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TOPIC HIGHLIGHT

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Therapy for alcoholic liver disease

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Abstract

Alcoholism results in about 2.5 million deaths annually worldwide, representing 4% of all mortality. Although alcoholism is associated with more than 60 diseases, most mortality from alcoholism results from alcoholic liver disease (ALD). ALD includes alcoholic steatosis, alcoholic hepatitis, and alcoholic cirrhosis, in order of increasing severity. Important scoring systems of ALD severity include: Child-Pugh, a semi-quantitative scoring system useful to roughly characterize clinical severity; model for end-stage liver disease, a quantitative, objective scoring system used for prognostication and prioritization for liver transplantation; and discriminant function, used to determine whether to administer corticosteroids for alcoholic hepatitis. Abstinence is the cornerstone of ALD therapy. Psychotherapies, including twelve-step facilitation therapy, cognitive-behavioral therapy, and motivational enhancement therapy, help support abstinence. Disulfiram decreases alcohol consumption by causing unpleasant sensations after drinking alcohol from accumulation of acetaldehyde in serum, but disulfiram can be hepatotoxic. Adjunctive pharmacotherapies to reduce alcohol consumption include naltrexone, acamprosate, and baclofen. Nutritional therapy helps reverse muscle wasting, weight loss, vitamin deficiencies, and trace element deficiencies associated with ALD. Although reduced protein intake was previously recommended for advanced ALD to prevent hepatic encephalopathy, a diet containing 1.2-1.5 g of protein/kg per day is currently recommended to prevent muscle wasting. Corticosteroids are first-line therapy for severe alcoholic hepatitis (discriminant function $\geqslant$ 32), but proof of their efficacy in decreasing mortality remains elusive. Pentoxifylline is an alternative therapy. Complications of advanced ALD include ascites, spontaneous bacterial peritonitis, esophageal variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, and portopulmonary hypertension. Alcoholic cirrhotics have increased risk of developing hepatomas. Liver transplantation is the ultimate therapy for severe ALD, but generally requires 6 mo of proven abstinence for eligibility. Alcoholic cirrhotics who maintain abstinence generally have a relatively favorable prognosis after liver transplantation.

Key words: Alcoholic liver disease; Alcoholic steatosis; Alcoholic hepatitis; Alcoholic cirrhosis; Alcoholism; Liver disease; Corticosteroids; Pentoxifylline; Liver transplantation

Core tip: Alcoholism results in about 2.5 million deaths annually worldwide, representing 4% of all mortality. Most of this mortality is from alcoholic liver disease (ALD). ALD includes alcoholic steatosis, alcoholic hepatitis, and alcoholic cirrhosis, in order of increasing severity. This work reviews this clinically important subject, with a focus on informing clinicians of recent advances in therapy to reduce the currently high mortality from alcoholic hepatitis and alcoholic cirrhosis.

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INTRODUCTION

Alcoholism results in an estimated 2.5 million deaths annually worldwide, representing 4% of all mortality[1]. This mortality is much greater than that caused by acquired immunodeficiency syndrome (AIDS) or tuberculosis[1]. It is the leading risk factor for mortality for ages 15-59 in males, and the eighth leading risk factor for mortality for all ages in both sexes[1]. Alcoholism is associated with more than 60 diseases, and is commonly associated with accidental injuries, including motor vehicle injuries[1]. Alcoholic liver disease (ALD), moreover, accounts for 40% of mortality from cirrhosis[2]. Annual mortality for ALD is 4.4 per 100000 in the general population, compared to 2.9 per 100000 for hepatitis C virus (HCV)[3].

Alcoholism, or alcohol use disorder, is defined, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), as a problematic pattern of alcohol use leading to clinically significant impairment or psychological distress[4]. Development of ALD is dose-dependent, and drinking ≥ 30 g/d of alcohol ("standard" drink: contains 0.6 fluid ounces or 14 g "pure" alcohol[5] increases the risk of ALD in both sexes[6]). Women have a greater risk of ALD than men, likely secondary to differences in ethanol metabolism[7-13]. For example, one study reported the threshold level of alcohol intake for developing ALD is 12-22 g/d in women *vs* 24-46 g/d in men[7]. Many alcoholic patients, however, do not develop clinically significant ALD[14]. Genetic and environmental factors are important, but the specific genes or environmental factors that predispose to ALD are poorly understood[14]. Potentiating factors for ALD include metabolic syndrome[13,15], diabetes[16,17], obesity[17,18], smoking[13,15], iron overload[12,13,17,19], and chronic viral hepatitis B or C[12,13,20,21].

The only definitive treatment for ALD is liver transplantation (LT). Abstinence is critical, but usually cannot reverse advanced ALD. Supportive therapy and nutritional management are also important. Several medical therapies have been studied, including corticosteroids and pentoxifylline, but no medical therapy has been proven to improve survival. This review discusses the spectrum of ALD; reviews the classification of severity and prognostic criteria for ALD; analyzes the current therapies for ALD, including abstinence, nutritional therapy, drugs, and LT; discusses the controversies regarding survival benefits for individual therapies; and reports professional society guidelines for management of cirrhosis and its complications.

SPECTRUM OF ALD

ALD is classified into alcoholic fatty liver (steatosis), alcoholic hepatitis (AH; steatohepatitis), and alcoholic cirrhosis. About 90% of alcoholics develop alcoholic steatosis, about 25% develop alcoholic hepatitis, about 15% develop alcoholic cirrhosis, and about 10% develop hepatocellular carcinoma[13,22-24]. Alcoholic steatosis, the earliest manifestation of ALD, is pathologically characterized by microvesicular and macrovesicular fat accumulation within hepatocytes, minimal inflammatory reaction, and no hepatic fibrosis[23]. It is often reversible with abstinence[25]. Patients are often asymptomatic, and the diagnosis is usually incidental. They do not exhibit stigmata of chronic liver disease, such as spider angiomata and palmar erythema. Patients typically present with mild elevations of liver enzymes, including gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels[25]. The serum bilirubin level and liver synthetic function [international normalized ratio (INR), albumin level] tend to be normal.

AH is an inflammatory process with predominantly neutrophilic infiltration, characterized by ballooning degeneration of hepatocytes, hepatocyte necrosis, steatosis, and presence of Mallory bodies (homogeneous, eosinophilic cytoplasmic perinuclear inclusions) within hepatocytes[23] (Figure 1A). Clinical findings include jaundice, pyrexia, unintentional weight loss, malnutrition, and tender, enlarged liver[26]. Patients typically present with moderate elevations in AST (usually < 300 IU/L), ALT, GGT, and serum bilirubin[25]. An AST:ALT ratio of ≥ 2:1 is strongly suggestive of ALD[27], likely from up-regulated mitochondrial AST molecular expression and synthesis by alcohol[28]. AH may be complicated by ascites, encephalopathy, or gastrointestinal (GI) bleeding from esophageal varices or portal gastropathy[26]. Imaging may show hepatomegaly, but this finding is nonspecific, and imaging is generally performed to identify radiologic evidence of cirrhosis, to identify its complications, and to exclude focal hepatic lesions[25,29]. Definitive diagnosis is by liver biopsy, but this is rarely necessary in clinical practice.

