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REVIEW

Management of alcoholic hepatitis: Current concepts

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Abstract

Alcoholic hepatitis is a devastating form of acute liver injury seen in chronic alcohol abusers with significant morbidity and mortality. It is a multisystem disease that is precipitated by ingesting large quantities of alcohol with genetic and environmental factors playing a role. Prognostic criteria have been developed to predict disease severity and these criteria can serve as indicators to initiate medical therapy. Primary therapy remains abstinence and supportive care, as continued alcohol abuse is the most important risk factor for disease progression. The cornerstone of supportive care remains aggressive nutritional support, and although acute alcoholic hepatitis has been extensively studied, few specific medical therapies have been successful. Corticosteroids remain the most effective medical therapy available in improving short term survival in a select group of patients with alcoholic hepatitis; however, the long-term outcome of drug therapies is still not entirely clear and further clinical investigation is necessary. While liver transplantation for acute alcoholic hepatitis have demonstrated promising results, this practice remains controversial and has not been advocated universally, with most transplant centers requiring a prolonged period of abstinence before considering transplantation. Extracorporeal liver support devices, although still experimental, have been developed as a form of liver support to give additional time for liver regeneration. These have the potential for a significant therapeutic option in the future for this unfortunately dreadful disease.

Key words: Alcholic hepatitis; Acute liver injury; Abstinence; Nutrition; Corticosteroids; Transplantation; Extracorporeal liver support

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INTRODUCTION

Alcoholic hepatitis is a multi-system disease seen in patients who have abused large quantities of alcohol over an extended period of time, often years. The development of alcoholic hepatitis is complex and dependent on a variety of genetic and environmental factors. In general, men who ingest more than 100 g of ethanol daily for more than 5 years are at highest risk of developing alcoholic hepatitis; however, women may develop alcoholic hepatitis after ingesting smaller amounts of ethanol for shorter periods of time. Alcoholic hepatitis can adversely affect multiple organ systems: the gastrointestinal system, central nervous system, hematologic system, cardiovascular system, and renal system. Symptoms

are non-specific and may include fatigue, right upper quadrant abdominal pain, anorexia, weight loss, jaundice, and fever. There is usually a history of recent binge drinking. Clinical signs may include tender hepatomegaly often with a systolic hepatic bruit, jaundice, fever, ascites, and encephalopathy in more severe cases. Physical stigmata of underlying chronic liver disease may be present including spider angiomata, splenomegaly, palmar erythema, gynecomastia, parotid gland enlargement, testicular atrophy, and Dupuytren's contractures. Laboratory tests classically show modest elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (typically not greater than 300 mg/dL), with AST greater than ALT, bilirubin levels as high as 30 mg/dL, marked coagulopathy, leukocytosis, anemia, and renal failure in the most severe cases. Diagnosis can be made on clinical and biochemical grounds and liver biopsy is not routinely needed to confirm the diagnosis. Based on the American Association for the Study of Liver Disease (AASLD) guidelines set forth in 2010 for alcoholic liver disease, it is recommended that for patients with a clinical diagnosis of severe alcoholic hepatitis for whom medical treatment is contemplated, or for those in whom reasonable uncertainty exists regarding the underlying diagnosis, a liver biopsy should be considered[1].

Patients with severe alcoholic hepatitis frequently deteriorate within a few days to weeks in the hospital with progressive hepatic and renal failure despite supportive measures. Severe alcoholic hepatitis is associated with a high short-term mortality rate, approaching that of fulminant hepatic failure without orthotopic liver transplantation. Indeed, nearly one-half of patients with severe alcoholic hepatitis die within one month of hospitalization. In an effort to determine prognostic criteria for these gravely ill patients with acute alcoholic hepatitis, Maddrey *et al*[2] found significant independent associations with prothrombin time prolongation, peak serum bilirubin and mortality. Using these parameters, the discriminant function (DF) was devised as a disease specific prognostic scoring system [DF = 4.6 × prothrombin time (seconds prolonged more than control) + serum total bilirubin (mg/dL)]. Patients with the most severe disease, as defined by a DF greater than 32 have the highest risk of dying, with a one month mortality of 30%-50%[3]. Furthermore, spontaneous hepatic encephalopathy or the model for end-stage liver disease score greater than 18 in patients with acute alcoholic hepatitis carries a similar poor prognosis and has been used along with the DF to predict disease severity. Moreover, in patients who survive the initial hospitalization, alcoholic hepatitis is a well-known precursor of alcoholic cirrhosis, especially in patients who continue to drink.

