to its evolution to severe AH and its relationship to the development of cirrhosis in the absence of severe AH.

Guidance Statements

- **Lab-based prognostic scores should be used to determine prognosis in AH.**
- **The MDF (≥32) should be used to assess the need for treatment with corticosteroids or other medical therapies.**
- **A MELD score greater than 20 also should prompt consideration of steroid treatment.**
- **Abstinence from alcohol should be promoted to improve long-term prognosis in AH.**

TREATMENT OF AH

Treatments of Proven Benefit

ABSTINENCE

Continued alcohol use in the setting of AH results in increased rates of variceal bleeding, ascites, hepatic encephalopathy, and risk of developing HCC and death.[117,149,150] All patients with ALD should be advised to abstain completely from alcohol use, although harm reduction models, which favor alcohol reduction over total abstinence based on a patient's stated goals, may be appropriate in some contexts.

Treatments of Likely Benefit

NUTRITIONAL THERAPY

Nutritional therapy has been studied for decades, as patients with AH are typically very malnourished.[151]

Enteral nutritional supplements are recommended by consensus.[152] Two meta-analyses of nutritional support for AH suggested improvement in hepatic encephalopathy and fewer infections, but called for higher quality trials.[153,154] A recent trial comparing intensive enteral nutrition to conventional nutrition (both arms received corticosteroids) showed no additional survival benefit of intensive nutrition, with poor toleration of nasogastric tubes and adverse events.[155] Daily calorie intake of fewer than 21.5 kcal/kg/day was associated with increased rates of infection and mortality at 6 months than those with higher intake (65.8% versus 33.1%; $P < 0.0001$).

Supplementation with specific nutrients has focused on those potentially countering the oxidative stress associated with AH (e.g., beta-carotene, vitamins A, C and E, and selenium). A meta-analysis found no evidence for benefit in these studies, and a comparison of nutritional antioxidants to corticosteroids showed worse outcomes in the antioxidant group.[156,157] However, most patients with chronic alcohol abuse and AH are zinc-deficient. Zinc has been shown to contribute to improving the gut mucosal barrier integrity in animal models of ALD and in small pilot human clinical trials.[158] Because of the established role of gut-derived pathogen-associated danger molecules in AH, use of therapeutic doses of zinc should be considered in moderate and severe AH. In AC, recent trials of enteral nutrition have not shown benefit.[159]

CORTICOSTEROIDS

Corticosteroids are the most extensively studied intervention in AH, with more than 20 clinical trials, including a dozen placebo-controlled trials, dating back more than 40 years. These trials have yielded inconsistent results, with most having a high risk of bias due to heterogeneity and lack of power to detect differences in survival.[160] Further complicating the interpretation of studies and the design of future trials is the declining mortality of severe AH over time, ranging from 30%-50% at 28 days in early trials compared with 14%-18% more recently, while several meta-analyses have yielded conflicting conclusions.[161-164] Mathurin et al. combined the individual patient data sets of three, five, then recently 11 RCTs, which ultimately included 2,111 patients. In the latest iteration, corticosteroid treatment significantly reduced mortality at 28 days compared with placebo (hazard ratio, 0.64; 95% CI, 0.48-0.86), representing a 36% risk reduction.[164-167]

The largest RCT in severe AH is the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, a multicenter, double-blind, 2-by-2 factorial, randomized trial, that enrolled 1,103 patients with clinically diagnosed severe AH in the United Kingdom over 3 years.[148] The study did not demonstrate a statistically significant survival benefit at 28 days in patients receiving corticosteroids compared with placebo (odds ratio [OR] 0.72; 95% CI 0.52-1.01, $P = 0.06$), whereas, on a *post hoc* multivariable analysis, corticosteroids were associated with improved 28-day survival (OR 0.609; $P = 0.015$), but not at 90 days (OR 1.02) or 1-year (OR 1.01). The absence of liver biopsy confirmation of diagnosis and lower than expected mortality in the placebo groups may have reduced the ability of the study to identify a positive effect of corticosteroids (assuming one exists). The inclusion of patients with AKI up to serum creatinine 5.7 mg/dL and permitted use of terlipressin may have affected the benefit of pentoxifylline. The *post hoc* analysis, which accounted for potential confounders, did demonstrate a short-term survival benefit. The STOPAH trial, taken together with the previously mentioned meta-analyses, offers modest support for prednisone but not for using pentoxifylline as recommended in the previous AASLD guideline[167] (Fig. 3).