Alcoholic cirrhosis is pathologically characterized by severely disorganized liver architecture, with both bridging fibrosis and regenerating nodules, that are typically uniformly-sized and micronodular[23] (Figure 1B). Patients usually present with stigmata of chronic liver disease, including gynecomastia, palmar erythema, spider angiomata, testicular atrophy, and parotid gland enlargement; and signs of portal hypertension, including caput medusa. Dupuytren's contracture is often present in patients with alcoholic cirrhosis[30]. Alcoholic cirrhosis is associated with multiple complications, as discussed below. Laboratory findings often include hypoalbuminemia, hyperbilirubinemia, thrombocytopenia, and prolonged prothrombin time (PT) and increased INR[26]. These abnormalities typically worsen with progression of cirrhosis. Imaging studies often demonstrate findings consistent with cirrhosis, including a small, shrunken liver, hepatic nodularity, abnormal tortuous vessels from intra-abdominal varices, and other abnormalities, such as ascites or focal hepatic lesions[25,31]. These findings assist in diagnosing cirrhosis,

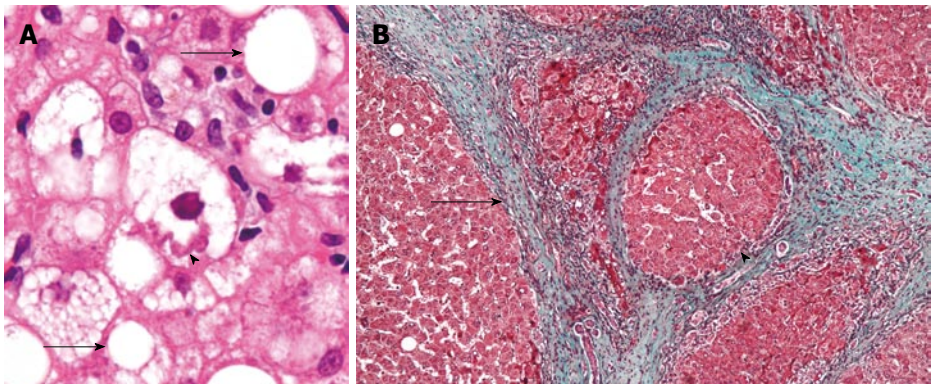

Figure 1 Photomicrograph. A: Photomicrograph showing a Mallory body (arrowhead), with twisted rope-like appearance, and fat vacuoles (arrows) as seen in alcoholic steatohepatitis (image from http://en.wikipedia.org/wiki/Alcoholic_hepatitis, licensed under Creative Commons Attribution-Share Alike 3.0 Unported); B: Photomicrograph showing a regenerating nodule (arrowhead) and bridging fibrosis (arrow) as seen in alcoholic cirrhosis (image from http://en.wikipedia.org/wiki/Alcoholic_cirrhosis, licensed under Creative Commons Attribution-Share Alike 3.0 Unported).

but cannot, by themselves, establish alcohol as the etiology[26,32]. Magnetic resonance imaging (MRI) findings suggestive of alcoholic cirrhosis include caudate lobe enlargement, presence of the right posterior hepatic notch, and smaller regenerative nodules (micronodular) than in other etiologies of cirrhosis[31]. Alcoholic cirrhosis is diagnosed by history of excessive alcohol intake, with exclusion of other causes of cirrhosis (Table 1)[33-36]. The evolution of alcoholic fatty liver to alcoholic hepatitis to alcoholic cirrhosis is usually progressive with continued alcohol use, but different stages can occur simultaneously in one patient (*e.g.*, AH with alcoholic cirrhosis).

PROGNOSTIC CRITERIA AND MONITORS OF DISEASE SEVERITY

Several scoring systems assess severity of liver disease and predict patient survival. Child-Turcotte-Pugh (CTP) score, the oldest scoring system, uses serum bilirubin level, albumin level, PT, severity of ascites, and severity of encephalopathy[37]. Patients are categorized as: class A = scores 1-6, class B = scores 7-9, and class C = scores 10-15; the higher the score, the worse the disease[37,38]. Although heuristically useful, CTP scores are limited by subjectivity in grading and by use of PT instead of the more accurate INR[39]. It was previously used to prioritize candidates for LT, but was supplanted in 2002 by the more quantitative and less subjective model for end-stage liver disease (MELD) score[40]. MELD score was originally developed to assess short-term prognosis in cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), but was found to also reliably estimate short-term survival in patients with any type of chronic liver disease[41-43]. MELD score includes serum bilirubin level, creatinine level, and INR[42]. It can be calculated on-line at a free website[44]. The United Network for Organ Sharing (UNOS) uses MELD score to prioritize LT candidates because it relatively accurately predicts 3-mo mortality in patients awaiting LT[39,40]. Recently, addition of serum sodium concentration (MELD-Na score) has been proposed to more accurately predict mortality in patients awaiting transplant[45,46]. The MELD-Na score, if used for liver allocation, can avert an additional 7% mortality in patients awaiting LT[45]. It is not yet widely used, but is a promising scoring system that may better predict mortality and improve donor liver allocation.

While CTP and MELD scores are applicable to all etiologies of cirrhosis, other scoring systems are specific for ALD. Discriminant function (DF), which includes only PT and serum bilirubin, is used to predict early mortality in AH patients and to objectively select AH patients likely to benefit from corticosteroid therapy[47,48]. DF < 32 is classified as non-severe AH, with 10% mortality, whereas DF $\geqslant$ 32 is classified as severe AH, with mortality ranging from 30%-60% without treatment[48-55]. Glasgow alcoholic hepatitis score (GAHS) is calculated as the sum of scores for the following individual parameters: age, leukocyte count, serum urea level, PT ratio (ratio of patient-to-control PT), and serum bilirubin level[56]. A score > 8 predicts poor prognosis[56]. ABIC, the most recent scoring system, includes age, serum bilirubin, INR, and serum creatinine[57]. It stratifies risk of mortality from AH as low (score < 6.71), intermediate (score: 6.71-8.99), and high (score $\geqslant$ 9.0), with 90 d mortality at 0%, 30%, and 75%, respectively ($P < 0.0001$)[57]. These last two scoring systems are promising prognostic indicators and treatment guides, but are currently rarely used clinically.

