Treatment of alcoholic liver disease

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***Abstract*:** Alcoholic liver disease (ALD) remains a major cause of liver-related mortality in the US and worldwide. The correct diagnosis of ALD can usually be made on a clinical basis in conjunction with blood tests, and a liver biopsy is not usually required. Abstinence is the hallmark of therapy for ALD, and nutritional therapy is the first line of therapeutic intervention. The role of steroids in patients with moderate to severe alcoholic hepatitis is gaining increasing acceptance, with the caveat that patients be evaluated for the effectiveness of therapy at 1 week. Pentoxifylline appears to be especially effective in ALD patients with renal dysfunction/hepatorenal syndrome. Biologics such as specific anti-TNFs have been disappointing and should probably not be used outside of the clinical trial setting. Transplantation is effective in patients with end-stage ALD who have stopped drinking (usually for ≥6 months), and both long-term graft and patient survival are excellent.

***Keywords*:** alcoholic liver disease, cytokines, diagnosis, nutrition, steroids, transplantation, treatment

Introduction

Alcoholic liver disease (ALD), which ranges from simple steatosis to cirrhosis and hepatocellular carcinoma (HCC), continues to represent a major health issue in the United States and abroad. Despite significant advances in the understanding of the pathogenesis of alcohol-related liver injury, there are no FDA-approved treatments for ALD. The purpose of this review is to examine the diagnosis and current modalities of treatment for ALD. At present, abstinence remains the cornerstone for successful treatment of ALD. Aside from treatment of the underlying addiction, aggressive nutritional intervention and 'off-label' use of various pharmacotherapies aimed at the underlying mechanisms of injury (e.g., cytokine dysregulation, endotoxin translocation and oxidative stress) represent our approach to treating ALD.

Epidemiology and impact

Despite our best efforts, alcohol remains one of the most common causes of both acute and chronic liver disease in the United States [Sofair *et al.* 2010]. In Western countries, up to 50% of cases of end-stage liver disease have alcohol as a major etiologic factor [Orholm *et al.* 1985]. Excessive alcohol consumption is the third leading preventable cause of death in the United States. Alcohol-related deaths, excluding accidents/homicides, accounted for 22,073 deaths in the United States in 2006 with 13,000 of those specifically attributed to ALD [Heron *et al.* 2009]. Cirrhosis from any cause represents the 12th leading cause of death in the United States and 45.9% of all cirrhosis deaths are attributed to alcohol [Centers for Disease Control, 2008]. The mortality from alcoholic cirrhosis is higher than that of nonalcoholic cirrhosis with a survival rate at 5 and 10 years of only 23% and 7%, respectively [Propst *et al.* 1995]. Given these grim statistics, the mortality of this liver disease is more than that of many major forms of cancer, such as breast, colon and prostate [Chedid *et al.* 1991]. Alcohol represents a major financial burden on the overall economy as well, with an estimated cost of US$185 billion annually (lost productivity, motor vehicle accidents, etc.) [Kim *et al.* 2002].

Risk factors

The development of liver disease from alcohol ingestion is dependant on several factors. First, a 'threshold' must be reached regarding the duration of use and daily intake of alcohol. Daily intake of alcohol for 10–12 years with doses in excess of 40–80 g/day for males and of 20–40 g/day for females are generally needed to

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cause ALD [Thun *et al.* 1997; Becker *et al.* 1996; Fuchs *et al.* 1995; Grant *et al.* 1988]. Because different types of alcoholic beverages have varying alcohol content, the threshold is different for each type of beverage. As an example, daily drinking of 3–6 cans (12 oz each) of beer/day for males or 1.5–3 cans of beer/day for females for 10 years or longer can cause ALD [Arteel *et al.* 2003].

Despite reaching the required 'threshold' for alcohol intake, only 10–35% of heavy, long-term alcohol drinkers will develop alcoholic hepatitis and only 8–20% will develop cirrhosis [Espinoza *et al.* 1987]. As implied by these statistics, host attributes (e.g., gender and polymorphism(s) of alcohol-metabolizing enzymes) and coexisting external factors (e.g., obesity and hepatitis C infection) combine to determine the likelihood of developing associated liver disease. For example, the risk for HCC increases fivefold with a daily alcohol consumption of 80 g; in the presence of hepatitis C infection it is increased 20-fold; and a combination of both risk factors leads to a more than 100-fold increased risk for HCC development [Mueller *et al.* 2009]. There are several studies demonstrating that women develop liver disease after exposure to lower quantities of alcohol and over shorter time periods [Becker *et al.* 1996; Fuchs *et al.* 1995].

Spectrum

Alcohol-induced liver injury represents a wide spectrum of pathologic abnormalities: from mild steatosis to HCC in the setting of cirrhosis [Lefkowitch, 2005]. Macrovesicular steatosis represents the first and most common pathologic change seen with chronic alcohol ingestion (in up to 90% of heavy alcohol users) [Mathurin *et al.* 2007]. Macrovesicular change also represents an easily reversible finding when abstinence from alcohol is achieved. Hepatocyte death by apoptosis as well as areas of microvesicular steatosis can also be seen, although more commonly in steatohepatitis. Ballooning degeneration of hepatocytes, infiltrating neutrophils, Mallory bodies and fibrosis represent a more concerning collection of pathologic findings indicative of steatohepatitis (alcoholic hepatitis) [Lefkowitch, 2005].

The clinical relevance of alcoholic hepatitis is twofold: severe alcoholic hepatitis is associated with a 40% 6-month mortality, and progression to cirrhosis is nine times greater than in those with steatosis alone [Lucey *et al.* 2009a]. HCC develops in 5–15% of those with alcoholic cirrhosis, most commonly in individuals with macronodular cirrhosis [Lefkowitch, 2005].

Diagnosis of alcohol abuse

Although alcohol abuse and/or dependency are not prerequisites to the development of ALD, the two often correlate with one another. Alcohol addiction is divided into two categories: abuse and dependence. Alcohol abuse is defined as excessive drinking without harmful physical and social consequences. In contrast, alcohol dependence is defined as continued drinking despite physical and social harms [Lucey, 2009]. These diagnoses are commonly based on history and evidence of harm (e.g., organ damage, legal/social difficulties and/or increased injuries secondary to intoxication).