TREATMENT

Abstinence

The primary and most effective intervention for alcoholic hepatitis is complete abstinence from alcohol consumption. Abstinence is the single most important factor in the prevention of disease progression and can improve survival. However, survival decreases with concurrent portal hypertension and cirrhosis. Furthermore, abstinence is crucial for those patients with advanced liver disease who may eventually require orthotopic liver transplantation. Several medications have been investigated in hopes of maintaining alcohol abstinence. Disulfiram was one of the first United States Food and Drug Administration approved agents; however, its use has largely been abandoned due to poor tolerability and lack of supporting data[4]. Alternatively, short term treatment with the opiod antagonist naltrexone has been shown to reduce the risk of alcohol relapse[5]. Similarly, acamprosate, an inhibitory neurotransmitter similar to gamma-aminobutyric acid, has been shown to decrease the rate of alcohol relapse and maintain abstinence[6]. Nonetheless, some patients with alcoholic hepatitis will progress despite abstinence and supportive medical care. Thus, several potential therapies have been studied in an attempt to achieve a more favorable disease course.

Supportive care

In addition to abstinence, the most vital therapy for a patient with acute alcoholic hepatitis is supportive care. This includes intensive care unit monitoring and intubation for airway protection when appropriate, especially in the setting of advanced hepatic encephalopathy. Alcohol withdrawal must be treated with benzodiazepines as needed. Intravenous fluids should be administered with electrolyte, mineral and vitamin supplementation, including replacement of phosphate, potassium, magnesium, multivitamins, thiamine and folate. A single dose of vitamin K may be given, but will not correct the coagulopathy if due to underlying hepatic synthetic dysfunction. Administration of fresh frozen plasma should be reserved only for active hemorrhage.

Hepatotoxic medications should be avoided, as should nephrotoxic medications, including aminoglycosides, angiotensin converting enzyme inhibitors and non-steroidal anti-inflammatory medications. Sepsis is a common cause of mortality in these gravely ill patients; however, it is often difficult to determine the presence of concomitant infection, as fever and leukocytosis are often encountered in acute alcoholic hepatitis, even in the absence of infection. Accordingly, a vigilant search for infection with appropriate cultures, including diagnostic paracentesis is crucial.

Nutrition

Patients with severe protein-calorie malnutrition have been found to have a significantly higher mortality compared to those who are only mildly malnourished[7]. In fact, hepatic dysfunction in alcoholics was initially thought to be due to nutritional deficiencies. Thus, supplemental nutrition with high-calorie, high-protein diets administered either enterally or parenterally to these malnourished patients was advocated at the outset in hopes to improve outcomes. However, subsequent clinical tri-

als of supplemental nutrition administered to patients with acute alcoholic hepatitis have not been shown to improve mortality in this disease. Despite these findings, high-calorie, high-protein formulations have been shown to improve nutritional parameters during the acute illness and high catabolic state[8-10]. Therefore, it may be worthwhile to utilize supplemental enteral nutrition during the acute phase of illness, especially in anorexic patients who do not meet their calculated daily requirements[11]. Newer and more expensive branched-chain amino acid formulations have been proposed to have a lower incidence of hepatic encephalopathy. However, even standard amino acid preparations have not been shown to cause hepatic encephalopathy in cirrhotic patients with portal hypertension[9,12]. Thus, branched-chain amino acid formulations do not likely offer an efficacy advantage and given the large discrepancy in price, are not cost-effective. It is also important to replace deficiencies in certain vitamins and minerals, including vitamins A, D, pyridoxine, thiamine, folate and zinc.