Lille score includes 6 variables: age, albumin level, bilirubin level at day 0, bilirubin level at day 7, PT, and presence of renal insufficiency[58]. It helps stratify patients with AH. It may be more accurate than other scoring systems, but is mostly used to predict 6-mo survival in patients with AH treated with corticosteroids[59]. It predicts about 75% of observed 6-mo mortality[59]. A score < 0.45 predicts 15% mortality, whereas a score $\geqslant$ 0.45 predicts 75% mortality ($P < 0.0001$)[59]. Alternative therapies should be considered when the score is $\geqslant$ 0.45 at day 7 of corticosteroid therapy[59].

Table 1 Differential diagnosis of cirrhosis, excluding alcoholic cirrhosis[1]

Diseases	Diagnostic studies	Liver biopsy
Wilson's disease	Serum ceruloplasmin < 20 mg/dL; 24-h urine copper excretion > 100 μg/24 h; slit-lamp ophthalmologic examination for Kayser-Fleischer rings	Steatosis; glycogenated nuclei in hepatocytes; focal hepatocellular necrosis, fibrosis, and ultimately, cirrhosis, usually macronodular[34]; copper retention in hepatocytes; hepatic copper concentration > 250 μg/g dry weight
Hemochromatosis	Serum transferrin-iron saturation > 45%; serum ferritin typically > 1000 μg/L; genotyping for detection of *HFE* mutations: C282Y and H63D; non-contrast CT of liver demonstrates attenuation values of > 70 HU[36]	Grade 4 stainable iron in hepatocytes, with periportal distribution and sparing of Kupffer cells; hepatic iron concentration > 80 μmol/g dry weight; hepatic iron index > 1.9
Hepatitis C	Anti-HCV; HCV RNA in patients who test positive for HCV antibody	Triad of histological findings with acute infection: lymphoid aggregates in portal tracts, epithelial damage of small bile ducts, and prominent microvesicular and macrovesicular steatosis; chronic infection: periportal necrosis, intralobular necrosis, portal inflammation, and fibrosis; no characteristic pathognomonic features
Chronic hepatitis B	HBsAg; serum level of HBV DNA > 2000-20000 IU/mL	Acute infection: lobular disarray, ballooning degeneration, numerous apoptotic (Councilman) bodies, Kupffer cell activation, and lymphocyte-predominant lobular and portal inflammation; chronic infection: varying degree of predominantly lymphocytic portal inflammation with interface hepatitis and spotty lobular inflammation[34]; presence of HBcAg staining in the liver
Autoimmune hepatitis	Antinuclear antibody (ANA); smooth muscle antibody (SMA); antibodies to liver and kidney microsomes (anti-LKM1); anti-soluble liver antigen (anti-SLA); asialoglycoprotein receptor antibodies	Interface hepatitis at junction of portal region and liver lobule; lobular hepatitis with lymphocytoplasmacytic infiltration; intrahepatic bile ducts generally appear normal
α1-antitrypsin deficiency	Serum α1-antitrypsin genotype or phenotype (homozygous PiZZ or heterozygous PiSZ phenotype)	Giant-cell hepatitis with multinucleated giant cells; lobular disarray; cellular and canalicular cholestasis; neoductular proliferation; bridging hepatic fibrosis; PAS-positive and diastase-resistant cytoplasmic granules in periportal hepatocytes
Primary biliary cirrhosis	Antimitochondrial antibodies (AMA) ⩾ 1: 80 titer; ANA, with immunofluorescence typically revealing speckled, homogeneous, nuclear dot, centromere, or rim-like patterns	Focal and segmental nonsuppurative cholangitis; "florid duct lesion": bile duct surrounded by intense lymphocytic or granulomatous infiltrate with basal integrity of the bile duct breached by individual lymphocytes; granulomas in close proximity to bile duct; bile ductular proliferation (cholangioles or pseudoducts) along periphery of portal tract
Non alcoholic fatty liver disease	Diagnosis of exclusion, correlated with: metabolic syndrome: diabetes mellitus, hypertension, hyperlipidemia, abdominal obesity with waist circumference > 102 cm for men and > 88 cm for women; obesity (BMI ⩾ 30 kg/m^2); obstructive sleep apnea; sedentary lifestyle	Macrovesicular steatosis; early hepatocyte inflammation, predominantly neutrophilic; late nondescript fibrosis and cirrhosis

[1]Patients may have more than one disease contributing to cirrhosis (*e.g.*, alcoholism and iron overload, or alcoholism and hepatitis C). *HFE*: Human hemochromatosis protein; CT: Computed tomography; HU: Hounsfield units; HCV: Hepatitis C virus; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; HBcAg: Hepatitis B core antigen; PAS: Periodic acid-Schiff; BMI: Body mass index.

THERAPY

Abstinence supportive therapies for abstinence

Abstinence is the cornerstone of therapy. It markedly reduces mortality[60-64]. However, this benefit may not become statistically significant until at least ⩾ 1.5 years of abstinence[65]. Five-year mortality for patients with alcoholic cirrhosis who cease drinking decreases to 10%, compared to 30% for patients who continue to drink[22]. Alcohol consumption increases portal pressure and increases porto-collateral blood flow in cirrhotic patients[66]. Even moderate alcohol consumption significantly worsens hepatic hemodynamics[66]. Abstinence results in a decreased rate of rebleeding after acute variceal bleeding [hazard ratio (HR) 0.26, $P = 0.002$][64]. Abstinence may also decrease hepatic fibrosis, as measured by transient elastography, a noninvasive measure of liver stiffness[67-69]. Liver transplant programs in the United States generally mandate abstinence for ⩾ 6 mo for eligibility for LT[70]. Therefore, strict, long-term abstinence is essential, and physicians should be vigilant for relapses and aggressively intervene in such cases.

Psychotherapies promoting abstinence include twelve-step facilitation therapy (TSF), cognitive-behavioral therapy (CBT), and motivational enhancement therapy (MET)[71]. TSF assumes that alcoholism is a progressive illness for which the only effective remedy is abstinence[72]. It provides a structured program to facilitate active involvement in alcoholics anonymous (AA)[72]. TSF emphasizes the twelve spiritual principles (traditions) of AA, including the first five critical principles focusing on acceptance, surrender, and moral inventories[72]. In "acceptance" patients accept they have a drinking problem. In "surrender" patients accept faith in a "Higher Power" and follow the AA path[72]. CBT identifies "high-risk" situations that increase the risk of alcoholism and encourages patients to assume responsibility and acquire self-control skills to prevent relapse[73]. It consists of 12 sessions to train clients to adopt active behavioral and cognitive methods, rather than alcohol, as coping mecha-

nisms during "high-risk" situations[73]. Lastly, MET employs motivational psychology to produce internally motivated change, *i.e.,* employs strategies to mobilize patient's internal resources for change, rather than continuous external guidance[74]. A large RCT, incorporating 1726 patients, showed all three of these psychotherapies were beneficial and all produced roughly equivalent outcomes[71].