Only 24% of problem drinkers will actively seek assistance, and just 13% will receive specialized addiction treatments. Primary care physicians represent the first line of detection, but only 50% of problem drinkers were identified by their physicians. In light of this, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) published guidelines in 2007 to assist primary care physicians in screening for problematic drinking. Methods as basic as a single question inquiring how often has the maximum daily alcohol limit been exceeded in the past year have greatly improved diagnosis of alcohol abuse and dependence [Willenbring *et al.* 2009]. Other screening tools such as the CAGE (need to *c*ut down, *a*nnoyed by criticism, *g*uilty about drinking, need for an *e*ye-opener in the morning) and the AUDIT-C (Alcohol Use Disorders Identification Test) have also increased detection of problem drinking in the physician's office [Bradley *et al.* 2007]. On the CAGE questionnaire, two positive answers indicate alcohol dependency with a sensitivity of more than 70% and specificity of more than 90% [Girela *et al.* 1994; Buchsbaum *et al.* 1992].

A large obstacle in making the diagnosis of alcohol abuse is patient reluctance to openly share a drinking history if it may be viewed as excessive or problematic. A recent study reiterated this by demonstrating that electronic administration of the AUDIT-C was more likely to identify at-risk drinking than the same screening questionnaire

administered orally or on paper [Graham *et al.* 2007].

Given the reluctance of patients to be open with regard to their alcohol use, biomarkers to reliably detect problematic drinking have been investigated extensively. The most sensitive and specific indicator of recent alcohol use is the blood or breath alcohol test. This modality of testing has been found to be especially useful in binge drinkers [Savola *et al.* 2004]. Of course, blood or breath testing is limited by the relatively short half-life of ethanol in the breath, blood and urine and will not detect those patients who have not recently had alcohol intake. Among other biomarkers studied are carbohydrate-deficient transferrin (CDT) and gamma-glutamyltransferase (GGT). In multiple studies GGT levels have proven to be more sensitive than CDT or alanine transaminase (ALT). However, specificity is very low and values are affected by multiple other factors including age, obesity and diabetes. CDT is a biomarker which has shown promise with specificity and sensitivity greater than GGT when alcohol ingestion tops 150 g per day. Unfortunately, CDT levels are also affected by age, gender, body mass and tobacco use, limiting its clinical use to date [Niemela, 2007]. CDT is currently the only FDA-approved test for the detection of heavy alcohol use. A recent study demonstrated a 90% sensitivity and 98% specificity using a combination of GGT and CDT in a weighted equation to correctly identify heavy drinkers, raising the possibility of combined CDT–GGT equation as a potential biomarker of excessive alcohol use [Hietala *et al.* 2006]. Mean corpuscular volume (MCV) and mitochondrial aspartate transaminase (mAST)/total aspartate transaminase (AST) ratios have also been studied as possible measures of alcohol use. As with the aforementioned biomarkers, these values are influenced by multiple other factors which have limited their usefulness in the diagnosis of excessive alcohol use, and the search for new biomarkers is ongoing [Das *et al.* 2008].

Diagnosis of alcoholic liver disease

History

Patients with only steatosis or compensated cirrhosis will commonly be asymptomatic. Patients with alcoholic steatohepatitis (ASH) may relate symptoms of anorexia, fever, jaundice, weight loss, diarrhea, abdominal pain, weakness, nausea and vomiting [Whitfield *et al.* 2009]. Once a patient develops decompensated cirrhosis and resultant portal hypertension, symptomatology will reflect the underlying complication. Melena, hematemesis, dyspnea on exertion and fatigue accompany patients with gastrointestinal bleeding. Increasing abdominal girth, shortness of air and peripheral edema accompany sodium retention and resultant ascites. Confusion, insomnia or other sleep disturbances and decreased concentration are common complaints associated with portosystemic encephalopathy (PSE).

Physical examination

Regardless of the severity of the disease process, the most common physical exam finding in patients with either steatosis or alcoholic hepatitis is hepatomegaly. Up to 70% of hospitalized patients with steatosis have hepatomegaly [Leevy, 1962]. Those patients with more severe ALD and resultant portal hypertension may present with tender hepatomegaly, peripheral edema, spider angiomata, splenomegaly, jaundice, ascites and, rarely, a bruit over the liver. Patients with well-compensated cirrhosis may exhibit only hepatomegaly and/or splenomegaly, although the liver will decrease in size as fibrosis progresses. Decompensated cirrhosis will be more likely to present with ascites, cachexia, palmar erythema, Dupuytren's contractures, and clubbing of the digits if hepatopulmonary syndrome is present. Parotid and lacrimal gland enlargement can also be seen. PSE can also be present and can include a wide range of signs and symptoms such as slow reaction time, asterixis and coma. It is important to note that these physical signs of ALD are not pathognomonic [Arteel *et al.* 2003].

Laboratory findings

As with the physical signs of ALD, no one laboratory abnormality is sufficient to make the diagnosis of an alcohol-related liver injury. In patients with benign steatosis, two-thirds will have normal laboratory findings. The vast majority of patients with ASH will have elevation of AST > ALT, with both below 300 IU/ml [Himmelstein *et al.* 1984; Matloff *et al.* 1980; Cohen and Kaplan, 1979]. Up to 80% of patients with ALD will have an AST : ALT ratio of >2 [Skude and Wadstein, 1977; Galambos, 1974]. In cirrhosis, the specificity of these generalizations is decreased, as cirrhosis secondary to any cause will likely result in modest or normal AST > ALT levels. Alkaline phosphatase levels may be normal or significantly

elevated, while albumin levels are commonly decreased in ALD patients. Hypertriglyceridemia, hyperuremia, hypokalemia, hypomagnesemia, and an elevated MCV can also be seen with chronic alcohol consumption and subsequent liver disease [Morse and Hurt, 1979].

Patients with ASH will often have leukocytosis and thrombocytopenia. Leukemoid reactions with counts of >100,000 white blood cells (WBC)/mm^3 in the absence of infection can be seen in patients with ASH. While thrombocytopenia that is secondary to heavy alcohol consumption may resolve with abstinence, it is persistent in patients with concomitant cirrhosis. Elevation of bilirubin, prolongation of prothrombin time (PT) and hypoalbuminemia are markers of severe alcoholic hepatitis and/or cirrhosis. Maddrey's Discriminant Function (DF), which is calculated using the equation [4.6 × (PT patient − PT control) + total bilirubin (mg/dl)], is the most commonly utilized tool for evaluating the severity of ASH. If this value exceeds 32, the mortality during the current hospitalization is in excess of 50% [Carithers *et al.* 1989; Maddrey *et al.* 1978]. Other validated models for severity in ASH include MELD, the Glasgow score, and others; we recommend becoming familiar with one [Maher, 2007]. While they are not used in routine clinical practice, pro-inflammatory cytokine serum concentrations such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8) have been demonstrated to correlate with mortality in patients with alcoholic hepatitis [McClain *et al.* 2004b]. Finally, an elevated creatinine can also be seen in patients with ALD and, in the setting of severe ASH without other causes of acute kidney injury, may indicate the ominous diagnosis of hepatorenal syndrome.

