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ACG Clinical Guideline: Alcoholic Liver Disease

Ashwani K. Singal, MD, MS, FACG[1], **Ramon Bataller, MD, PhD, FACG**[2], **Joseph Ahn, MD, MS, FACG**[3] **[(GRADE Methodologist)]**, **Patrick S. Kamath, MD**[4], and **Vijay H. Shah, MD, FACG**[4]

[1]Division of Gastroenterology and Hepatology, University of Alabama at Birmingham School of Medicine , Birmingham , Alabama , USA

[2]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Liver Research Center , Pittsburgh , Pennsylvania , USA

[3]Division of Gastroenterology and Hepatology, Oregon Health and Science University , Portland , Oregon , USA

[4]Division of Gastroenterology and Hepatology, Mayo Clinic , Rochester , Minnesota ,USA

Abstract

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.

Correspondence: Vijay H. Shah, MD, FACG, Division of Gastroenterology and Hepatology, Mayo Clinic , 200 1st Street SW , Rochester , Minnesota 55905 ,USA . shah.vijay@mayo.edu.

CONFLICT OF INTEREST

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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 NonIndexed Citations, Ovid MEDLINE (R) Daily and Ovid MEDLINE (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.

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

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 nonalcoholic 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

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

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 bopsy 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

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

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 chlordi-azepoxide) 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

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 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.

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 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,

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

LT is a definitive therapy for patients with cirrhosis and endstage 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 longterm 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

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

Key concepts and statements

1. Liver function tests and ultrasound examination should be performed among patients with harmful alcohol use and/or AUD.
2. Liver biopsy is not routinely recommended for diagnosis of alcoholic fatty liver disease. However, liver biopsy and noninvasive tools of fibrosis may be considered for diagnosis of steatohepatitis and/or liver fibrosis.
3. The Alcohol Use Disorders Inventory Test (AUDIT) is a validated tool for identifying patients with alcohol abuse and dependence
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.

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.

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

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

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

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.

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

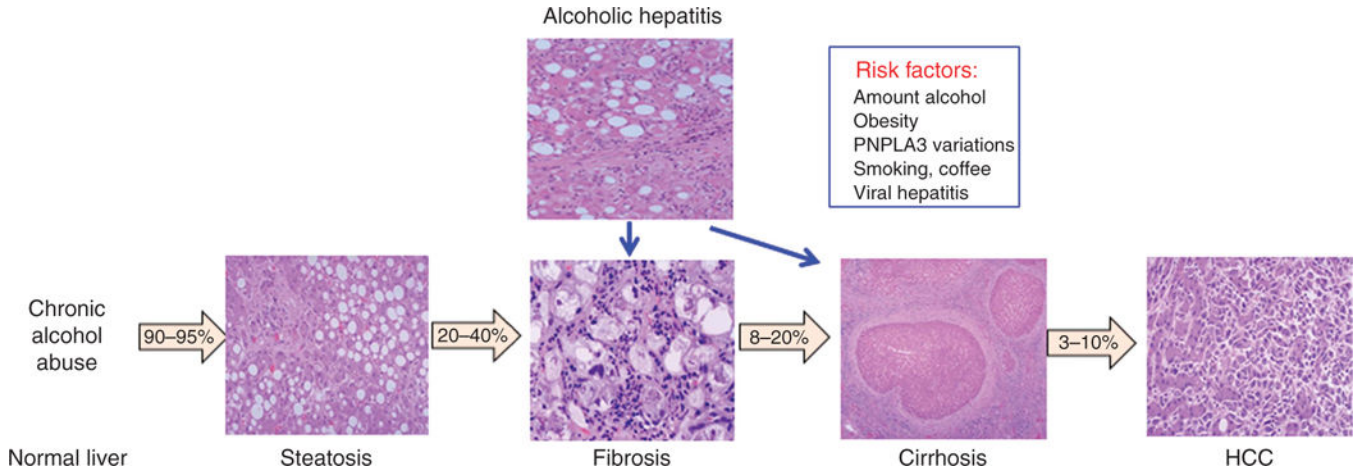

Figure 1.
Disease spectrum of alcoholic liver disease.