Disulfiram, naltrexone, acamprosate, and baclofen are used to treat alcohol dependence. Disulfiram (Antabuse), an acetaldehyde dehydrogenase inhibitor, alters alcohol metabolism to cause accumulation of serum acetaldehyde, which produces unpleasant sensations of nausea, vomiting, flushing, light-headedness, abdominal pain, and tachycardia[75]. Such unpleasant sensations provide negative reinforcement for ethanol ingestion[75]. However, disulfiram-related hepatotoxicity may result in up to 16% mortality[76], and it must be cautiously administered in patients with ALD. Naltrexone, a mu, kappa, and delta opioid receptor antagonist, decreases alcohol craving by blocking the central pleasurable effects of alcohol. It effectively decreases alcohol intake and prevents relapse[77,78]. A Cochrane meta-analysis reported that naltrexone reduced heavy alcohol consumption by 83%[77]. An extended-release, injectable formulation of naltrexone was reported to improve quality of life, including mental health, social functioning, general health, and physical functioning[79]. It produces relatively mild side effects, mainly nausea, abdominal pain, anorexia, and mild-to-moderate sedation, but is rarely hepatotoxic[77,78,80].

Acamprosate also helps decrease alcohol dependence. It decreases the rate of relapse and helps maintain abstinence[81-85]. Its mechanism of action is unknown[81]. It improves life expectancy and reduces lifetime medical costs in alcoholic patients[86]. It has a favorable safety profile. Diarrhea is the most frequent side effect[81,83]. Baclofen, a gamma-aminobutyric acid-B agonist, is a new, promising, adjuvant treatment for alcohol dependence. It helps alcoholic patients suppress alcohol craving, reduce alcohol intake, and achieve and maintain abstinence[87-90]. It also improves liver function parameters, including serum ALT, bilirubin, GGT, and albumin levels, and INR[88]. These favorable effects occur in alcoholic patients with cirrhosis, with or without concomitant HCV infection[88,90]. Most affirmative studies have been performed in Europe, but a large, randomized controlled trial (RCT) performed in the United States suggested that baclofen is not superior to placebo in treating alcohol dependence[91]. Baclofen produces minimal side effects and has no apparent hepatotoxicity[87-91], rendering it safe in patients with ALD. For all these aforementioned drugs, there are limited data on efficacy in patients with advanced liver disease. Psychotherapy and family support are essential components in the overall management of alcoholics with liver disease.

Nutritional therapy

Muscle wasting, weight loss, and nutritional deficiencies commonly occur in patients with ALD. These abnormalities are associated with increased morbidity and mortality[92,93]. The etiology of weight loss and malnutrition is multifactorial, including poor dietary intake from anorexia, altered sense of taste and smell, and nausea and vomiting; malabsorption; hypermetabolic state; and impaired protein synthesis from cytokine-induced inflammatory responses[92-95]. Nutritional deficiencies can include fat-soluble vitamins (A, D, E and K), folate, thiamine, niacin, and pyridoxine; and the trace elements zinc, magnesium, and selenium[92]. Each deficiency produces specific symptoms, signs, and complications[92]. For example, thiamine deficiency causes Wernicke's encephalopathy.

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends enteral or parenteral nutritional support for patients with liver disease to improve nutritional status, liver function, mental status, and overall survival[96,97]. Nutritional support also reduces the incidence of complications after LT[96,97]. However, a recent Cochrane review of 37 RCTs found no significant difference in mortality in patients with advanced liver disease receiving either enteral or parenteral nutritional support *vs* those receiving neither[95]. The investigators did, however, note improvement in serum bilirubin level, nitrogen balance, and hepatic encephalopathy; and reduced incidence of post-operative complications, particularly infections. The reviewed RCTs generally had methodological flaws, which could have caused overestimation of the observed effects[95]. The American Association for the Study of Liver Diseases (AASLD) and American College of Gastroenterology (ACG) recommend regular assessment of patients for nutritional, vitamin, and mineral deficiencies; appropriate supplementation for identified deficiencies; enteral nutritional therapy for severe ALD; and frequent interval feedings, emphasizing breakfast and a nighttime snack[32]. The diet should include 1.2-1.5 g of protein/kg per day and 35-40 kcal/kg per day to improve nitrogen balance[32]. These recommendations revise prior recommendations to reduce protein intake to prevent hepatic encephalopathy, in order to maintain positive protein balance and prevent muscle wasting in cirrhotics[98].

Therapies for alcoholic hepatitis

Although nutritional and supportive management are important, the mainstay of therapy for AH remains alcohol abstinence. Treatment varies according to severity. Patients who have DF < 32 have only 10% 28 d mortality without treatment[55]. Supportive management is adequate for such patients. However, patients who have DF ⩾ 32 have mortality between 30%-60% without treatment[48-54], and treatment may be lifesaving in this population.

Treatment options for severe AH include corticosteroids and pentoxifylline, which are well established, albeit controversial, therapies. Other treatment options, including infliximab, etanercept, antioxidants, and complemen-

Table 2 Meta-analyses of randomized controlled trials of corticosteroid therapy *vs* placebo for severe alcoholic hepatitis

Ref.	Inclusion criteria	Number of RCTs (total number of patients)	Endpoint parameters (primary endpoint listed on first line of each entry)	RR, HR or OR for primary endpoint	95%CI	Comments
Imperiale *et al*[102], 1990	RCTs of patients with acute AH receiving corticosteroids *vs* placebo	11 (562)	Mortality Hepatic encephalopathy	RR = 0.63	0.5-0.8	Positive study (P = 0.025)
Christensen *et al*[101], 1995	RCTs evaluating short term effect on survival of treatment with glucocorticoids *vs* placebo for AH	13 (659)	Mortality Age Serum bilirubin Ascites Male gender Hepatic encephalopathy	RR = 0.78	0.51-1.18	Negative study (P = 0.2)
Mathurin *et al*[55], 2002	RCTs during 1984-1992 of patients receiving glucocorticoids *vs* placebo	3 (215)	Survival Age Liver function tests DF Hepatic encephalopathy Gender Serum creatinine Ascites Leukocyte count	OR = 0.39	0.22-0.71	Positive study (P = 0.002) Used individual patient data analysis to increase statistical rigor for the meta-analysis
Rambaldi *et al*[100], 2008	RCTs of patients with severe, clinically overt AH diagnosed by clinical and biochemical criteria, treated with glucocorticoids *vs* placebo (or no intervention)	15 (721)	Mortality Liver-related mortality Symptoms and complications Liver function tests Liver histology Adverse events	RR = 0.83	0.63-1.11	Negative study (P = 0.21)
Mathurin *et al*[99], 2011	RCTs from 1984 to 2006 with specific data on DF ⩾ 32 or hepatic encephalopathy, of corticosteroids *vs* placebo, enteral nutrition or antioxidants	5 (418)	Survival DF Lille score Liver function tests	Complete responder: HR = 0.18	Complete responder: 0.05-0.71	Positive study Complete responders (P = 0.005)
			Serum creatinine Ascites	Partial responder: HR = 0.38	Partial responder: 0.17-0.87	Partial responders (P = 0.03)
			Hepatic encephalopathy Age	Null responder: HR = 0.81	Null responder: 0.45-1.45	Null responders (P = 0.46)
			Gender Leukocyte count			Used individual patient data analysis to increase statistical rigor for the meta-analysis

RCT: Randomized controlled trials; AH: Alcoholic hepatitis; DF: Discriminant function.

tary medicines have not been shown to improve clinical outcome[24].