Histopathology

ALD is most often a clinical diagnosis, with a careful history being of vital importance. In an educated population, the clinical diagnosis of ALD has a sensitivity of 91%, specificity of 96%, and a positive predictive value of 88% and negative predictive rate of 97% [Van Ness and Diehl, 1989]. While liver biopsy is rarely needed to establish a diagnosis, it is sometimes needed to clarify atypical cases, to better define the alcohol contribution in patients with possible coexisting conditions, and to stage the severity of liver disease [Arteel *et al.* 2003].

When biopsy is warranted, the pathognomonic histopathology of the entire spectrum of ALD is well established. Up to 90% of heavy, chronic alcohol users will demonstrate macrovesicular steatosis in the centrilobular or perivenular region (benign steatosis). Patients with liver biopsies revealing severe mixed micro/macrovesicular pattern, and/or giant mitochondria are more likely to develop fibrosis and evolve to cirrhosis [Fromenty *et al.* 1995; Teli *et al.* 1995]. ASH is characterized by moderate to severe fatty infiltration (82%), Mallory bodies (76%), sclerosing hyaline necrosis (68%), ballooning degeneration of hepatocytes with polymorphonuclear cell infiltration (97%) and increased fibrosis (54%) [MacSween and Burt, 1986]. In contrast to benign steatosis secondary to alcohol use, megamitochondria seen in the setting of ASH are associated with a favorable prognosis [Chedid *et al.* 1986]. Collagen is deposited in a characteristic perivenular and pericellular distribution. Approximately 40% of patients with this lesion (zone 3 fibrosis extending in a lattice-like perihepatocyte network) will develop cirrhosis within 5 years [Alexander *et al.* 1971]. Cirrhosis secondary to alcohol use is most often micronodular although a mixed pattern can be seen. Coexisting ASH is often seen and 95% of these biopsies will reveal Mallory bodies. Sclerosing hyaline necrosis and fatty infiltration are also commonly seen in this setting [MacSween and Burt, 1986].

Alcoholic liver disease treatment

Abstinence and lifestyle modification

Addressing the underlying addiction to alcohol is the paramount step in managing ALD. Abstinence from alcohol leads to resolution of alcoholic fatty liver disease (benign steatosis) and abstinence improves survival in alcoholic cirrhotic patients, even those with decompensated liver function. Furthermore, reducing alcohol consumption, but not completely stopping, has been shown to improve survival in patients with ALD [Sofair *et al.* 2010; Heron *et al.* 2009]. While there is no question regarding the benefit of abstinence, motivating patients to follow this treatment regimen, monitoring their compliance, and preventing relapse remain major obstacles to the treatment of ALD. Certainly, inpatient and outpatient rehabilitation programs have demonstrated effectiveness in assisting patients to achieve and maintain sobriety [Miller *et al.* 2001]. Referral to and communication with an addiction specialist, and encouraging active

participation in Alcoholics Anonymous, represents the best method of assisting patients with alcoholism and concomitant ALD. While this may not be available to all patients, studies indicate that heavy drinkers who receive brief interventions (less than 1 hour in length and incorporating motivational counseling techniques) are twice as likely as control patients to have modified their drinking habits 6–12 months after the intervention [Kaner *et al.* 2009]. Recognition and treatment of comorbid psychiatric conditions is also a useful step in assisting patients with alcohol dependence [Moos *et al.* 1996].

Pharmacotherapy in combination with psychosocial interventions can aid patients in maintaining abstinence from alcohol. Naltrexone and acamprosate have been shown to assist in reducing or eliminating alcohol intake in chronic heavy drinkers [Bouza *et al.* 2004]. Disulfiram, which has long been approved by the FDA for the treatment of alcoholism, is still widely used but less clearly supported by clinical trial evidence [Williams, 2005]. Disulfiram is still believed to have a role in alcoholism treatment and it is hypothesized that under supervised administration, disulfiram can have favorable outcomes for patients [Garbutt *et al.* 1999]. Topiramate has demonstrated safety and efficacy in multiple clinical trials in decreasing both craving and withdrawal symptoms and increasing quality of life measures among alcohol-dependent individuals [Kenna *et al.* 2009]. Finally, baclofen has proven effective in promoting alcohol abstinence in alcohol-dependent patients with liver cirrhosis [Addolorato *et al.* 2007]. Given the high likelihood of chronic, heavy alcohol use, the consequent difficulty in achieving/maintaining sobriety and the low margin for error in patients with ALD, the coordination of both pharmacotherapy and psychosocial intervention is best handled by an addiction specialist.

Other lifestyle modifications, such as smoking cessation and weight loss, if applicable, are also crucial to improving the outcome of those suffering from ALD. Smoking is an independent risk factor for advancement of hepatic fibrosis which can lead to more severe ALD, and may be linked to the development of HCC [Corrao *et al.* 1994; Klatsky and Armstrong, 1992]. Obesity, which can also cause fatty liver, nonalcoholic steatohepatitis, and cirrhosis, may be an independent risk factor for the progression of ALD [Naveau *et al.* 1997].

Nutritional support

It has long been established that patients with ALD (both severe ASH and cirrhosis) are nearly all malnourished, and the degree of malnutrition correlates with disease severity [Halsted, 2004; Mendenhall *et al.* 1995a]. In addition, complications of ALD (e.g. infections, encephalopathy, ascites, and variceal bleeding) have been shown to be strongly associated with protein-calorie malnutrition (PCM) [Stickel *et al.* 2003; Mendenhall *et al.* 1995a]. Micronutrient deficiencies of folate, vitamin B6, vitamin A and thiamine are among the most commonly encountered. Mineral/element (e.g., selenium, zinc, copper, and magnesium) levels are often altered in ALD and, in some instances, are thought to be involved in its pathogenesis [Halsted, 2004]. In particular, zinc is decreased in patients with ALD. In animal models, zinc supplementation has been shown to improve, attenuate, and/or prevent ALD through a variety of mechanisms [Kang and Zhou, 2005].