Notably, a commonly cited Veterans Affairs study in patients with AH with MDF greater than 54 receiving corticosteroids were found to have lower survival compared with placebo, suggesting a ceiling beyond which corticosteroids are harmful.[168] However, this study was not powered to examine survival differences at this higher MDF threshold, and subsequent studies have not substantiated this observation. The meta-analysis using individual patient data from 11 RCTs demonstrated that patients with AH in the highest MDF quartile (≥68) had statistically similar responses to corticosteroid treatment compared to those with lower MDF scores.[166] This suggests that even very sick patients based on MDF, in the absence of contraindications, can benefit from corticosteroid treatment. Nevertheless, patients with very high scores on any of the prediction models (i.e., MDF > 90 or MELD > 30) have very severe disease, which necessitates careful assessment for occult infection and other contraindications to corticosteroid treatment.

EVALUATING FOR CONTRAINDICATIONS TO CORTICOSTEROIDS

There are several relative contraindications to corticosteroid use in severe AH (Fig. 3). Because infections (spontaneous bacterial peritonitis, pneumonia, cellulitis, and urinary tract infections) are common in AH and have overlapping clinical presentations, providers should obtain corresponding cultures and a chest radiograph on presentation. Abdominal imaging (preferably ultrasound with Doppler) is important to evaluate for other causes of jaundice. Sufficient time should be allowed to assess for the presence of infection or other contraindications to treatment with observation and the return of relevant data. For example, the average time from presentation to starting prednisolone from the Lille group (with biopsy) and the STOPAH trial (without biopsy) was within 6 days of presentation.[144,148] Whether empiric antibiotics in the absence of confirmed infection improves outcomes in severe AH is unknown and is being evaluated in a clinical trial.[169] If infection is present, appropriate antibiotics should be started immediately. Although there have been reports of frequent fungal infections resulting in high mortality, particularly *Aspergillus* species, in corticosteroid-treated patients with AH in France and Belgium,[170,171] this has not been reported elsewhere in Europe or the United States.[145,172] Despite these concerns, the presence of infection alone has not been shown to be a driver of short-term mortality.[144] Rather, the response to corticosteroids based on the Lille score is significantly associated with improved survival as a result of improved liver function despite the presence of infection.

AKI has been an exclusion criterion in most AH clinical trials, so the evidence for corticosteroids in patients with AKI is lacking. If AKI can be resolved, corticosteroid treatment should be reconsidered. The prognostic significance of AKI in patients with severe AH is discussed in an earlier section.

Patients with gastrointestinal bleeding (GIB) have similarly been excluded in many clinical trials in AH. In a retrospective study of 105 patients with biopsy-proven AH, 55% presented with GIB and the remainder did not.[173] Both groups were given prednisolone, and GIB patients started at a mean of 5 days after the bleeding episode (mostly variceal hemorrhage). GIB patients had a lower incidence of infections likely due to prophylactic antibiotics, but there were no differences in survival at 1, 3, and 6 months between the two groups. This study suggests that GIB is not an absolute contraindication for corticosteroids, and that after control of GIB, prednisolone can be given safely.

Treatments of Potential Benefit

N-ACETYLCYSTEINE

In an RCT in France, co-administration of intravenous N-acetylcysteine (NAC) with corticosteroids reduced some early complications (infection, HRS) compared with corticosteroids alone.[174] Furthermore, the prednisolone plus NAC arm improved 1-month mortality compared with prednisolone plus placebo (8% versus 24%; $P = 0.006$), although this benefit was not seen at 3 or 6 months. Because 6-month mortality was the primary endpoint, the study was considered a negative trial, but deserves recognition in light of the STOPAH trial. The dose, duration, and administration route used were the same as those used for the treatment of acetaminophen and early-stage nonacetaminophen acute liver failure.[175,176] A recent network meta-analysis of 22 RCTs (2,621 patients) also supported the addition of NAC providing survival benefit beyond corticosteroids alone (relative risk 0.28; 95% credible interval 0.10-0.69).[177] In summary, prednisolone plus NAC should be considered as promising, but requires further validation.

