ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Management of Alcoholic Hepatitis

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G&H What could you describe the pathophysiology of alcoholic hepatitis?

TM The pathophysiology of alcoholic hepatitis is not well understood. However, there are several abnormalities that could contribute to liver injury. The first is the production of oxidative stress as a by-product of the metabolism of ethanol. The second is the "leakage" of endotoxin through the intestinal wall and into the portal circulation. Endotoxin binds to receptors on Kupffer cells and activates an inflammatory response. The inflammatory response in the liver leads to hepatocyte dysfunction and death. Among the most important inflammatory cytokines is tumor necrosis factor (TNF)-alfa, elevated levels of which correlate with severity of liver disease. Recent studies have suggested that hepatocyte apoptosis correlates with clinical and histologic severity of alcoholic hepatitis.

From a clinical standpoint, we know that one must drink more than 60–80 g of ethanol per day (equivalent to 5–8 drinks of alcohol [1 drink defined as 12 ounces of beer, 4 ounces of wine, or 1 ounce of spirits]) daily for decades in order to be at risk of developing alcoholic hepatitis or alcoholic cirrhosis. For women, the rate of alcohol intake required may be somewhat lower than in men. However, only approximately 25% of people drinking this amount of alcohol ever develop significant liver disease. It is unclear what differentiates patients who develop liver disease from those who do not develop alcoholic liver disease or cirrhosis. It is also not known why alcoholic hepatitis requires such long periods of exposure to develop or what precise mechanism triggers onset at a particular point in time.

G&H What are the presenting symptoms and attributes of patients with alcoholic hepatitis?

TM The hallmark of alcoholic hepatitis is jaundice (elevation in total and direct bilirubin). Severe alcoholic hepatitis is marked by bilirubin levels over 10–15 mg/dL. Levels of aspartate aminotransferase (AST) are usually between 100 and 200 U/L and are almost always less than 400 U/L. Alanine aminotransferase (ALT) is usually approximately 25–50% the value of AST, somewhere in the range of 50–150 U/L. Other typical findings include fever, leukocytosis (white blood cell >10,000/µL), ascites, and tender hepatomegaly.

In the United States, most clinicians do not perform liver biopsy, or, at least, liver biopsy is not considered a requirement to make a positive diagnosis. One study has suggested that patients with neutrophil counts over 5,500/µL most likely have alcoholic hepatitis and do not require confirming biopsy. In Europe, it is fairly common to perform a transjugular liver biopsy to make the diagnosis of alcoholic hepatitis. Fibrosis is present on liver biopsy in all patients with alcoholic hepatitis. Approximately 50% of patients with alcoholic hepatitis will also have cirrhosis at the time of diagnosis.

In my own practice, I am comfortable in making the diagnosis of alcoholic hepatitis based on a long history of alcohol use, bilirubin elevated above 10 mg/dL, characteristic AST and ALT values, and no evidence of other liver diseases (eg, hepatitis B, drug toxicity, autoimmune liver disease). It should, however, be noted that approximately 20–50% of people who have alcoholic hepatitis also have chronic hepatitis C virus infection. In practice, it is usually not difficult to differentiate severe alcoholic hepatitis from acute hepatitis C.

Maddrey's discriminant function (DF) is the standard test to determine severity of liver injury. DF is calculated as total bilirubin in mg/dL added to 4.6 times the

prothrombin prolongation in seconds (ie, [total bilirubin (mg/dL)] + 4.6 × [prothrombin time – prothrombin control (seconds)]). When the DF is greater than 32, the general consensus is that the patient has severe alcoholic hepatitis and is a candidate for treatment. More recently, clinicians have begun using the model for end-stage liver disease (MELD) score to evaluate for alcoholic hepatitis. A MELD score over 20–21 on admission is somewhat analogous to a DF greater than 32.

G&H Can you describe the typical course of treatment in patients with alcoholic hepatitis?