Corticosteroids: Corticosteroids are the oldest and most investigated pharmacologic therapy for severe AH. Several RCTs have been performed with contradictory results[48-54]. Ramond *et al*[49] reported 12.5% mortality among patients receiving prednisolone *vs* 55% mortality among patients receiving placebo (P = 0.001). Contrariwise, a large study of 178 patients by Mendenhall *et al*[50] reported no statistically significant difference in mortality among patients treated with corticosteroids *vs* placebo. Both studies had limited statistical power because of small-to-moderate study size. Several investigators performed meta-analyses of the numerous RCTs to increase statistical power[55,99-102]. Three of these meta-analyses showed improvement in short-term survival in AH patients receiving corticosteroid treatment[55,99,102], whereas two meta-analyses showed no improvement[100,101] (Table 2). For example, a Cochrane meta-analysis incorporating 721 randomized patients demonstrated no statistically significant improvement in mortality among AH patients treated with corticosteroids; however, a subgroup analysis performed on low-bias risk trials revealed significantly reduced mortality in corticosteroid-treated patients with either DF ⩾ 32 or hepatic encephalopathy (RR = 0.33, 95%CI: 0.11-0.97)[100]. One affirmative meta-analysis performed individual patient data meta-analysis, considered the gold standard for meta-analysis with the least bias[103]; it showed that AH patients receiving corticosteroids had a 28-d mortality of only 20% *vs* 34% for controls (P = 0.0005)[99]. Furthermore, a prior meta-analysis demonstrated the importance of corticosteroid therapy in AH patients, showing that the number needed to treat (NNT) with corticosteroids

to prevent one death was only five[55]. Additionally, corticosteroids, specifically prednisolone, have been shown to significantly reduce mortality for at least 1 year[104].

The meta-analyses generally included only RCTs that analyzed patients with either DF ≥ 32 or hepatic encephalopathy, but none of the individual RCTs analyzed whether there was a maximum severity of AH (*e.g.*, maximum DF) beyond which patients no longer benefited from corticosteroid therapy. One study[99] analyzed this question and noted that patients respond rapidly (≤ 7 d) to corticosteroids with sustained response until the conclusion of treatment. They stratified patients according to Lille score as complete responders (score ≤ 0.16), partial responders (score = 0.16-0.56), and null responders (score ≥ 0.56). Survival benefit was limited to patients who were partial or complete responders; therefore, this study suggests modifying corticosteroid therapy according to therapeutic response[99].

Clinical application of corticosteroid therapy for AH is currently limited by insufficient data on its molecular therapeutic mechanisms. However, in a recent study of mice heavily exposed to alcohol for 10 d, administration of prednisolone, a corticosteroid, enhanced ethanol-induced liver injury and fibrosis compared to untreated controls[105]. This study further investigated potential mechanisms for the deleterious effects of prednisolone after hepatotoxic injury. In carbon tetrachloride-induced liver injury in mice models, prednisolone led to attenuation of macrophage and neutrophil functions that normally help clear apoptotic cells and resolve hepatic inflammation, and caused delayed hepatocyte regeneration by inhibiting expression of genes involved in hepatocyte proliferation and repair, such as pSTAT3[105]. These data may help modify and improve clinical management of corticosteroid therapy for AH.

Despite variable survival benefit among studies, no severe complications were reported in patients receiving corticosteroid therapy, including no significantly increased risk of infections. Corticosteroid therapy should not be precluded in patients who have preexistent infections, after initiation of appropriate antibiotic therapy[106]. Although the current data are somewhat contradictory, use of corticosteroids is generally recommended as first-line therapy for severe AH[26,32].

Pentoxifylline: Pentoxifylline, a nonspecific phosphodiesterase inhibitor, has anti-inflammatory properties, including inhibition of tumor necrosis factor (TNF)-α, that may retard hepatic inflammation and fibrosis[107]. It prevents development of hepatopulmonary syndrome and development of a hyperdynamic circulatory state in cirrhotic rats[108]. It decreases the risk of hepatorenal syndrome (HRS), and significantly improves renal function in patients with severe AH or cirrhosis[107,109-111]. In a study of 50 patients, it decreased DF by > 50%, *vs* a decrease of only 7.1% in patients receiving placebo (P = 0.001)[109].

Despite these positive effects, improved survival from pentoxifylline remains controversial. Four RCTs of pentoxifylline *vs* placebo reported contradictory findings (Table 3)[107,109,110,112]. Two trials showed no statistically significant improvement in short-term survival[107,112]; a third trial showed statistically significant improvement[110]; and a fourth trial showed a statistically insignificant trend towards improved short-term survival (20% mortality with pentoxifylline *vs* 40% with placebo) (P = 0.216)[109]. A Cochrane review, incorporating 5 RCTs, was inconclusive, and recommended further RCTs on this drug[113]. Another meta-analysis, incorporating 884 patients, supported previous findings that pentoxifylline decreases the risk of severe HRS, but failed to demonstrate significantly improved survival[111]. Further research with larger patient studies is necessary to determine whether pentoxifylline improves survival. Nevertheless, the AASLD, ACG, and the European Association for the Study of the Liver (EASL) recommend pentoxifylline as a second-line therapy in patients with severe AH who have contraindications to corticosteroid therapy[26,32].

Combination therapy: Corticosteroids or pentoxifylline are used in patients with severe AH, but the survival benefit for either drug remains controversial. Investigators combined both therapies to assess whether combination therapy is superior to corticosteroid monotherapy, especially for severe AH. However, two published RCTs found no significant difference in 6 mo mortality between combination therapy *vs* monotherapy[114,115]. The most recent RCT revealed 6-mo mortality of 30.1% in combination therapy *vs* 30.8% in monotherapy (P = 0.91)[115]. Although one RCT reported a significantly lower cumulative risk of HRS in the combination therapy group at 1 mo (P = 0.007)[115], the benefit was no longer significant at 6 mo[114,115]. Further studies are needed to explore combined treatment options to improve survival for severe AH.