GRANULOCYTE-COLONY STIMULATING FACTOR AND OTHER INTERVENTIONS

Granulocyte-colony stimulating factor (G-CSF) stimulates liver regeneration.[178] A randomized pilot study comparing pentoxifylline plus G-CSF with pentoxifylline alone for 5 days in severe AH demonstrated significant reduction in prognostic scores and mortality at 90 days with the combination therapy.[179] G-CSF is intriguing on the basis of its capacity to promote hepatic regeneration rather than abrogation of inflammation, but it requires more study (including patients outside of Asia) before being recommended for wider clinical use.[180]

Small pilot studies of the antioxidant metadoxine and of fecal microbiota transplantation have also been reported to improve liver function and survival in patients with AH.[181,182] These observations require

verification before they can be recommended for wider use.

Treatments of Unlikely Benefit

PENTOXIFYLLINE AND OTHER INTERVENTIONS

The use of pentoxifylline in severe AH was supported by an RCT comparing pentoxifylline to placebo demonstrating a decline in-hospital mortality.[183] Subsequent trials have failed to confirm this survival benefit, but have shown a reduction in the development of HRS in patients with AH who received pentoxifylline.[148,184] Two trials from France failed to show a benefit of pentoxifylline either as a rescue agent in prednisolone nonresponders or in combination with prednisolone when compared with prednisolone alone.[184,185] Although the network meta-analysis by Singh et al. did find low-level evidence of benefit, the STOPAH trial and the higher-quality meta-analysis of individual patient data have failed to demonstrate any benefit of pentoxifylline.[148,165,166,177]

Clinical trials of tumor necrosis factor-α inhibitors, infliximab and etanercept, in patients with severe AH, were terminated early due to infection-related mortality in the treatment arm.[186,187] Extracorporeal cellular therapy was studied in a multinational, prospective trial that did not show survival benefit compared with standard of care.[188] Older trials of various agents, including antioxidants like S-adenosylmethionine and vitamin E, insulin and glucagon, and oxandrolone and propylthiouracil have failed to demonstrate improvement in survival.[189-193]

Future Treatments

The overlapping pathophysiology of ALD with NASH (impaired fatty acid metabolism, apoptosis, inflammation driven by enteric endotoxin) provides the opportunity for future repurposing of pharmacologic treatments being developed for NASH. In addition, a major initiative from the NIAAA has supported large multi-institutional consortia with the task of identifying new therapeutic targets and performing early-phase clinical studies to develop and test new treatments for AH.[194,195] These treatments attempt to influence different pathophysiologic mechanisms in AH, including disrupted gut-barrier function leading to bacterial and endotoxin translocation; innate immune system activation in the liver; and hepatocellular apoptosis, necrosis, and injury.

Guidance Statements

- **Prednisolone (40 mg/day) given orally should be considered to improve 28-day mortality in patients with severe AH (MDF ≥32) without contraindications to the use of corticosteroids (Fig. 3).**
- **The addition of intravenous NAC to prednisolone (40 mg/day) may improve the 30-day survival of patients with severe AH.**
- **The Lille score should be used to reassess prognosis, identify nonresponders, and guide treatment course after 7 days of corticosteroids.**
- **Patients with AH should have malnutrition addressed and treated, preferably with enteral nutrition.**
- **Abstinence is key to long-term survival; methods discussed previously for treatment of AUDs should be used to increase abstinence.**
- **Pentoxifylline is no longer recommended in the treatment of AH.**