Corticosteroids

In view of the dismal prognosis associated with alcoholic hepatitis, many drugs have been investigated as potential mediators to alter the clinical course of this disease. Due to their well-known anti-inflammatory effects, corticosteroids have been the most extensively studied medication in patients with alcoholic hepatitis, many randomized controlled trials have produced inconsistent results[2,13-23]. Thus, in 1990, Imperiale *et al*[24] reviewed 11 of the earlier trials conducted between 1971 and 1989 in hopes of reaching a consensus statement on the efficacy of corticosteroids for the treatment of alcoholic hepatitis[2,13-22]. In this landmark meta-analysis, steroids were determined to be most beneficial in a subset of patients with severe acute alcoholic hepatitis and spontaneous hepatic encephalopathy, reducing the risk of short-term mortality to 0.66 for a protective efficacy of 34%. In contrast, Christensen *et al*[25] determined that glucocorticoids had no statistically significant beneficial or harmful effect. This meta-analysis found a high probability of publication bias in this area and cautioned against the routine use of glucocorticoids in patients with acute alcoholic hepatitis. The most recent meta-analysis on this subject confirmed that while corticosteroids were not beneficial for all patients with alcoholic hepatitis, there was a survival benefit in patients with severe disease, defined as the presence of spontaneous hepatic encephalopathy and/or DF $\geqslant$ 32[26]. In a reanalysis of individual data from the last three randomized placebo controlled trials of corticosteroids, Mathurin *et al*[27] found a significant increase in one month survival for patients with severe alcoholic hepatitis (DF $\geqslant$ 32) treated with steroids (85% *vs* 65%). Thus, five patients needed to be treated to prevent one death. In an attempt to predict those individuals not responding to corticosteroids, a recently developed model was created using six clinical variables to calculate a Lille score (www.lillemodel.com). After 7-d of corticosteroids, a Lille score > 0.45 indicates a poor response to therapy and a 6-mo mortality of > 75%[28].

In accord with the recommendations by the American College of Gastroenterology and AASLD, corticosteroids use cannot be supported in patients with alcoholic hepatitis with concomitant gastrointestinal hemorrhage, pancreatitis, active infection or renal failure, as these patients were excluded in many of the clinical trials advocating corticosteroid treatment[1,29]. Prednisolone 40 mg per day orally for four weeks followed by a taper or discontinuation is favored over prednisone, which requires hepatic conversion to the active prednisolone.

Of note, corticosteroids have not been shown to improve long-term survival, as follow-up in clinical studies have rarely extended beyond a few months, due to the high initial mortality rate associated with this disease. In a study comparing prednisolone to enteral feedings for 28 d for severe alcoholic hepatitis, there was no significant difference between groups in the treatment phase (25% *vs* 31%, respectively)[30]. However, 37% of the survivors in the steroid group died during the one-year follow-up compared with 8% of the survivors in the enteral feeding group. Most of these deaths were due to infections. Thus, despite the many years of investigation, the long-term benefits of corticosteroids in severe alcoholic hepatitis remain unclear.

Tumor necrosis factor alpha inhibition

Pentoxifylline is an oral phosphodiesterase inhibitor which also decreases tumor necrosis factor alpha production, which is known to be elevated in patients with alcoholic hepatitis. In a randomized controlled trial with 101 patients with severe alcoholic hepatitis defined as a DF $\geqslant$ 32, pentoxifylline was given to 49 patients at a dose of 400 mg three times daily for 4 wk[31]. The remaining 52 patients received placebo. As expected, the control group had a mortality rate of 46%, but the treatment group demonstrated a significant improvement in survival with a mortality rate of 25%. Moreover, the reduction in mortality appeared to correlate with a significantly lower incidence of hepatorenal syndrome in the pentoxifylline group compared to the control group (8% compared with 35%). The findings of this study are encouraging and need to be confirmed with long-term follow-up.

Other clinical trials investigating anti- tumor necrosis factor agents including infliximab and etanercept given in conjunction with corticosteroids for acute alcoholic hepatitis showed no mortality benefit[32,33].

