ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

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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.

Introduction

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

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

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

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

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, 46, 47, 48, 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

Table 2. Key concepts and statements *continued*	
13.	Infections are common in AH patients and comprehensive infectious screen is recommended as part of routine work-up of these patients. The development of bacterial infections during hospitalization is associated with poor prognosis
14.	Response to treatment with corticosteroids should be determined at 7 days using the Lille score. Treatment should be discontinued among non-responders to therapy, defined as those with a Lille score >0.45
15.	Patients non-responsive to corticosteroids, ineligible for early LT, and with multiple organ failures, may be considered for palliative therapy
Liver transplantation in alcoholic liver disease	
Liver transplantation for alcoholic cirrhosis	
16.	Physicians should consider LT while formulating a management plan for patients with end-stage ALD
17.	The decision on LT evaluation should not be based solely on minimum 6 months of alcohol abstinence, and other criteria should be taken into consideration
18.	Patients too sick to complete rehabilitation therapy may be considered for transplantation via exception pathway dependent on individual center policy and the patient's profile. These patients can complete rehabilitation therapy after transplantation
19.	Transplant recipients should be screened at each visit for use of alcohol and other substances especially tobacco and cannabis. Among recidivists, alcohol use should be quantified to identify harmful use
20.	Immunosuppression should be optimized to use lowest possible dose needed to prevent graft rejection. Use of sirolimus or everolimus may be considered over other immunosuppression drugs