Liver Transplantation for ALD

PREVALENCE OF LT FOR ALD

ALD is now a leading indication for patients undergoing LT in the United States, surpassing HCV infection.[12,196,197] Either alone or in combination with HCV infection, ALD accounted for 20% of all primary LT in the United States from 1988 to 2009 (>19,000 recipients), a figure unanticipated by previous expert consensus.[198,199] Furthermore, in the United States between 2004 and 2013, the number of new LT wait-list registrants with ALD increased by 45%, from 1400 to 2024.[200]

The true denominator of patients with ALD who could potentially benefit from LT is unknown, so whether patients with ALD are underreferred for LT compared to those with other liver diseases cannot be determined.[201,202] Negative perceptions among the general public and general practitioners that AUD and ALD are due to failures of personal responsibility, concern about the risk of relapse before and after LT,

and the perception of rationing of limited organs also likely reduce appropriate referral.[203] Furthermore, the plasticity of ALD, particularly improvement with abstinence, can render LT less beneficial and confound decisions regarding referral.[204] In contrast, the clinical events surrounding decompensated AC, such as gastrointestinal bleeding or SIRS, mimic or overlap acute-on-chronic liver failure due to recent alcohol use or comorbid infection. The complexity of management, lack of access to specialty care, and high mortality can limit the emergence of suitable LT candidates.[205]

TIMING OF REFERRAL AND SELECTION OF CANDIDATES FOR LT FOR ALD

The clinical indicators that inform the managing provider that LT evaluation should be considered are new onset decompensation (ascites, encephalopathy, jaundice, or variceal hemorrhage), an episode of spontaneous bacterial peritonitis, diagnosis of HCC, or MELD-Na greater than 21.[167,206] Patients with ALD who fail to improve after 3 months of abstinence, particularly with CPT class C cirrhosis, should be referred and considered for LT.[205] The selection of appropriate patients with ALD for LT is unique among LT indications, as the patient's history of addiction to alcohol is of primary importance. Determining the time of last alcohol use and predicting the likelihood of achieving abstinence before and after LT are best evaluated by an expert in addiction medicine working within the transplant team.[207-209]

Up until recently, LT centers in the United States required patients with ALD to be abstinent from alcohol for a minimum of 6 months before listing for LT, often called the "6-month rule."[208] In a 1997 consensus conference of the AASLD and American Society of Transplantation, the 6-month rule was justified on the grounds that it allowed time to assess liver recovery that in turn might obviate the need for LT.[210] It also has additional value in more stable patients by ascertaining commitment to abstinence through participation in alcohol rehabilitation. Since then, studies have demonstrated that, while duration of abstinence before LT is linked to future abstinence, the 6-month rule alone is an inadequate predictor of drinking after LT.[211] These studies are confounded by methodological flaws, such as failing to distinguish between a slip (brief alcohol use with regained abstinence after self-recognition of harm) and relapse (a sustained alcohol use of at least four drinks in a day, or at least one drink for at least 4 days in succession).[198] Furthermore, strict adherence to the 6-month rule penalizes some patients with recent drinking who are at low risk of relapse, because they are unlikely to survive that duration.[212] The emergence of early LT for severe AH (discussed subsequently) has changed the dynamic regarding the value of a fixed interval of pre-LT abstinence. Thus, the consensus regarding the appropriateness and application of the 6-month rule appears to be diminishing in the United States, just as it has done in Europe.[213]

The AASLD Practice Guideline recommends that potential LT candidates with ALD undergo evaluation by a mental health provider for full psychiatric diagnosis and adequate treatment planning.[214] A number of groups have attempted to codify the pre-LT psychosocial assessment into a prognostic score: the Michigan alcoholism prognostic scale, the high-risk alcoholism relapse, the "Alcohol Relapse Risk Assessment," and the Stanford Integrated Psychosocial Assessment for Transplantation.[215-219] These scores have some common features such as the favorable value of social integration indicators (e.g., a spouse or partner [sometimes called a "rehabilitation relationship"], stable home and work, insight into AUD) and the negative significance of a history of failed rehabilitation attempts or preexisting psychiatric disorders.[220] Regardless of the evaluation measures, a formal psychological evaluation is only able to separate an AUD LT candidate into high-risk or lesser-risk strata. Taken together with the complexity of AUD, it follows that there is no single measure that reliably predicts alcohol relapse after LT.