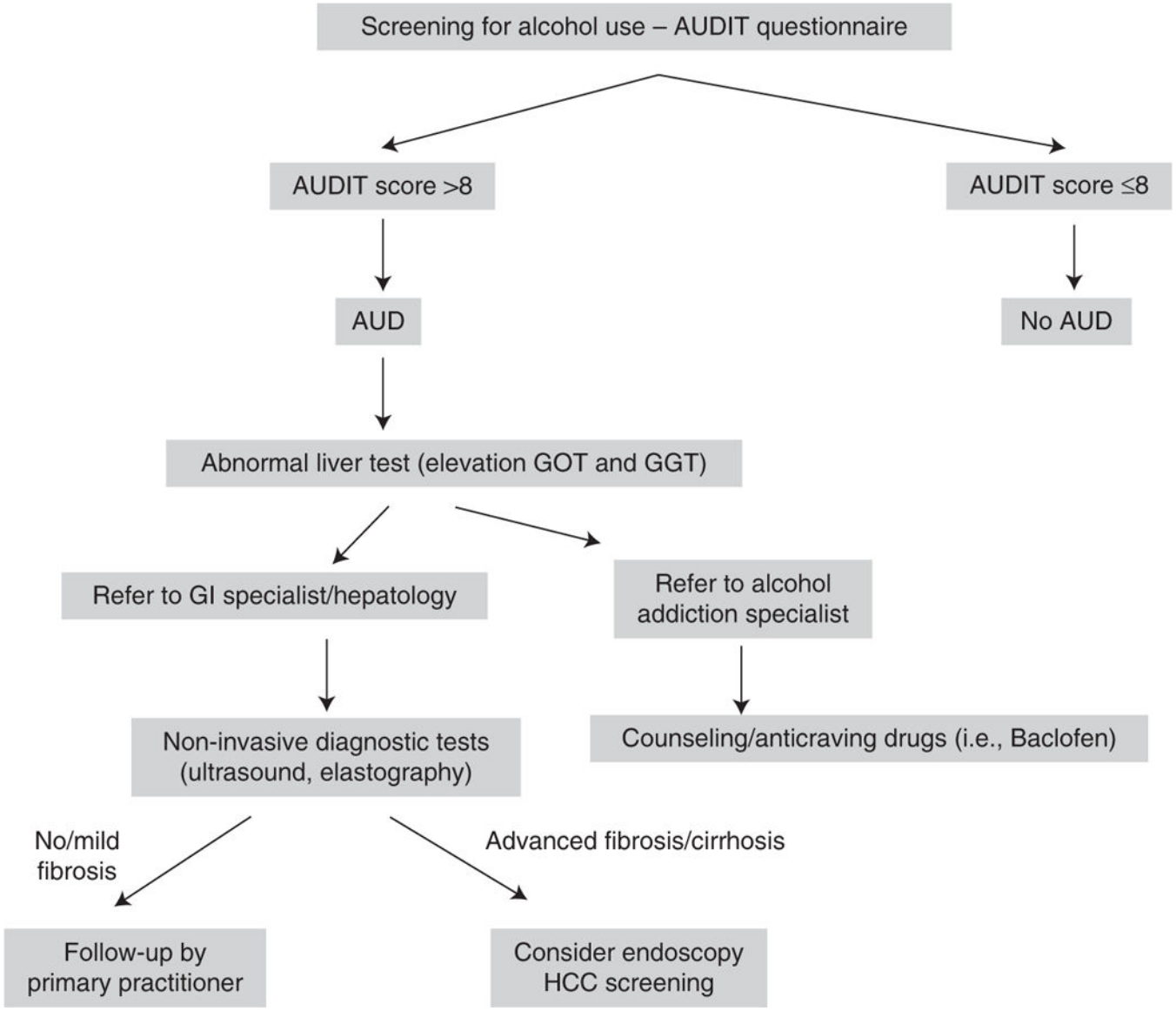

Figure 2.