Disease spectrum of alcoholic liver disease

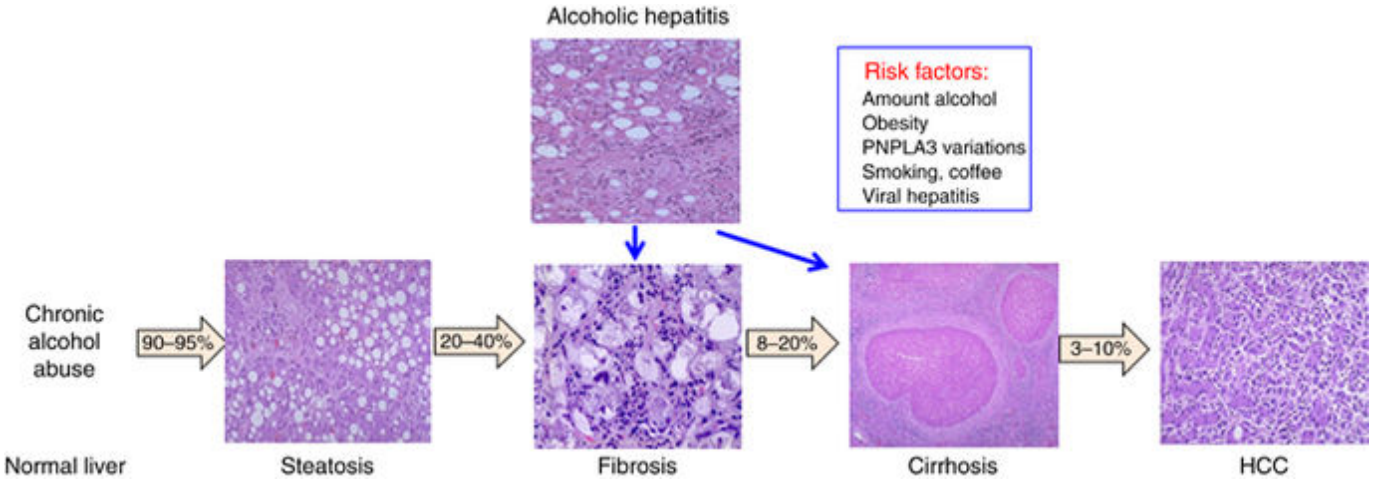

Figure 1: Disease spectrum of alcoholic liver disease**.**

Early alcoholic liver disease

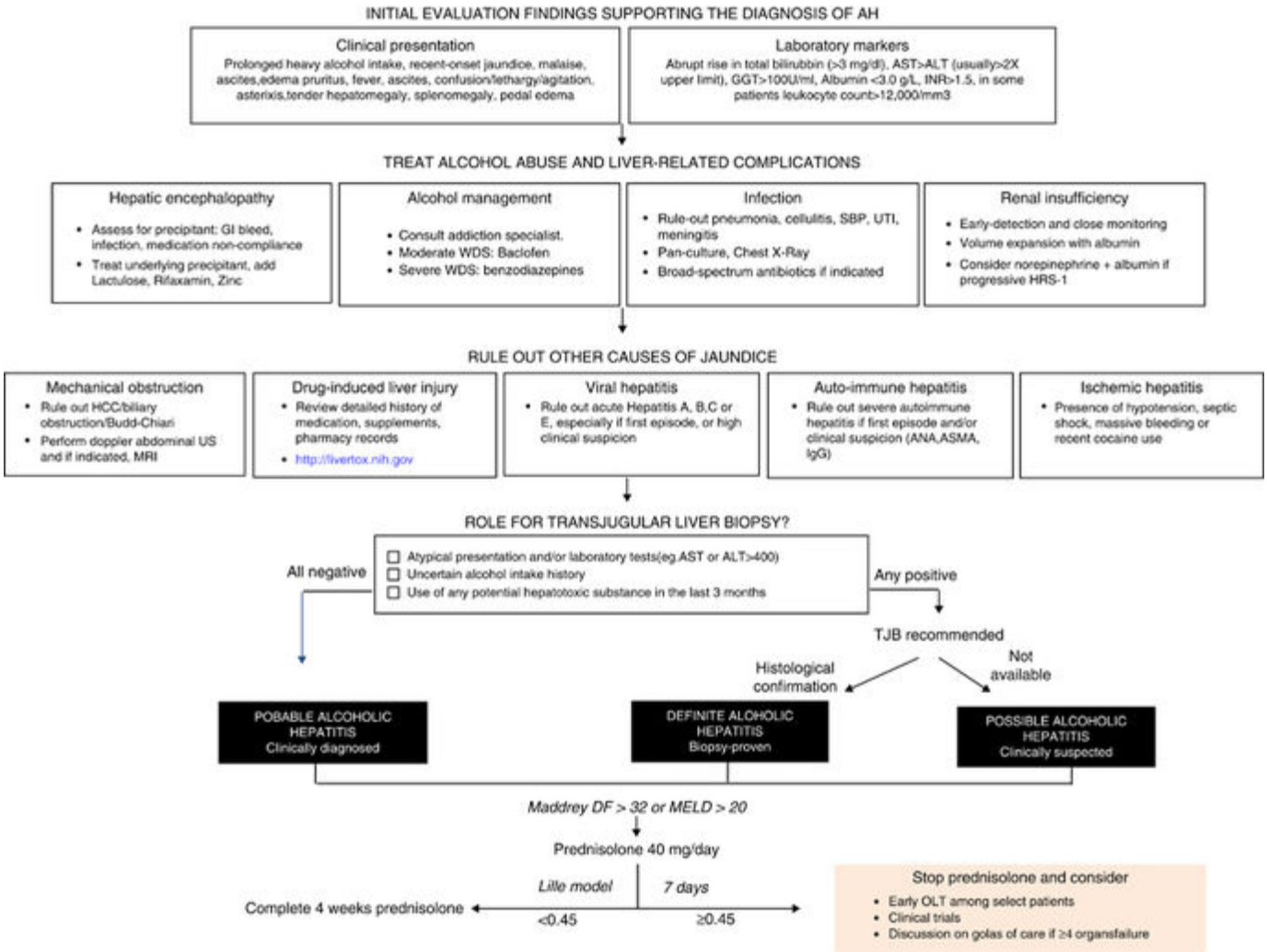

Figure 2: Algorithm for diagnosis of alcohol use disorder (AUD) using AUDIT tool and on management of early alcoholic liver disease (ALD).

Alcoholic hepatitis

Diagnosis of alcoholic hepatitis

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.