Liver transplantation

LT is the only cure for end-stage ALD. Recent data from Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) reveal 3563 alcoholic cirrhotics awaiting LT, constituting 23.2% of all patients awaiting LT[116]. Alcoholic cirrhosis is the second most common indication for LT, after cirrhosis from viral hepatitis[117]. Patients with alcoholic cirrhosis, however, have less likelihood of LT than other patients due to social factors. ALD is pejoratively thought as a "self-inflicted" disease, and donor organs are said to be better allocated to patients with other forms of end-stage liver disease (ESLD), which are not self-inflicted[118-120]. The critical, legitimate concern regarding LT for alcoholic cirrhosis is recidivism, with consequent disease recurrence in the allograft[117-121]. From 12%-46% of alcoholic cirrhotics resume alcohol consumption after LT[118-121]. The precise definition of recidivism var-

Table 3 Published randomized controlled trials of pentoxifylline *vs* placebo for severe alcoholic hepatitis *n* (%)

Ref.	*n*	Duration of treatment with pentoxifylline 400 mg PO *tid*	Mortality in placebo	Mortality in pentoxifylline	Relative risk or hazard ratio	95%CI	Comments
Akriviadis *et al*[110], 2000	101	28 d	24/52 (46)	12/49 (24)	RR = 0.59	0.35-0.97	Positive study (P = 0.037)
Fernández-Rodríguez *et al*[112], 2008	24	28 d	Not reported[1]	Not reported[1]	HR = 1.46	0.5-4.28	Negative study (P = 0.48)
Tyagi *et al*[107], 2011	61[2]	6 mo	2/31 (6)	1/30 (3)	Not reported	Not reported	Negative study[2] (P = 0.15)
Sidhu *et al*[109], 2012	50	28 d	10/25 (40)	5/25 (20)	RR = 0.5	0.19-1.25	Negative study (P = 0.216)

[1]Fernandez-Rodriguez *et al*[112] reported no statistically significant difference in short-term or long-term survival based on actuarial survival curve; [2]Tyagi *et al*[107] randomized 70 patients, but only 61 completed follow-up and were included in the analysis. The study did not show a significant difference in mortality, but showed a significant difference in the occurrence of hepatorenal syndrome. PO: Per overall survival; RR: Relative risk; HR: Hazard ratio.

ies among studies, and the rate of significant alcohol consumption post-transplant remains unclear[26]. Risk factors for recidivism include short duration of alcohol abstinence before LT, alcohol consumption just before LT, and patient denial of alcoholism[120,121]. To prevent recidivism, AASLD recommends LT candidates undergo assessment by an addictive behavior specialist, and delay of LT for ≥ 6 mo after commencing abstinence[70]. Six mo of abstinence may occasionally permit sufficient clinical improvement to render LT unnecessary[32]. EASL also supports this recommendation, and mandates a multidisciplinary approach, including psychological assessment, in addition to medical evaluation, to determine suitability for LT[26].

LT patients with alcoholic cirrhosis have at least comparable and perhaps even better survival than LT patients with other etiologies of ESLD[117,119,120]. For example, Burra *et al*[117] reported 1, 3, 5, and 10 years graft survival rates after LT in ALD patients to be 84%, 78%, 73%, and 58%, respectively; these rates are significantly higher than that for cirrhosis from viral hepatitis (P = 0.04) or cryptogenic cirrhosis (P = 0.05). Major causes of post-transplant mortality include infections, cardiovascular events and *de novo* malignancies[117], associated with immunosuppression[122,123]. *De novo* malignancies account for 23% of mortality in patients with alcoholic cirrhosis, compared to 11% of mortality in patients with cirrhosis from viral hepatitis without alcoholism or cryptogenic cirrhosis (P < 0.0001)[117]. The cumulative risk for *de novo* malignancies rises from 6% prior to LT to 55% 15 years after LT[26]. Therefore, regular screening for certain malignancies, including skin cancer, the most frequent post-transplantation cancer, is recommended[122].

NATURAL HISTORY AND COMPLICATIONS OF ALCOHOLIC CIRRHOSIS

Long-term management of complications of alcoholic cirrhosis is similar to that for other etiologies of cirrhosis (Table 4)[124-131]. Ascites is the most common complication of cirrhosis. Patients with new-onset ascites should undergo diagnostic paracentesis, to exclude other etiologies of ascites, such as cardiac disease, malignant ascites, or nephrotic syndrome; and to exclude spontaneous bacterial peritonitis (SBP). Ascitic fluid should be analyzed for cell count and differential, total protein, and serum-ascites albumin gradient (SAAG). A SAAG ≥ 1.1 g/dL supports the diagnosis of ascites secondary to portal hypertension; a SAAG < 1.1 g/dL supports other etiologies for ascites[132]. First-line treatment of ascites from cirrhosis includes alcohol cessation; dietary sodium restriction to ≤ 2 g/d; oral diuretics, usually spironolactone and furosemide; and discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs)[129]. In patients who develop hyponatremia, reduction of diuretic dose or its temporary discontinuation may be necessary[127].

Patients with refractory ascites may warrant second-line treatment, including serial, large-volume, therapeutic paracenteses, TIPS, and addition of midodrine, especially in patients with systemic hypotension[129]. Midodrine, an α-adrenergic agonist, improves systemic hemodynamics by causing arterial vasoconstriction (reversing arterial vasodilation that contributes to development of ascites)[127]. β-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers are no longer recommended for patients with ascites from cirrhosis, because of risks of life-threatening systemic hypotension[129]. Infusion of 6-8 g of albumin per liter of removed ascitic fluid is recommended during large-volume paracentesis (removal of > 5 liters of ascitic fluid)[129]. Peritoneovenous shunts used to be popular to treat refractory ascites, but are now restricted to patients with diuretic-resistant ascites who are poor candidates for serial paracenteses, transplantation, or TIPS, because of risks of disseminated intravascular coagulation and/or sepsis[129,133-135].

SBP, a complication of ascites, is diagnosed by presence of ≥ 250 polymorphonuclear cells/mm^3 in ascitic fluid. In the appropriate clinical setting, patients should receive empiric antibiotic therapy, preferably cefotaxime 2 g every 8 h, immediately after performing aerobic and anaerobic cultures of ascitic fluid[129]. Delaying antibiotic therapy to await culture results may cause life-threatening, overwhelming infection. Ascitic fluid culture is not

Table 4 Management of complications of cirrhosis, per professional society guidelines[1]