The spectrum of nutritional conditions among patients with ALD also spans from morbid obesity to profound underweight and malnutrition. Given the high caloric content of alcohol (7.1 kcal/g), patients with ALD and concomitant high-calorie diets can expect to develop truncal obesity and resultant progression of ALD [Stickel *et al.* 2003; Raynard *et al.* 2002]. Given similar mechanisms of pathogenesis (e.g., oxidative stress, cyokines, cytochrome P450), patients with the metabolic syndrome/insulin resistance and concomitant ALD would be expected to have more severe disease with a quicker progression to fibrosis [Lieber, 2004]. The effect of alcohol on adipokines such as adiponectin is currently under investigation [Yu *et al.* 2010]. With the obesity epidemic at hand, the possibility of concomitant ALD and obesity-related liver disease (including their combined effect on the rising incidence of HCC) is, and should continue to be, at the forefront of hepatology research [Baker *et al.* 2010]. Finally, patients with ALD and obesity are not necessarily resistant to the usual nutrient deficiencies associated with ALD patients who are normal or underweight.

Several mechanisms are hypothesized to contribute to malnutrition in ALD. Decreased caloric intake (secondary to anorexia and reduced intake of nonalcohol calories); decreased intestinal absorption/digestion of nutrients (secondary to altered gut integrity, pancreatic insufficiency, decreased bile excretion, and a decrease in intestinal enzymes); and decreased processing and storage of nutrients (secondary to decreased functional liver mass, abnormal oxidation of fat, and preferential metabolism of alcohol) are all thought to be involved in the malnutrition associated with ALD [Griffith and Schenker, 2006]. Increased catabolism of skeletal muscle and visceral proteins leading to a hypermetabolic state in alcoholic hepatitis is also a key component in the development of protein calorie malnutrition (PCM) in ALD [John *et al.* 1989].

With so many mechanisms at play, the diagnosis and treatment of malnutrition in patients with ALD is sometimes difficult. The laboratory tests most commonly used to assess nutritional status (e.g., anthropometry and serum albumin concentration) are often affected by concomitant liver disease. Alternative tests, such as the creatinine-height index, have been shown to be more reliable indicators of loss of muscle mass with severe ALD [Stickel *et al.* 2003; Mendenhall *et al.* 1995a]. Based on the available data demonstrating the prevalence of malnutrition in ALD and the difficulty in diagnosis, patients with severe forms of ALD should be considered malnourished and treated as such.

Nutritional support for patients with ALD depends on the severity of liver disease, concomitant factors leading to malnutrition (e.g., anorexia and pancreatic insufficiency), and the presence of obesity. Obese patients with less severe liver injury should be referred to a dietician and advised concerning dietary restriction and regular exercise. In outpatient therapy for patients with ALD, nutritional support in alcoholic cirrhotic patients improves nutritional status and cell mediated immunity, as well as decreases infectious complications and consequent hospitalizations [Hirsch *et al.* 1999, 1993]. Another study of cirrhotics (not exclusively ALD) demonstrated that a late-evening nutritional supplement over a 12-month period improved body protein stores in patients with cirrhosis [Plank *et al.* 2008]. Without question, there are limited data regarding outpatient nutritional therapy in patients with ALD. While more study is warranted, our general practice is to encourage bedtime nutritional supplements in outpatients with severe ALD (e.g., ASH and cirrhosis).

Most of the data regarding nutritional therapy and ALD pertain to inpatients with alcoholic hepatitis. Some of the most important of these data came from the Veterans Administration Cooperative Studies Program [Mendenhall *et al.* 1995a, 1995b, 1993, 1986, 1985, 1984]. In this group of studies (which includes over 600 patients with ALD), PCM was demonstrated to be present in virtually all patients with severe ALD. The degree of malnutrition correlated with the development of serious complications such as encephalopathy, ascites and hepatorenal syndrome. Moreover, nutritional support improved parameters indicative of PCM, severity of liver injury, and, most importantly, mortality in patients with moderate PCM and ALD (but not in patients with severe PCM). A major multicenter study demonstrated that enteral nutrition, when compared to corticosteroids, has similar short-term mortality rates, improved 1-year mortality rates and reduced infectious complications [Cabre *et al.* 2000]. An additional study demonstrated the benefit of tube-fed nutrition (improved PSE scores, bilirubin, and antipyrine clearance) compared with a regular diet in ALD [Kearns *et al.* 1992]. Parenteral nutrition for patients with ALD is rarely indicated but appears to improve liver function and nitrogen balance. However, it fails to convey a survival benefit over standard therapy [Cabre, 2008; Simon and Galambos, 1988].

Regarding the composition of the nutritional support, the available data are sparse. The American College of Gastroenterology (ACG) and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend 1.2–1.5 g/kg of protein and 35–40 kcal/kg of body weight per day in patients with ALD [McCullough and O'Connor, 1998]. The available clinical trials are widely varied regarding the make up of the nutritional support utilized [Griffith and Schenker, 2006]. In one randomized trial comparing oral branched-chain amino acids (BCAA) to lactoalbumin or maltodextrins, long-term nutritional supplementation with oral BCAA improved surrogate markers and perceived health status and decreased hospitalizations in patients with advanced cirrhosis [Marchesini *et al.* 2003].

Another study demonstrated that long-term BCAA supplementation is associated with decreased frequency of hepatic failure and overall complication frequency [Charlton, 2006]. Other studies have been less convincing [Calvey *et al.* 1985]. Interestingly, unsaturated fatty acids (corn oil, fish oil) have been shown to exacerbate experimental models of alcoholic liver injury by increasing oxidative stress, whereas saturated fatty acids are protective. The somewhat counter-intuitive benefit of saturated fatty acids is thought to attenuate ALD progression via the down-regulation of cyclooxygenase-2 and TNF-α; altering of fatty acid metabolism and membrane composition; and possibly through modulation of adiponectin activity [You *et al.* 2008, 2005; Purohit *et al.* 2004; Ronis *et al.* 2004, Nanji *et al.* 1997]. A comparison of different fat compositions in enteral formulas has not been studied in patients with ALD.

While some studies have failed to demonstrate a clear survival benefit for all patients with severe ALD receiving enteral nutrition [Tan *et al.* 2009; Cabre, 2008; Griffith and Schenker, 2006], we see no controversy regarding the implementation of aggressive nutritional support in these patients. This is especially true when considering risk *versus* benefit and the fact that nutritional support will improve nutritional status. Given the many obstacles to enteral feeding in patients with severe ALD (e.g., anorexia, nausea and vomiting), our general approach is to place naso-enteral access for early enteral feeding with a standard formula (1.2–1.5 g/kg of protein and 35–40 kcal/kg of body weight per day).