OUTCOMES OF LT FOR ALD

Liver allograft and recipient survival for ALD are among the highest of all indications for LT.[221] Studies that permit the patient to reveal alcohol use without penalty while on the transplant list suggest that up to 25% will drink during evaluation or waiting for LT.[64] After LT, studies using different methodologies, including retrospective review of the medical record, prospective protocol interviews or cross-sectional use of biomarkers like hair, serum, or urine

EtG and PEth, show that approximately 20%-25% of ALD recipients return to drinking in the first 5 years.[43,222-225] Because this is a highly selected group of patients, this may reflect the risk of relapse in the lowest-risk-stratified population. DiMartini et al. described several patterns of drinking after LT for ALD, including early relapse with restoration of sobriety, early relapse that persists, and relapse after many months of sobriety following LT.[223] Early recognition of the pattern of relapse may inform tailored interventions to restore sobriety. Relapse to harmful drinking, in contrast to minor slips, has damaging consequences for the liver allograft. New onset AH and recurrent fibrosis in the allograft progressing to cirrhosis are well-documented adverse outcomes following LT. In the post-transplant setting, severe AUD relapse leads to liver fibrosis and cirrhosis in as little as 5 years.[222] In a French multicenter study of 712 patients transplanted for ALD between 1990 and 2007, severe relapse (defined as mean alcohol consumption of >20 g/day in women and >30 g/day in men for a period of at least 6 months) occurred in 18% (n = 128), with a median delay between LT and severe relapse of 25 months.[222] In this group, 32% (n = 41) of patients developed cirrhosis after a little over 5 years following LT (range 1.8-13.9 years). Nearly two-thirds of these individuals died, with a median time from diagnosis of cirrhosis to death being 1.1 years (range 0.1-7.6 years). Furthermore, as mentioned previously, excessive alcohol use is harmful even when ALD had not been the primary indication cited for LT.[226] This highlights the clandestine nature of AUD and how the role of alcohol may be underappreciated in the LT evaluation.

Guidance Statements

- **Patients with decompensated alcohol-associated cirrhosis, CPT class C or MELD-Na of at least 21 should be referred and considered for liver transplantation.**
- **Candidate selection for liver transplantation in alcohol-associated cirrhosis should not be based solely on a fixed interval of abstinence.**

EARLY LT FOR SEVERE AH

Patients with severe AH not responding to medical therapy have a grim prognosis, with mortality rates as high as 70% at 6 months.[135] Until recently, adherence to the 6-month abstinence requirement by most LT centers essentially excluded these patients from consideration for LT.[211] Results from retrospective analyses of explant histology and United Network for Organ Sharing (UNOS) data demonstrate similar outcomes of survival and relapse in those with histologic or listing diagnosis of AH compared to patients with ALD adhering to the 6-month rule.[227,228] A seminal prospective, multicenter study in France and Belgium demonstrated that LT performed "early" (i.e., before 6 months of abstinence) was life-saving in patients with life-threatening liver failure due to AH.[170] Mathurin et al. applied a rigorous selection process to patients with severe AH having nonresponse to corticosteroids and requiring the complete consensus of multiple medical teams before wait-listing. Comprehensive psychosocial assessments by an addiction specialist were performed to identify those with lower risk of alcohol relapse. Severe AH as the first liver-decompensating event was a key inclusion criterion meant to prioritize those previously unaware of their liver disease from alcohol. After about 90% of patients with severe AH who had not responded to steroids were excluded for poor psychosocial profiles, 26 underwent early LT with improved 6-month survival compared with historical controls (77% ± 8% versus 23% ± 8%; $P < 0.001$), low impact on available organs, and low rates of relapse. The findings of this trial further challenged the notion of the 6-month waiting period as the only AUD-related criterion for LT eligibility. Efforts to confirm these findings have largely come from the United States.[229,230] A multicenter retrospective American study has extended these observations to 147 patients with AH, median MELD score of 39, who underwent LT before 6 months of abstinence (median abstinence of 55 days) from 2006 through 2017 at 12 US centers.[231] These patients had no prior diagnosis of liver disease or episodes of AH. Cumulative patient survival after LT was 94% at 1 year and 84% at 3 years, with cumulative incidence of sustained alcohol use of 10% at 1 year (95% CI, 6%-18%) and 17% at 3 years (95% CI, 10%-27%) after LT.