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

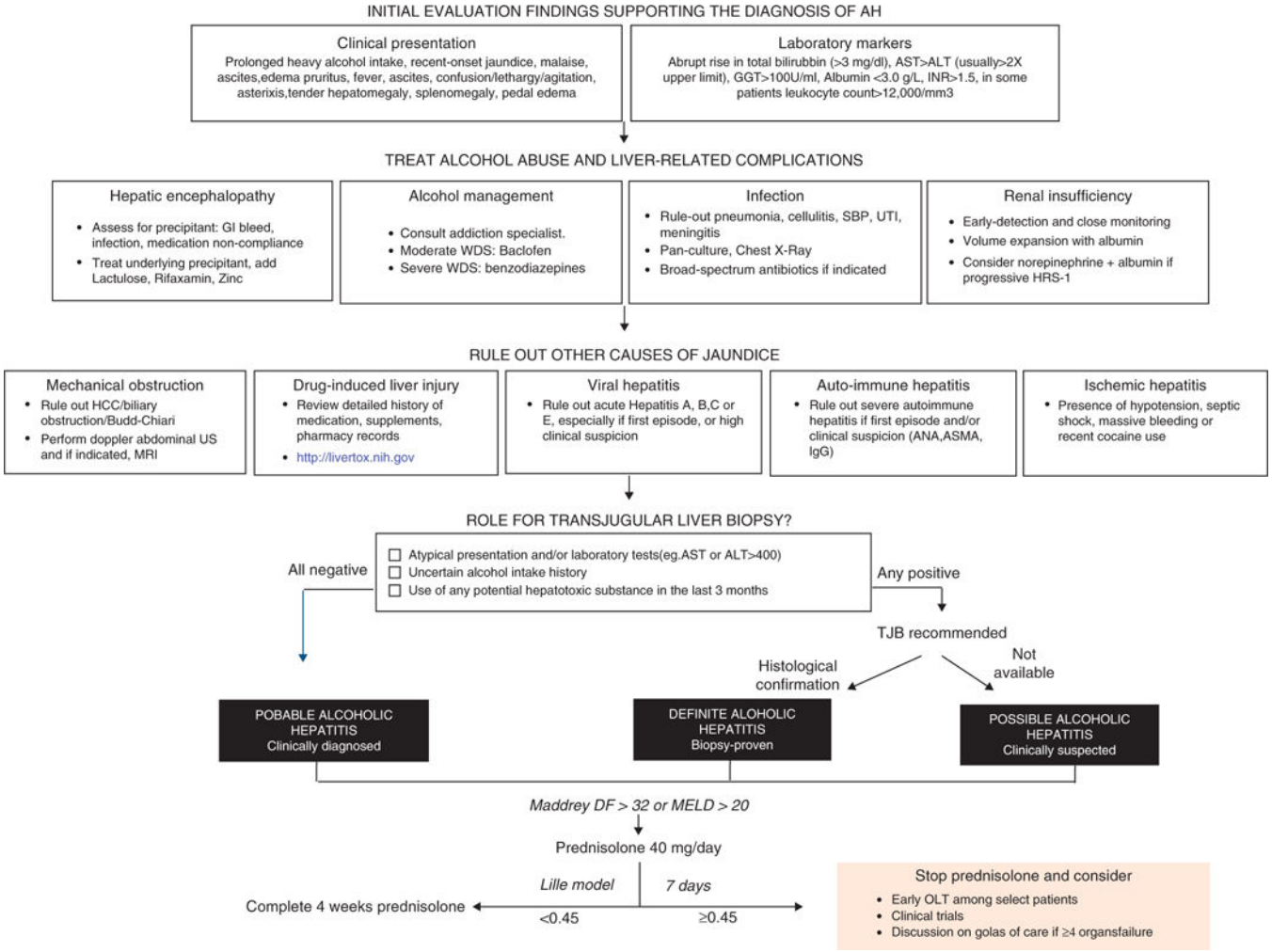

Figure 3.