Glucocorticosteroids

Despite over 35 years of clinical data including multiple clinical trials, several meta-analyses [Addolorato *et al.* 2009] and ACG/AASLD guidelines supporting the use of glucocorticoids [McCullough and O'Connor, 1998], their benefit still remains in some question [Christensen, 2002]. The effect of steroids on polymorphonuclear neutrophil functions, their ability to inhibit important pro-inflammatory transcription factors such as activator protein 1 (AP-1) and nuclear factor-κB (NF-κB), a reduction in soluble intracellular adhesion molecule 1, and their beneficial effects on pro-/anti-inflammatory cytokine levels are thought to be the underlying mechanisms of action leading to benefit in patients with severe ASH [Lucey *et al.* 2009a; Spahr *et al.* 2001; Taieb *et al.* 2000].

Glucocorticoids have been found to be beneficial in patients with hepatic encephalopathy and/or in patients with a Maddrey's DF score $\geq$32 or MELD score $\geq$21. Several studies have demonstrated a significant benefit in 30-day hospital survival [Ramond *et al.* 1992; Carithers *et al.* 1989; Maddrey *et al.* 1978]. Subsequent studies demonstrated that prednisolone reduced mortality at 1 year after treatment, but not at 2 years [Mathurin *et al.* 1996]. Importantly, a meta-analysis of the most recent studies of this subgroup of patients confirmed a substantial short-term mortality benefit *versus* placebo ($84.6 \pm 3.4\%$ *versus* $65.1 \pm 4.8\%$, respectively, $p = 0.001$) [Rambaldi *et al.* 2008]. Five patients need to be treated with corticosteroids to prevent one death [O'Shea and McCullough, 2006].

Perhaps the most pertinent recent discovery regarding ASH and corticosteroids is the importance of early response to treatment. Early response to glucocorticoids, demonstrated by a decrease in serum bilirubin level by day 7, has been shown to be a clinically useful indicator of both short- and long-term survival [Mathurin *et al.* 2003, 2002]. Response to steroids, in combination with additional confounders including age, renal insufficiency, albumin, prothrombin time, and bilirubin (incorporated into a logistical regression termed the Lille model) was found to be highly predictive of death at 6 months ($p < 0.000001$) [Louvet *et al.* 2007]. In those patients who fail to respond early to steroid therapy, there are no definitive answers as to how to improve their outcomes. A recent clinical trial demonstrated no benefit of pentoxifylline (PTX) in nonresponders [Louvet *et al.* 2008].

A very recent Cochrane systematic review included 15 trials with a total of 721 randomized patients. In this study that included both the largest meta-analysis conducted to date, as well as trial sequential analyses, glucocorticosteroids did not statistically reduce mortality compared with placebo or no intervention (relative risk 0.83, 95% CI 0.63–1.11). Glucocorticosteroids significantly reduced mortality in the subgroup of trials with patients with Maddrey's DF $\geq$32 or hepatic encephalopathy and with low-bias risk. The authors concluded that heterogeneity and risk-bias were extremely common among the available clinical trials and that the current evidence base is insufficient to recommend or refute glucocorticosteroids for patients with alcoholic

hepatitis or for any subgroup of patients with alcoholic hepatitis [Rambaldi *et al.* 2008].

Among the most worrisome of complications in patients undergoing corticosteroid treatment for severe ASH is the development/worsening of life-threatening infections. An active infection is generally regarded as a contraindication to therapy, and most clinical trials involving corticosteroids for ASH excluded these patients. In an attempt to shed light on this issue, a recent prospective study examined 246 patients with severe ASH regarding infection before and after corticosteroid use. The study demonstrated that patients infected before using corticosteroids had 2-month survival similar to that of others: $70.9\% \pm 6.1\%$ *versus* $71.6\% \pm 3.4\%$, respectively, $p = 0.99$. Interestingly, the authors found that steroid use alone was not a major determinant of infection or complications from infections. Rather, nonresponsiveness to steroids was the key factor in development of infection and prediction of survival [Louvet *et al.* 2009].

Glucocorticosteroids represent the most widely accepted therapy in patients with severe ASH (defined as Maddrey's DF $\geq$ 32 or MELD score $\geq$ 21). Corticosteroids plus aggressive enteral nutrition is a reasonable approach to the treatment of such patients. It is currently recommended that patients with severe ASH should be given a short course of glucocorticoid therapy (e.g., prednisone 40 mg daily for 28 days, followed by 20 mg daily for 7 days, and 10 mg daily for 7 days). Based on the above clinical data, we recommend discontinuation of therapy if there is no decrease in serum bilirubin levels by day 7. Owing to potential adverse effects of glucocorticoid therapy, steroids are generally avoided in patients with gastrointestinal bleeding requiring transfusion, chronic hepatitis B virus infection, evidence of active infection, and probably in hepatorenal syndrome [Depew *et al.* 1980].

Pentoxifylline

The 2010 ACG/AASLD guidelines for the treatment of severe alcoholic hepatitis (DF $\geq$ 32), recommend the use of glucocorticoids as first-line therapy except in patients with early renal failure or clear contraindication to steroids [O'Shea *et al.* 2009]. Despite these proposed recommendations, the literature now supports the use of PTX, in combination with enteral nutrition, as a reasonable alternative to corticosteroids in patients with severe ASH.

PTX is a nonselective phosphodiesterase inhibitor that increases intracellular concentrations of adenosine 3′,5′-cyclic monophosphate (cAMP) and guanosine 3′,5′-cyclic monophosphate (cGMP). PTX is thought to improve outcomes in alcoholic hepatitis via downregulation of pro-inflammatory cytokines (e.g., TNF-α) that are thought to play a role in the pathogenesis of ASH and are known to be elevated and correlate with disease severity. PTX has also been shown to have antifibrotic effects through the attenuation of both profibrogenic cytokine and procollagen I expression [Raetsch *et al.* 2002]. Finally, based on clinical data demonstrating a mortality benefit via a reduction in the incidence of hepatorenal syndrome (HRS), a beneficial effect on renal microcirculation and hemodynamics (independent of anti-TNF-α action) has also been postulated as a mechanism of benefit [Assimakopoulos *et al.* 2009].