There are several issues that require further study in early LT for AH. The most critical is how best to consistently and uniformly select appropriate patients who have excellent post-LT survival and low risk of

relapse following LT. Because existing studies are limited to patients with severe AH not responding to or ineligible for medical therapy presenting with their first liver decompensating event (i.e., no prior diagnosis of liver disease or episodes of AH), these should be important considerations in selecting candidates for early LT. Furthermore, among patients who fulfilled these criteria, the previously mentioned multicenter American study group recently derived a predictive model of four pre-LT variables that may identify patients at low risk for sustained alcohol use following LT, but that require validation.[232] These variables were greater than 10 drinks/day at initial presentation (4 points), multiple prior rehabilitation attempts (4 points), prior alcohol-associated legal issues (2 points), and prior illicit substance use (1 point), with a composite "SALT" score of less than 5, having a 95% negative predictive value (95% CI: 89%-98%) for sustained alcohol use following LT. Also, the optimal use and timing of AUD treatment following LT remains to be defined.[233] In addition, there are concerns about potentially negative public perception and its effects on organ donation, which together with the other issues outlined previously, have limited wider adoption of this emerging indication for LT.[234] However, survey and UNOS studies suggest a growing interest in early LT for AH in the United States, with at least one-quarter of all centers having performed at least one (but most less than five) with representation from every UNOS region, so consultation with those centers could be considered for a minority of appropriate patients with life-threatening AH.[235,236]

Guidance Statements

- **Liver transplantation may be considered in carefully selected patients with favorable psychosocial profiles in severe AH not responding to medical therapy.**

SUGGESTIONS FOR FUTURE RESEARCH

The following are important areas in the diagnosis and treatment of patients with ALD for which additional research/data are needed:

1. Studies providing the accurate assessment of the prevalence of ALD, particularly identifying earlier, asymptomatic stages of ALD such as ASH or moderate AH, are needed, and may become feasible with broader use of noninvasive steatosis and fibrosis assessment tools.
2. Well-constructed studies of the incidence of AH in the United States are needed. Particular attention should be paid to diversity of sex, racial background, and age.
3. Patients with ALD have been omitted from studies of efficacy of treatments for AUD. Studies are needed to assess the efficacy of psychosocial and pharmacological treatments in initiating and maintaining abstinence by patients with ALD.
4. The potential for serial measurements of biomarkers in patients with ALD are needed, with the dual endpoints of abstinence and stabilization or improvement in liver disease.
5. Studies of medical agents that abrogate the pathophysiological mechanisms that lead to chronic alcohol-associated liver injury are needed. These processes include chronic inflammation, the role of the gut microbiota, progressive fat accumulation, and progressive fibrotic injury.
6. New clinical trials are needed both in moderate (MELD ≤ 20) and severe AH (MELD >20) to improve the management of AH.
7. Prospective clinical studies of the utility of LT in selected patients with severe AH are needed. In particular, areas for investigation include processes of patient selection, monitoring alcohol use before and after LT and treatment of AUD before and after LT.

AASLD APPROVAL

This practice guidance was approved by the American Association for the Study of Liver Diseases on February 21, 2019.

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M.D., MPH; Patricia D. Jones, M.D., MSCR; Patrick S. Kamath, M.D.; David G. Koch, M.D.; Lopa Mishra, M.D., FAASLD (Board Liaison); David J. Reich, M.D., FACS; Barry Schlansky, M.D., MPH; Amit G. Singal, M.D., M.S. (Vice-Chair); James R. Spivey, M.D.; and Elizabeth C. Verna, M.D., M.S.

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