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

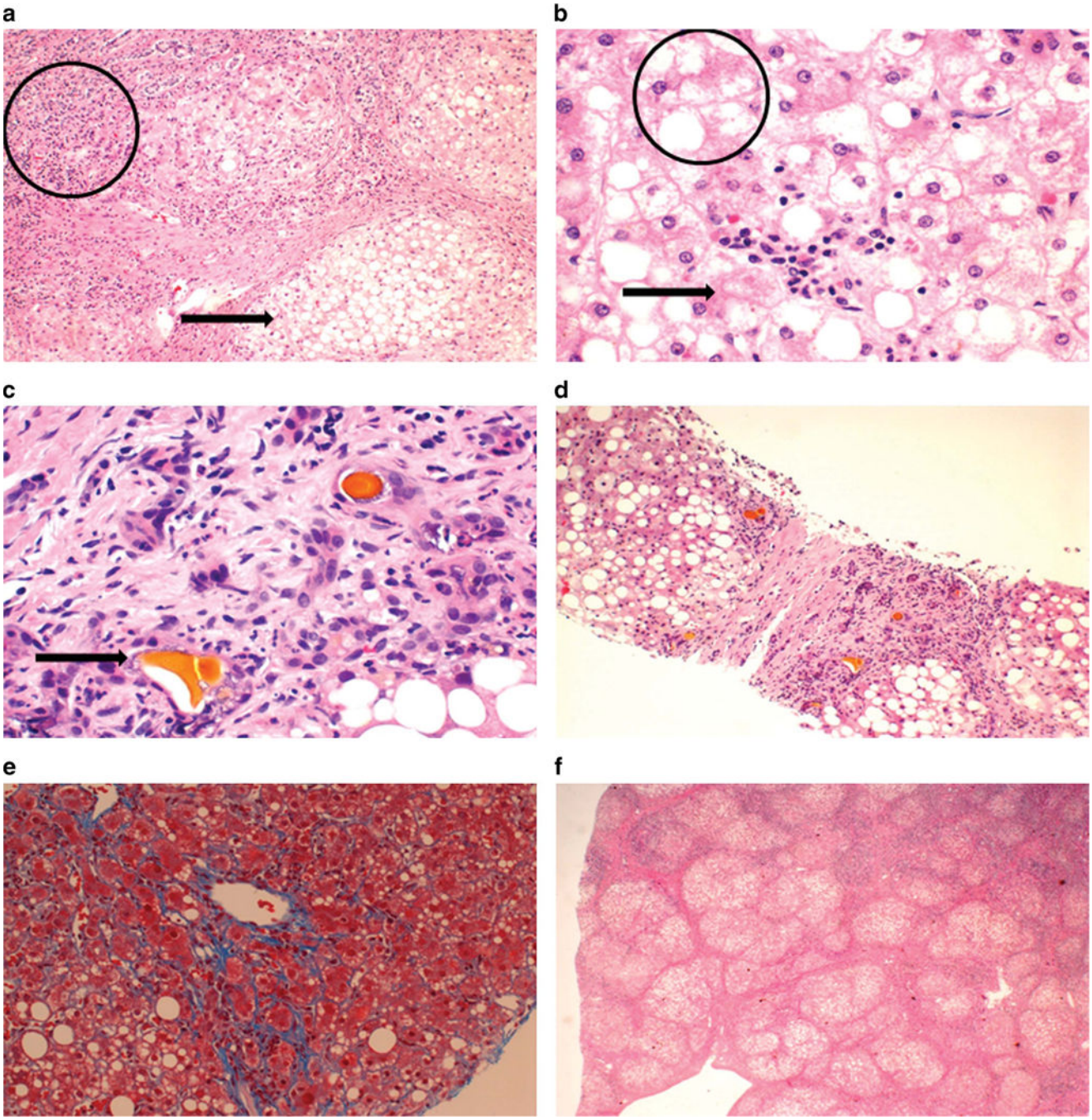

Figure 4.

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.

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)

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 nonresponders 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

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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

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.

Table 4.

Specifi c 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

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