Phosphatidylcholine

In an effort to prevent alcohol-induced hepatocyte mitochondrial dysfunction, supplementation with the phospholipid phosphatidylcholine has been studied. In alcohol-fed baboons, phosphatidylcholine prevented the progression of pericentral and interstitial fibrosis to septal fibrosis and cirrhosis[34]. Currently, a large randomized controlled trial is under way in humans.

S-adenosysl-methionine

S-adenosyl-methionine (SAMe) helps to maintain mitochondrial glutathione stores in alcoholic liver disease. At a dosage of 1200 mg per day for 2 years, SAMe exhibited a decrease in mortality and a delay in transplantation exclusively in Child-Turcotte-Pugh class A and B cirrhotics[35]. It has not been studied in acute alcoholic hepatitis.

Antioxidants

Vitamin E may have a beneficial antioxidant role in alcoholic liver disease, but the outcomes of trials have been disappointing[36,37]. Milk thistle, which contains the antioxidant silymarin may provide a benefit, albeit small, in Child-Turcotte-Pugh class A alcoholic cirrhotics who continue to drink alcohol[38]. Most recently, the antioxidant effect of N-acetylcysteine was used in conjunction with glucocorticoids in patients with severe alcoholic hepatitis and demonstrated an increased 1 mo survival, although 6 mo survival was not improved[39].

Propylthiouracil

Alcohol induces a hypermetabolic state with pericentral hypoxia, similar to that seen in hyperthyroidism. Propylthiouracil has been tried in the hopes of reversing this hypermetabolic response and curtailing hepatocellular damage. In a randomized controlled trial with 67 patients with severe alcoholic hepatitis, propylthiouracil at 300 mg per day for 6 wk had no benefit on morbidity or mortality[40]. Subsequently, in a long-term randomized trial with 310 patients, propylthiouracil demonstrated a significant mortality benefit, especially in patients with the most severe alcoholic hepatitis (55% compared with 25% placebo). However, propylthiouracil only conferred a benefit to those who remained abstinent[41]. Furthermore, concerns regarding propylthiouracil-induced hypothryroidism have diminished the fervor for the use of propylthiouracil in alcoholic hepatitis.

Anabolic steroids

Androgens have been studied in an effort to improve the general nutritional status of patients with alcoholic hepatitis. In a large, multicenter population of United States veterans, oxandrolone at a dose of 80 mg per day for 1 mo did not affect short-term survival, but did increase survival at 6 mo in a subgroup of patients with moderate, but not severe alcoholic hepatitis[21]. Unfortunately, these results have been confirmed in subsequent studies. Hence, the use of oxandrolone for acute alcoholic hepatitis cannot be routinely recommended.

Colchicine

Colchicine has been examined in patients with cirrhosis due to its effects on collagen and hepatic fibrogenesis. Moreover, it inhibits leukocyte migration and function and has positive effects on cytokine production related to fibroblast proliferation. Consequently, a randomized controlled trial was conducted in a population of 72 hospitalized patients with severe alcoholic hepatitis[42]. At the standard dose of 1 mg orally per day for 1 mo, colchicine had no beneficial effect on morbidity, mortality or biochemical tests of liver function.

Amlodipine

Calcium channel blockers have been shown to have a hepatoprotective effect in animal models of alcohol-induced liver injury. However, a randomized, double-blind, placebo-controlled trial showed no conclusive evidence that amlodipine benefits patients with acute alcoholic hepatitis[43].

Insulin and glucagon

Insulin and glucagon have been known to enhance hepatic regeneration after partial hepatectomy in experimental animals. An early randomized clinical trial involving 50 patients administered insulin and glucagon infusions for the treatment of acute alcoholic hepatitis showed promise[44]. However, subsequent larger studies have failed to show a clinical benefit, including short-term or long-term survival benefit[45,46]. In fact, significant hypoglycemia became problematic, which limited the utility of this intervention in acute alcoholic hepatitis.