A pilot study examining the benefits of PTX in ASH, published in 1991, demonstrated that PTX could reduce mortality and HRS when compared with placebo [McHutchison *et al.* 1991]. The results were then duplicated in a double-blind placebo-controlled trial, which compared the effect of PTX (400 mg orally three times a day for 4 weeks) *versus* placebo in 101 patients with ASH (DF $\geq$ 32). Patients who received PTX had a decreased 28-day mortality compared to those who received placebo (24.5% *versus* 46%). Importantly, of those patients who died during the study, 50% of those in the PTX arm developed HRS, while 91.7% of patients who died in the placebo arm developed HRS [Akriviadis *et al.* 2000]. Another study examined PTX for patients with ASH who did not respond to corticosteroids (defined by no improvement in bilirubin after 7 days of therapy). That study demonstrated no survival benefit from switching to PTX [Louvet *et al.* 2008]. There have been no trials examining the combination of PTX and corticosteroids in patients who are nonresponsive to corticosteroid treatment (or treatment naïve patients).

In a recent double-blind randomized controlled trial, PTX was compared with prednisolone for the treatment of severe ASH. The study demonstrated an advantage of PTX (group I, $n = 34$) over prednisolone (group II, $n = 34$) in terms of survival and improved risk–benefit profile.

Patient mortality at 3 months was 14.7% in group I compared with 35.3% in group II. No patients in group I developed hepatorenal syndrome, while six patients in group II did. MELD score was decreased at the end of therapy in group I (15.53 ± 3.63) *versus* group II (17.78 ± 4.56). Reduced mortality with PTX was attributed to the prevention of hepatorenal syndrome and lower occurrence of gastrointestinal bleeding in comparison with prednisolone treatment [De *et al.* 2009].

In October of 2009, a meta-analysis of five trials studying the effect of PTX *versus* control, with a total of 336 randomized participants, was published. The statistical analysis of these trials indicated a possible positive intervention effect of PTX on all-cause mortality and mortality due to hepatorenal syndrome, and conversely, an increase in serious and nonserious adverse events. Four of the five trials were judged to have a high risk of bias, thus risking an overestimated intervention effect. For this reason, the authors were unable to make firm conclusions regarding the risk/benefit of PTX in patients with severe ASH [Whitfield *et al.* 2009].

Considering the high mortality associated with severe alcoholic hepatitis, the available literature regarding the benefits of PTX, the limitations on the use of corticosteroids (contraindicated in active infection and gastrointestinal bleeding), and PTX's excellent safety profile, PTX represents a viable alternative to corticosteroids in the treatment of ASH. In our own experience, the inability to deliver PTX via nasogastric/jejunal tubes and the propensity of PTX to cause nausea and vomiting are the main obstacles to its use.

Specific anti-TNF-α therapy

Alcoholic hepatitis was one of the first disease states in which dysregulated inflammatory cytokines were identified [McClain and Cohen, 1989]. Chronic alcohol use has been shown to increase gut permeability and increase endotoxemia (through gut derived lipopolysaccharides) which activates NF-κB to produce TNF-α-mediated pro-inflammatory cytokines [Hill and McClain, 2004; Honchel *et al.* 1992]. In addition, animal studies demonstrated an essential role for TNF-α in alcohol-induced liver injury in mice, as TNF receptor 1 deficient mice do not develop liver injury when exposed to alcohol [Yin *et al.* 1999]. A correlation between TNF-α levels, disease severity and mortality in alcoholic hepatitis has also been described [Felver *et al.* 1990]. However, because studies demonstrated that liver regeneration in the partial hepatectomy model were inhibited by antibodies to TNF, there were concerns regarding the complete inhibition of TNF-α [Akerman *et al.* 1993].

While initial pilot studies in humans were promising, larger clinical trials did not provide the same encouraging results [Tilg *et al.* 2003; Spahr *et al.* 2002]. A large double-blind randomized trial compared prednisolone alone with prednisolone plus high-dose infliximab therapy for the treatment of severe alcoholic hepatitis. This trial was terminated prior to completion because of an increase in severe infectious complications in the prednisolone plus infliximab arm of the study [McClain *et al.* 2004a; Naveau *et al.* 2004].

Given the disappointing outcome of the infliximab trial it was postulated that entanercept might be more appropriate for the treatment of alcoholic hepatitis given its shorter half-life and its role as a receptor antagonist. This was supported by a small pilot study with encouraging results [Menon *et al.* 2004]. A double-blind randomized control trial comparing entanercept with placebo in acute alcoholic hepatitis was undertaken. Concomitant corticosteroid therapy was not given. While 1-month mortality was unchanged between entanercept and placebo groups, 6-month mortality was significantly higher (57.7% *versus* 22.7%, respectively) in the entanercept arm with an associated higher number of serious infectious complications (34.6% *versus* 9.1%) [Boetticher *et al.* 2008].

Finally, an open-label trial was recently conducted comparing single-dose infliximab monotherapy with placebo in severe alcoholic hepatitis. Again, concomitant corticosteroid therapy was avoided. This study showed significant improvement in markers of severity including MELD score, absolute neutrophils count, bilirubin, and TNF-α levels. Five patients (26%) developed infection: three had pneumonia, while two developed a flare of pulmonary tuberculosis. The survival during the study at 1 and 2 months was 89% and 68%, respectively [Sharma *et al.* 2009].

Based on the information at hand, complete neutralization of TNF-α does not appear to be an appropriate course of therapy for alcoholic

hepatitis. Serious infectious complications, such as tuberculosis and disseminated nocardia infection, certainly will warrant intensive screening of patients prior to further study, and thus limit the clinical utility. Instead, medications such as PTX, which partially attenuate TNF-α levels, appear to be more beneficial with lower infectious complication rates. Striking the balance of too much or too little TNF-α and other cytokine activity is the difficult task ahead.

Antioxidants

Oxidative stress is thought to play a key role in the pathogenesis of ALD. Alcohol mediates oxidative stress in a number of ways including lipid peroxidation, the production of reactive oxygen species, and depletion of endogenous antioxidant capabilities [Dey and Cederbaum, 2006; Szuster-Ciesielska *et al.* 2002]. On this basis, it has been theorized that aggressive antioxidant therapy would improve outcomes in ALD. Unfortunately, to date, the results of clinical trials examining the benefit of antioxidant therapy in ALD have been disappointing.