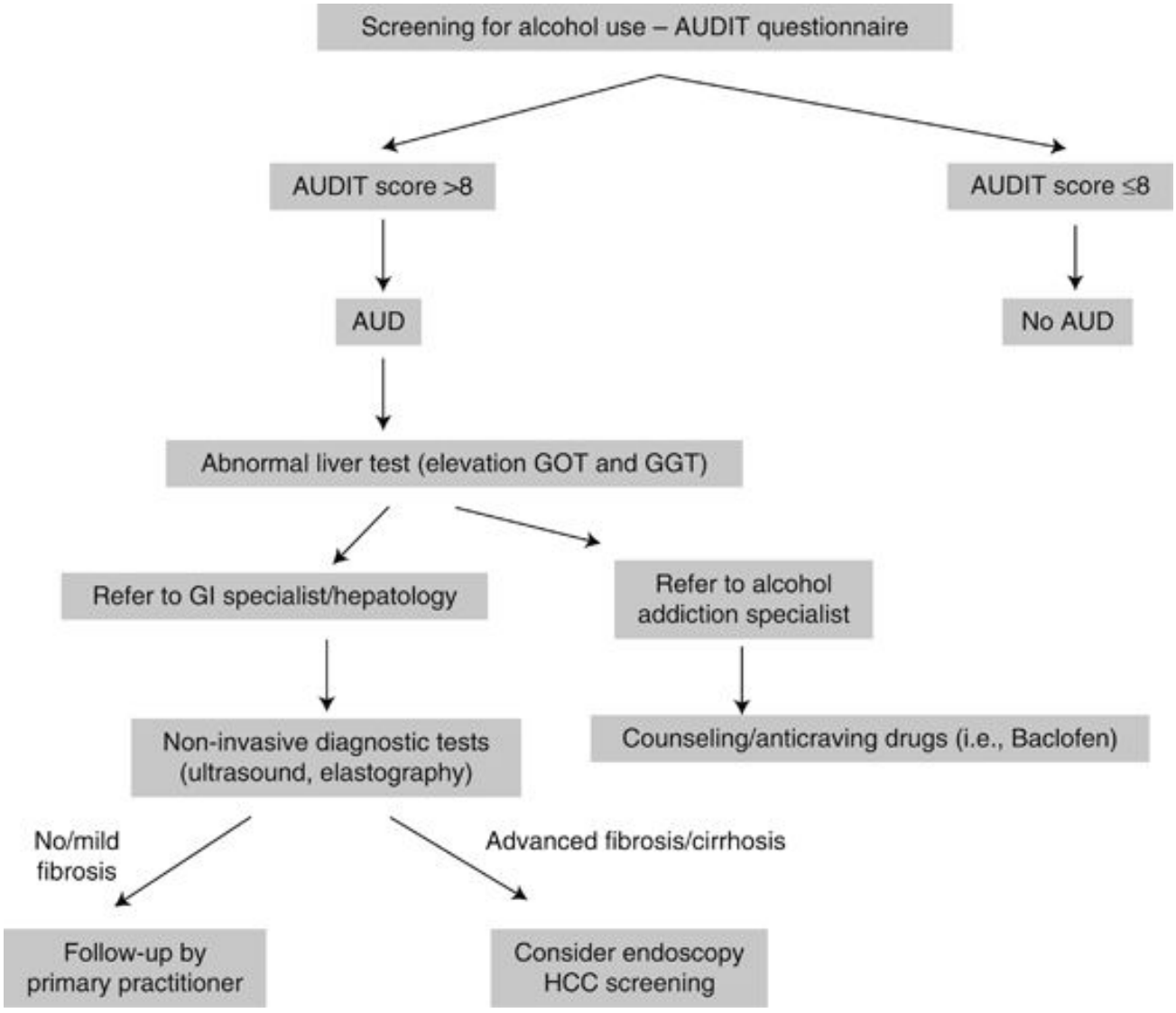

Figure 3: Approach towards the diagnosis and management of alcoholic hepatitis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalized Ratio.