Transplantation

In the setting of acute alcoholic hepatitis, orthotopic liver transplantation is highly controversial. Yet, patients receiving liver transplantation for this disease have generally resulted in good outcomes. In fact, it has been suggested that transplantation even for acute alcoholic hepatitis is successful with comparable outcomes to that of patients transplanted for decompensated alcoholic cirrhosis alone[47,48]. Most recently, Mathurin *et al*[49] demonstrated an improved 6 mo survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy who underwent early liver transplantation compared to those who did not (77% *vs* 23%). Conversely, other investigators demonstrated a poor prognosis after transplantation with rapidly progressive liver injury with active alcoholic liver disease[50]. Combining the high risk of recidivism in patients with acute alcoholic hepatitis along with the national shortage of donor organs, orthotopic liver transplantation has not been advocated for acute alcoholic hepatitis.

Initially, there was hesitation to transplant patients for decompensated alcoholic cirrhosis due to the perception that the disease was self-inflicted and concerns about post-transplantation compliance[51]. Nevertheless, it is now clear that in appropriately selected patients with decompensated alcoholic cirrhosis, orthotopic liver transplantation provides an excellent prognosis, with outcomes similar to other nonalcoholic chronic liver diseases. In these appropriately screened patients, recidivism after transplantation still occurs in one-fifth to one-half of patients, but only 5%-7% return to excessive drinking[52,53]. The most predictive variable of recidivism has been proposed to be a period of abstinence before transplantation[54]. A documented 6 mo of pre-transplantation

abstinence is usually required as a minimal criterion for liver transplantation listing[55]. Other factors including social support and functional level are also extremely important to maintain abstinence. Current endeavors are underway to incorporate multiple variables to better risk stratify patients and standardize selection criteria for orthotopic liver transplantation in this population of patients. It is conceivable similar criteria could be used to determine appropriate liver transplant candidacy in the setting of acute alcoholic hepatitis as well. Notwithstanding, it has been estimated that only 5% of patients with end stage liver disease related to alcohol are formally evaluated to be considered for liver transplantation[56].

Extracorporeal liver support

Although they are still experimental, extracorporeal liver support devices have been developed as a form of liver support to give additional time for liver regeneration. One approach utilizes membranes and adsorbents that can remove toxins associated with liver failure, similar to hemodialysis in patients with end-stage renal disease. This type of extracorporeal liver support with molecular adsorbents recirculating system (MARS) uses a dialysis module in which the patient's blood is dialyzed across an albumin-impregnated membrane, where detoxification can occur. Substances larger than 50 kDa, such as growth factors and essential hormones, are not removed. This device has shown promise in patients with acute liver failure superimposed upon chronic liver disease[57]. Recently, the MARS treatment was performed on 8 patients with severe acute alcoholic hepatitis superimposed on biopsy-proven cirrhosis[58]. These patients received 3 to 12 courses of 6 h of MARS treatment and encouraging results were seen in liver biochemistry, renal function, encephalopathy and mortality. However, the lack of power in this study does not allow definite conclusions. Nonetheless, a multi-center, randomized clinical trial is under way to study the efficacy of MARS treatment in acute alcoholic hepatitis.

CONCLUSION

Alcoholic hepatitis is a severe form of acute liver injury associated with significant morbidity and mortality. Although, prognostic criteria have been developed to help predict disease severity, it remains a challenge to treat. However, the primary intervention remains abstinence, as this is the most important risk factor for disease progression and is required if transplantation is eventually needed. Vigilant supportive care and adequate nutrition is crucial to help overcome this devastating illness. Several medications have been studied in an effort to alter the clinical course of this disease. Corticosteroids have been effective in reducing the short-term mortality in a subset of patients with severe alcoholic hepatitis with hepatic encephalopathy. Pentoxifylline also confers a significant short-term benefit for severe alcoholic hepatitis. Of note, despite more than 30 years of randomized controlled trials, no specific pharmacologic agent has clearly demonstrated a long-term survival benefit. Though outcomes in patients receiving liver transplantation for alcoholic hepatitis are similar to those transplanted for nonalcoholic liver diseases, liver transplantation in this patient population remains highly controversial. Extracorporeal liver support devices are still in their developmental infancy and may be an option in the future.

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