Vitamin E deficiency has been well documented in ALD [Arteel *et al.* 2003]. Vitamin E has experimentally proven hepatoprotective capabilities including membrane stabilization, reduced NFκB activation and TNF production, and inhibition of hepatic stellate cell activation [Arteel *et al.* 2003; Hill *et al.* 1999; Evstigneeva *et al.* 1998; Lee *et al.* 1995]. The first study examining vitamin E supplementation (500 mg) in decompensated ambulatory alcoholic cirrhotics failed to show benefit at 1-year follow up [de la Maza *et al.* 1995]. In a study of patients with mild to moderate alcoholic hepatitis, 1000 IU of vitamin E per day improved serum hyaluronic acid but had no beneficial effects on tests of liver function or mortality when compared with placebo [Mezey *et al.* 2004].

Another antioxidant, polyenylphosphatidylcholine (lecithin), is a lipid extract obtained from soybeans. It has been shown to prevent alcoholic liver cirrhosis in baboons [Lieber *et al.* 1994] and appears to have anti-inflammatory, anti-apoptotic, and antifibrotic effects [Okiyama *et al.* 2009; Cao *et al.* 2002]. Given its hepatoprotective capabilities demonstrated in animal studies, a VA Cooperative Study evaluated the effects of this drug in humans with early ALD [Lieber *et al.* 2003b]. While the study failed to show definitive benefit, the results were likely affected by patients decreasing their alcohol use markedly during the trial. Further study is warranted before recommending lecithin in patients with ALD.

In 2005, prednisolone or methylprednisolone was compared with an antioxidant regimen including: β-carotene, vitamin C, vitamin E, selenium, methionine, allopurinol, desferrioxamine, and N-acetylcysteine. This trial was terminated early following an interim analysis which showed significant survival benefit in the corticosteroid arm of the trial. The odds of death in the antioxidant group were 2.4 times greater than that of the corticosteroid arm [Phillips *et al.* 2006].

The latest attempt at studying antioxidant therapy for ASH compared antioxidant therapy alone to antioxidant therapy plus concurrent steroid therapy [Stewart *et al.* 2007]. The antioxidant cocktail utilized included N-acetylcysteine, vitamin A, vitamin E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid and coenzyme Q. The 6-month survival was not significantly different between patients receiving active drug and placebo (19/36; 52.8% *versus* 19/34; 55.8%, $p = 0.699$). A similar approach was taken in a large multicenter study from France which has been published in abstract form [Nguyen-Khac *et al.* 2009]. Patients were randomized to receive prednisolone plus N-acetyl cysteine. Patients receiving combination therapy had improved survival of 1 and 2 months, but this did not translate into longer-term survival at 3 or 6 months. It is important to note that the N-acetyl cysteine was only given for the first 5 days of the study. Had this been given longer, it is possible that better long-term survival may have been achieved. While antioxidant therapy is currently not recommended in the treatment of ALD, trials further examining the role of antioxidant therapy are warranted.

Selected complementary and alternative medicine

Silymarin

Silybum marianum (milk thistle) is one of the most popular forms of complementary and alternative medicine (CAM) therapy for patients with liver disease. In animal models, hepatoprotective effects of CAM in several forms of liver injury (toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis) have been shown. Mechanisms including

anti-inflammatory, anti-oxidative, antifibrotic, and immunomodulating effects are thought to explain the benefit of silymarin in liver disease [Lieber *et al.* 2003a]. Despite indications that silymarin may be beneficial in ALD, clinical data have, to date, been disappointing. One human randomized double-blind control evaluating placebo *versus* silymarin in alcohol- and non-alcohol-induced cirrhosis showed a 39% *versus* 58% 4-year survival, respectively [Ferenci *et al.* 1989]. However, similar trials have failed to show outcome benefit in ALD [Lucena *et al.* 2002; Pares *et al.* 1998]. In addition, Cochrane Database reviews have consistently failed to show a benefit for silymarin in ALD, but the available trials are fraught with methodological errors [Rambaldi and Gluud, 2006]. Ongoing NIH studies will likely provide the appropriate data concerning efficacy.

S-adenosylmethionine

Elevated methionine and decreased methionine clearance represent a possible therapeutic target for ALD. In human studies of alcoholic hepatitis and cirrhosis, abnormal hepatic gene expression in methionine and glutathione metabolism occurs and often contributes to decreased hepatic S-adenosylmethionine (SAM), cysteine, and glutathione levels [Lee *et al.* 2004]. Rodent and primate studies demonstrate that SAM depletion occurred in early stages of fatty liver infiltration in ALD and decreased SAM concentration, liver injury and mitochondrial damage can be reversed with SAM supplementation [Lieber, 2002]. S-adenosylmethionine appears to attenuate oxidative stress and hepatic stellate cell activation in an ethanol-LPS-induced fibrotic rat model [Karaa *et al.* 2008]. Most importantly, a randomized, double-blind trial was performed in 123 patients with alcoholic cirrhosis treated using SAM (1200 mg/day, orally) or placebo for 2 years. When Child C cirrhotics were excluded from the analysis, the overall mortality/liver transplantation was significantly greater in the placebo group than in the SAM group (29% *versus* 12%), and differences between the 2-year survival curves of the two groups (defined as the time to death or liver transplantation) were also statistically significant. A subsequent Cochrane review of SAM and ALD could not find evidence supporting or refuting the use of SAM for patients with ALD [Rambaldi *et al.* 2007]. The need for long-term, high-quality randomized trials is clear.

Betaine

Betaine (trimethylglycine) is a key nutrient for humans and is obtained from a variety of foods and nutritional supplements [Purohit *et al.* 2007]. In the liver, betaine can transfer one methyl group to homocysteine to form methionine. This process removes toxic metabolites (homocysteine and S-adenosylhomocysteine), restores SAM levels, reverses steatosis, prevents apoptosis and reduces both damaged protein accumulation and oxidative stress [Kharbanda, 2009; Purohit *et al.* 2007]. Betaine also appears to attenuate alcoholic steatosis by restoring phosphatidylcholine generation via the phosphatidylethanolamine methyltransferase pathway [Kharbanda *et al.* 2007]. Studies suggest that betaine offers hepatic protection against ethanol-induced oxidative stress by decreasing sulfur-containing amino acid breakdown as well [Kim *et al.* 2008]. A multitude of animal studies have demonstrated much promise and we await clinical trials in human subjects.

Liver transplantation

Orthotopic liver transplant (OLT) remains the only definitive treatment for hepatic failure associated with ALD. Despite clinical research detailing clear benefit from OLT, the issue of transplantation in alcoholics remains controversial. Understandably, there are concerns regarding the risk of recidivism and its effect on outcome and public opinion, poor compliance with postoperative care, and use of transplantation in patients with what is perceived as a self-inflicted disease [Tan *et al.* 2009]. In addition, there is a perception that these patients are more likely to have contraindications to transplantation, and this ultimately leads to a reluctance at many centers to offer OLT to patients with ALD [Tome *et al.* 2002].