Complication	Screening/diagnosis	Treatment	Long-term management surveillance
Ascites	Diagnostic paracentesis for new-onset ascites: ascitic fluid analyzed for cell count and differential, total protein, and SAAG	Alcohol cessation; dietary sodium restriction; oral diuretics; discontinuation of NSAIDs	Refractory ascites: periodic large-volume therapeutic paracenteses; TIPS; midodrine; or peritoneovenous shunts
Spontaneous bacterial peritonitis	Diagnostic paracentesis: ≥ 250 polymorphonuclear cells/mm^3	Empiric antibiotic therapy with cefotaxime 2 g every 8 h, while awaiting culture results	Prophylaxis with norfloxacin or trimethoprim-sulfamethoxazole after one documented episode of SBP or if patient presents with variceal bleeding
Esophageal and gastric varices	Esophagogastroduodenoscopy	Treatment depends upon size of varices or risk of variceal bleeding: Prophylaxis with nadolol or propranolol for small varices at high risk of bleeding or for medium/large varices; EVL for medium/large varices at high risk of bleeding	No varices: EGD every 3 yr (earlier if hepatic decompensation occurs) Small varices: EGD every 2 yr Medium/large varices: EGD every 6-12 mo
Hepatic encephalopathy	Diagnosed by serum ammonia level and clinical findings of confusion, personality and mental status changes, and asterixis (exclude other causes of mental status changes)	Investigation and correction of precipitating factors; lactulose and/or rifaximin, supportive care	Secondary prophylaxis with lactulose and/or rifaximin indefinitely
Hepatorenal syndrome (type 1-rapidly progressive renal insufficiency; type 2-slowly progressive renal insufficiency)	Serum creatinine > 1.5 mg/dL, in the absence of other identifiable cause of renal failure (exclude other causes by urine chemistries, urine culture, and/or renal imaging)	Initial fluid challenge; albumin and terlipressin or albumin and combined octreotide plus midodrine; dialysis; LT definitive	Serial serum creatinine monitoring
Hepatocellular carcinoma (HCC)	Abdominal ultrasound every 6 mo; alpha fetoprotein determination every 6 mo no longer recommended, but optional	For HCC treatment[124]	Abdominal ultrasound every 6 mo
Hepatopulmonary syndrome	Screening by arterial blood gas; Confirmation by CEE	Symptomatic management with long-term oxygen therapy; LT definitive	
Portopulmonary hypertension	Screening by transthoracic Doppler echocardiography; Confirmation by right heart catheterization	Intravenous or inhaled prostacyclin; long-term oxygen therapy	

[1]American Association for the Study of Liver Diseases[124,128,129]; American College of Gastroenterology[125,126]; Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program[127]; European Association for the Study of the Liver[130]; and European Respiratory Society[131]. SAAG: Serum-ascites albumin gradient; NSAID: Non-steroidal anti-inflammatory drugs; TIPS: Transjugular intrahepatic portosystemic shunt; SBP: Spontaneous bacterial peritonitis; GI: Gastrointestinal; EGD: Esophagogastroduodenoscopy; EVL: Endoscopic variceal ligation; CEE: Transthoracic echocardiography with contrast enhancement.

necessary for diagnosis because up to 60% of patients have negative cultures[129]. Risk factors for persistent SBP include MELD score > 25, SAAG > 1.5, and positive ascitic fluid culture[136]. After one episode of SBP, patients should receive long-term prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole[129]. Cirrhotic patients presenting with GI bleeding should also receive SBP antibiotic prophylaxis, with either intravenous ceftriaxone or oral norfloxacin, for 7 d[129].

Cirrhotic patients should undergo screening esophagogastroduodenoscopy (EGD) to diagnose or exclude esophageal and gastric varices. Classification of varices has been simplified to: small varices - minimally elevated veins above esophageal mucosal surface; medium varices - tortuous veins occupying < 1/3 of esophageal lumen; and large varices - tortuous veins occupying > 1/3 of esophageal lumen[128]. Patients with no varices undergo repeat EGD every 3 years, or sooner if hepatic decompensation occurs. Patients with small varices at increased risk of bleeding should receive primary prophylaxis with nonselective β-blockers, such as propranolol or nadolol, and should undergo EGD every 2 years. Patients at high risk of bleeding includes those with red wale markings at EGD or those with CTP stage B or C cirrhosis[128]. Patients with medium/large varices should also receive primary prophylaxis with nonselective β-blockers, but should undergo endoscopic variceal ligation when at high risk for variceal bleeding. This high-risk population should undergo surveillance EGD every 6-12 mo[127,128].

Hepatic encephalopathy is a potentially reversible neuropsychiatric disturbance resulting from hepatic insufficiency. It is characterized by confusion, personality and mental status changes, asterixis, and hyperammonemia. Hepatic encephalopathy is staged according to West-Haven criteria as: 0, normal; 1, mild; 2, lethargy; 3, somnolence-to-stupor; and 4, coma[126]. Precipitating factors, including GI bleeding, infections, electrolyte disturbances (especially hyponatremia), medications (primarily

narcotics and sedatives), constipation, and excessive nitrogenous dietary intake, should be assiduously investigated and corrected[126]. Acute pharmacologic management includes lactulose and/or rifaximin therapy[125,126]. Lactulose, a non-absorbable disaccharide cathartic, reduces nitrogenous load in gut, thereby reducing ammonia production[126]. Rifaximin, an antimicrobial agent with minimal systemic absorption, reduces ammonia-producing enteric bacteria. Rifaximin has been shown to reduce the risk of breakthrough hepatic encephalopathy during a 6 mo period of remission and to be superior to lactulose in treating hepatic encephalopathy[137]. Supportive management includes fall prevention, nursing care, prophylactic intubation in cases of severe hepatic encephalopathy, and adequate nutritional support[126]. After recovery, patients require secondary prophylaxis indefinitely with lactulose, rifaximin, or combination therapy to prevent recurrence.

HRS is characterized by serum creatinine > 1.5 mg/dL in a patient with ESLD, in the absence of other identifiable causes of acute or chronic renal failure[130]. It is a diagnosis of exclusion. It is classified into: type 1 HRS, characterized by rapidly progressive impairment in renal function (100% increase in baseline creatinine or creatinine level > 2.5 mg/dL, usually within 2 wk); and type 2 HRS, characterized by slowly progressive (> 2 wk) worsening renal function[127,130]. All cirrhotic patients with sudden increases in serum creatinine to > 1.5 mg/dL should have discontinuation of diuretics and receive a fluid challenge with 1.5 L intravenous normal saline[138]. Patients who are prerenal respond to fluid challenge, with decrease in creatinine levels and improved urine output, whereas patients with HRS are mostly unresponsive to fluid challenge[127,138]. Other causes of renal toxicity should be excluded, such as NSAIDs, hypotension, hypovolemia, obstructive uropathy, and sepsis. First-line therapy for HRS includes albumin and terlipressin, a vasopressin analogue that improves splanchnic circulation[130], or albumin and combined octreotide plus midodrine[127]. Patients not responding to these therapies may require dialysis and subsequent LT (usually with simultaneous renal transplant), the only definitive treatment for HRS. Pentoxifylline, as aforementioned, can decrease the incidence of HRS[107].