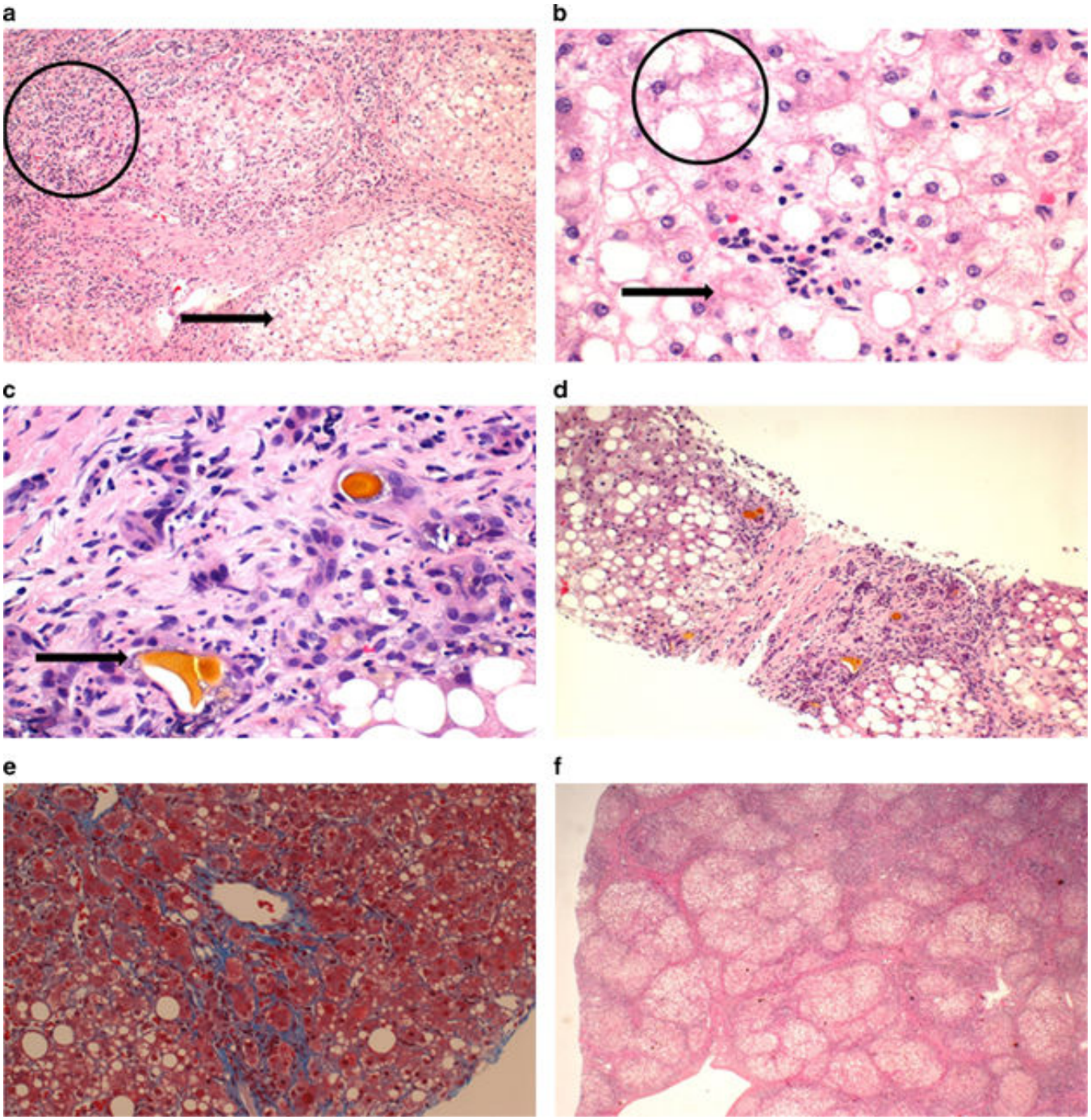

Figure 4: Histologic features of alcoholic hepatitis and Alcoholic Hepatitis Histologic Score. (a) Circle represents lobular inflammation and arrow represents steatosis, (b) circle and arrow represent cell ballooning, (c) arrow represents cholestasis with bile canalicular and hepatocyte plugging, (d)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

Treatment of alcoholic hepatitis

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

Conclusion 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).