Liver transplantation for ASH

While most transplant centers will not consider severe ASH as an indication for OLT, retrospective data, anecdotal reports and, more recently, a study presented in abstract form, detail survival benefit from OLT in select patients [Castel *et al.* 2009; Tome *et al.* 2002]. A small study of nine patients with retrospectively diagnosed severe alcoholic hepatitis had long-term survival rates comparable to those of patients receiving transplants with alcoholic cirrhosis alone and those with a milder degree of alcoholic hepatitis and cirrhosis [Shakil *et al.* 1997]. Moreover, histological

alcoholic hepatitis in the explanted livers of patients transplanted for apparently chronic stable ALD is not associated with a worse prognosis or an increased risk of recidivism [Tome *et al.* 2002]. While most transplant centers apply 6-month abstinence requirements for patients with ALD, one study of Child-Pugh C alcoholic cirrhotics suggested that patients who fail to respond to abstinence and medical therapy within 3 months are not likely to live long enough to meet these requirements [Veldt *et al.* 2002].

The reluctance to list patients for OLT in the setting of acute alcoholic hepatitis arises from concern that patients will return to drinking and concern about inappropriately transplanting a patient who may recover with medical therapy [Lucey, 2002]. Previous studies have indicated that patients transplanted for ALD, despite recidivism, rarely experience allograft injury as a result [Lucey, 2002; Neuberger *et al.* 2002]. Furthermore, the current practice of requiring 6 months of abstinence has failed to adequately predict relapse with alcohol [Neuberger *et al.* 2002]. Finally, recent data revealing the importance of failure to respond to corticosteroids and survival in patients with ASH have identified the group of patients most likely to benefit from OLT. While more data are required, the benefit of OLT in patients with severe ASH who fail to respond to corticosteroids is a promising area of research.

Liver transplantation for alcoholic cirrhosis

Alcoholic cirrhosis is a leading indication for OLT in North America. Multiple studies consistently indicate improved survival in severe ALD, and similar outcomes in patients receiving liver transplantation for ALD and other etiologies [Day, 2007; Arteel *et al.* 2003]. A recent case–control study comparing long-term outcomes of OLT in patients with ALD *versus* hepatitis C virus (HCV) infection confirmed 9-year survival rates in patients with ALD is comparable to HCV [Biselli *et al.* 2010]. Another recent comparison of ALD and HCV as indications for OLT, evaluated the effects of ALD and HCV infection on waiting list mortality, posttransplant mortality, and the survival benefit (i.e., liver transplant survival benefit). The study revealed that the presence of ALD does not influence liver transplant survival benefit [Lucey *et al.* 2009b]. Patients grafted for ALD do appear to have a higher incidence of some malignancies following liver transplantation (e.g., upper airway and upper gastrointestinal track) [Neuberger *et al.* 2002]. Finally, quality of life appears to improve in patients who undergo OLT for ALD and this rate of improvement is similar to that associated with other forms of liver disease [Arteel *et al.* 2003; Levy *et al.* 1995].

Regarding the severity of liver disease and transplantation, a recent randomized trial compared immediate listing for liver transplantation *versus* standard care for Child-Pugh stage B alcoholic cirrhosis. The study revealed immediate listing for liver transplantation did not show a survival benefit compared with standard care for Child-Pugh stage B alcoholic cirrhosis. Furthermore, there was an increased the risk for extrahepatic cancer in patients in the immediate listing arm [Vanlemmens *et al.* 2009]. Importantly, other studies have likewise indicated that patients with more severe disease are more likely to benefit from OLT [Neuberger *et al.* 2002; Poynard *et al.* 1999].

Among the major concerns regarding liver transplantation for ALD, a return to drinking after transplant is perhaps the most vexing. Extensive attempts at identifying potential pretransplant predictors of recidivism have revealed conflicting results. In addition, studies examining the likelihood of posttransplant drinking on survival and graft failure are equally inconsistent. The current practice in most transplant centers is to require a 6-month period of abstinence prior to listing for OLT. The 6-month period is not based on prospectively gathered data but rather on custom and practice [Neuberger *et al.* 2002]. As to pretransplant predictors of recidivism, several factors have been studied including: mental illness, the lack of a stable partner, grams per day consumed in the years before assessment for transplant, reliance on 'family or friends' for posttransplant support, tobacco consumption at time of assessment, lack of insight into the alcohol etiology, duration of pretransplant abstinence, number of prior alcoholism inpatient treatment experiences, a family history of alcoholism and others. Results from the multitude of studies have failed to show consistent conclusions [Carbonneau *et al.* 2010; Tandon *et al.* 2009; Gedaly *et al.* 2008; De Gottardi *et al.* 2007; Kelly *et al.* 2006; Jauhar *et al.* 2004; Miguet *et al.* 2004].

While some patients will inevitably return to some level of alcohol use, there is conflicting evidence that this has a significant influence on either patient or graft survival. One important distinction appears to be in differentiating abusive from nonabusive drinking when examining outcomes. For example, in a recent retrospective analysis studying survival and alcohol use in 300 patients transplanted for ALD, survival rates of patients who resumed abusive drinking were significantly lower than survival rates of abstinent patients or patients with minor lapses [Pfitzmann *et al.* 2007]. In contrast, in the aforementioned study comparing long-term outcomes of OLT in patients with ALD *versus* HCV infection, the alcoholic recidivism rate was 28% without influence on patients or graft survival [Biselli *et al.* 2010]. The study did not differentiate patterns of recidivism (abusive *versus* nonabusive drinking).

Conclusion

ALD remains a major cause of liver related mortality in the US and worldwide. Clinicians should be well versed on the diagnosis and treatment of the wide spectrum of hepatologic conditions associated with ethanol intake. In conjunction with the 2010 AASLD/ACG guidelines on the treatment of severe alcoholic hepatitis, PTX should be considered an alternative to corticosteroids and appears to especially effective in ALD patients with renal dysfunction/hepatorenal syndrome. Biologics, such as specific anti-TNFs, have been disappointing and should probably not be used outside the clinical trial setting. Future areas of research include the safety, efficacy, and ethical considerations of liver transplant in severe ASH for patients who are not responding to medical therapy, the role of insulin resistance/metabolic syndrome in ALD, and a larger emphasis on altering the course of ALD in the outpatient setting.

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Conflict of interest statement

None declared.

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