HCC occurs in 5%-15% of patients with alcoholic cirrhosis[23]. The precise incidence is, however, uncertain, as patients with alcoholic cirrhosis are often co-infected with HCV, which acts synergistically to potentiate the risk of HCC[124]. Nevertheless, screening for HCC is recommended in all patients with alcoholic cirrhosis. HCC surveillance is usually performed by abdominal ultrasound every 6 mo. Surveillance with serial serum alpha-fetoprotein determinations is no longer recommended because of insufficient specificity and sensitivity[124], but is still frequently performed. Diagnosis and treatment are similar in all patients with HCC, regardless of etiology of cirrhosis. The reader is referred to a comprehensive review on this subject[124].

Pulmonary vascular complications of chronic liver disease include hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN). HPS is defined as an arterial oxygenation defect caused by intrapulmonary vascular dilatation in patients with liver disease, especially cirrhosis[139]. It occurs in approximately 20% of patients awaiting LT. Symptoms include dyspnea and platypnea, a characteristic finding of increased shortness of breath on rising from supine to upright position[131]. Screening, using arterial blood gas, is done in LT candidates and patients with liver disease who present with such symptoms. Transthoracic echocardiography with contrast enhancement (CEE) is the gold standard for diagnosis of HPS. CEE is commonly accomplished by hand agitation of 10 mL normal saline, resulting in microbubbles ($\leqslant$ 90 μm in diameter), which are injected into an upper extremity vein[131]. Detection of microbubbles within the left atrium is considered a positive CEE[131]. Diagnostic criteria include: (1) presence of liver disease; (2) alveolar-arterial oxygen tension difference (A-a gradient) $\geqslant$ 15 mmHg; and (3) positive CEE[131]. The only curative treatment for HPS is LT, but patients can be managed symptomatically with long-term oxygen therapy.

PPHTN is defined as pulmonary artery hypertension associated with portal hypertension, likely secondary to imbalance in vasoactive substances reaching the pulmonary circulation from portosystemic shunts or defective hepatic metabolism[140]. It occurs in approximately 5% of patients awaiting LT. Patients present with dyspnea, chest discomfort, or syncope. Transthoracic Doppler echocardiography is used for screening; PPHTN is suspected by finding of right ventricular systolic pressure > 40-50 mmHg. Diagnosis is confirmed by right heart catheterization, that reveals: (1) mean pulmonary artery pressure > 25 mmHg; (2) mean pulmonary artery occlusion pressure < 15 mmHg; and (3) pulmonary vascular resistance > 240 dyn-s/cm^{-5}[131]. Treatment may include pulmonary vasodilator therapy with intravenous and inhaled prostacyclin, as well as long-term oxygen therapy. LT is reserved for patients who fail to improve with these therapies.

FUTURE DIRECTIONS

Current research on ALD involves non-invasive diagnosis of ALD and novel treatment options. Non-invasive diagnostic liver tests, including FibroScan, have been studied, but the diagnostic accuracy of these tests have not been compared to the gold standard of liver biopsy, to define cut-off values for ALD[141]. The current prognostic scoring systems account for only 75%-85% of mortality for ALD or other causes of liver disease. Scoring systems incorporating more linearly independent variables may increase prognostic accuracy.

Currently, LT remains the only curative treatment. Further studies are needed for currently popular therapies, such as corticosteroids and pentoxifylline, to deter-

mine efficacy, especially to prove survival benefit. Combined medical therapies may be useful to achieve synergy in improving survival.

New treatment options that target pathways implicated in ALD pathogenesis, including oxidative stress, endotoxin production, cytokine production, and immune regulators[12] are being investigated. Recently investigated antioxidants include milk thistle (silymarin extracts) and *S*-adenosyl-*L*-methionine, both of which have not been proven beneficial[142,143]. However, most studies have been of low quality, and high quality RCTs regarding these relatively nontoxic, and possibly helpful treatments should be performed. Other TNF-α inhibitors, including etanercept and infliximab, have been studied, but only 3 RCTs with small study sizes have been published on these medications[144-146]. Reported adverse events and likely increased mortality limit their use, but further studies may be needed to confirm these findings.

Interleukin-22 (IL-22) is a potential therapy for ALD[14]. IL-22 ameliorates hepatic steatosis and liver injury in animal models after acute or chronic-binge ethanol feeding[147]. It may promote hepatocyte proliferation or hepatic regeneration and inhibit hepatic fibrosis in response to alcohol-induced liver injury[147]. IL-22 theoretically appears to be relatively safe because only hepatocytes, epithelial cells, and a few other cell types have IL-22 receptors. IL-22, however, promotes proliferation of preexisting hepatomas, even though it does not initiate hepatoma formation[148]. It is therefore likely contraindicated in patients with ALD complicated by hepatoma and may have limited use in patients with alcoholic cirrhosis.

Increased intestinal permeability to gut-derived microorganisms appears to increase morbidity and mortality in AH[149]. Several multi-institutional consortia are developing therapies for AH based on preventing or neutralizing these effects of increased intestinal permeability. For example, lipopolysaccharide (LPS) antibody may help neutralize injury from lipopolysaccharide from exposure to gut-derived microorganisms. One study will compare the effects of lipopolysaccharide (LPS) antibody in combination with corticosteroids *vs* corticosteroid monotherapy in patients with severe AH[149]. Other studies will examine the efficacy of probiotics *vs* placebo for moderately severe AH, or the effect of adding zinc, a mineral that improves gut barrier function, to other therapies for severe AH.

Another promising approach to AH therapy is targeting macrophage/Kupfer cell activation in AH which leads to increased IL-1 beta activation. A clinical trial is examining a combination of Anakinra, an interleukin 1 receptor antagonist, and traditional therapy *vs* traditional therapy alone for severe AH[150]. Another attractive approach is to inhibit caspases which are death induction molecules downstream to TNF-alpha activation during hepatotoxic injury. Emricasan, a pancaspase inhibitor, is proposed to be tested to block hepatocyte injury induced by TNF-beta, without blocking the beneficial hepatic effects of TNF-beta on liver regeneration and immune cell function[150]. Other novel potential therapies are in the process of development or undergoing preliminary clinical trials[14].

CONCLUSION

ALD is a prominent and preventable cause of morbidity and mortality. The cornerstone of therapy is abstinence, which improves overall survival. Psychological and pharmacologic therapies can support abstinence. Nutritional and supportive therapies are also important. Several therapies for AH, such as corticosteroids and pentoxifylline, are widely administered, but their survival benefit remains unproven. These drugs are generally well tolerated, without significant toxicity. Other potential therapies include TNF-α inhibitors other than pentoxifylline, antioxidants, and complementary medicine, none of which have demonstrable benefits for ALD and are not recommended as therapies. LT remains the only definitive treatment for alcoholic cirrhosis, and multidisciplinary management, including aggressive psychosocial therapy to prevent relapse should be instituted post-transplant. Patients with advanced ALD have complications that are similar to cirrhosis of other etiologies. Prophylaxis, surveillance, and aggressive treatment are important to prevent significant morbidity and mortality.

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