TM The basic treatment algorithm for these patients is as follows. First, the diagnosis of alcoholic hepatitis must be made based on history, physical examination, and blood tests. Then, the severity of alcoholic hepatitis must be measured using Maddrey's discriminant function or possibly MELD score. In addition, patients should be evaluated for spontaneous hepatic encephalopathy (confusion or asterixis). If patients have a discriminant function greater than 32 or spontaneous hepatic encephalopathy, they are considered to have severe alcoholic hepatitis and are candidates for treatment. If a patient has a discriminant function of less than 32, most hepatologists would not recommend treatment as the patient is likely to spontaneously recover without treatment.

Approximately 10 years ago, the American College of Gastroenterology (ACG) published guidelines on the treatment of alcoholic hepatitis, which recommended the administration of oral prednisolone 40 mg daily for 1 month in patients with a discriminant function greater than 32 or with spontaneous hepatic encephalopathy. Those guidelines were based on multiple randomized clinical trials and meta-analysis of those trials, and have not been changed by the ACG. Contraindications to prednisolone treatment include the presence of infection.

In 2000, an article was published showing that pentoxifylline, at a dose of 400 mg three times daily for 1 month, improved survival when compared with placebo treatment. As a result, a considerable number of clinicians are now using pentoxifylline as primary treatment in patients with severe alcoholic hepatitis. In particular, pentoxifylline is a reasonable alternative for patients with a contraindication to corticosteroids (eg, patients with chronic hepatitis B or other active infections). The anti–TNF-alfa agent infliximab has also been tested but has been associated with increased infections and increased mortality. Future research with infliximab or other anti-TNF agents may provide data supporting their use in the treatment of alcoholic hepatitis, but for now they should not be considered except in research situations.

All patients with severe alcoholic hepatitis are malnourished, and provision of adequate nutrition is essential. Nutritional supplementation has been utilized as a primary treatment for alcoholic hepatitis and in some studies has been found to impart equal if not better survival when compared with corticosteroid treatment. At present, nutritional support alone is not considered by most hepatologists as first-line treatment. However, many of these patients are anorexic and do not want to eat. In these cases, a nasogastric feeding tube may be required to ensure proper nourishment. Historically, there has been a concern regarding hepatic encephalopathy associated with dietary protein. However, most hepatologists who currently deal with this condition feel it is more important that patients be fed properly and monitored for signs of encephalopathy.

Abstinence from alcohol is a requirement for long-term survival. These patients should be referred to an alcohol treatment clinic or program for alcohol cessation. All of these patients have serious alcohol problems, and although most gastroenterologists are not trained to treat alcoholism, referral is certainly part of long-term care.

G&H Will cessation of drinking alone reverse the course and effects of alcoholic hepatitis?

TM Long-term outcomes from alcoholic hepatitis vary considerably. With severe alcoholic hepatitis, the mortality rate at 6 months, even with corticosteroid treatment, is approximately 40%. Although many patients continue to have ascites and evidence of significant liver disease (low albumin, prolonged prothrombin time), some patients show a dramatic improvement. At 2 years, some patients appear normal, with no ascites and essentially normal blood work. However, liver biopsy may still show cirrhosis. Such patients can function well and often live for many years. However, if these patients continue to drink, their liver disease will progress and they will come back to the hospital with cirrhosis or ascites. Finally, an uncommon, but recognized, problem in long-term survivors with cirrhosis is the development of hepatocellular carcinoma. Thus, these patients should be monitored regularly by ultrasound for masses in the liver.

G&H What are the concerns surrounding candidacy for liver transplant among patients with severe alcoholic hepatitis?

TM Concerns regarding liver transplantation in the setting of alcoholic hepatitis are twofold. First, patients are severely ill and their prognosis immediately following transplant, although not completely known, is considered to be poor. Because the prognosis of liver transplant in

acute alcoholic hepatitis is not clear, a group of researchers in France are starting a small clinical trial to prospectively evaluate early transplant of selected alcoholic hepatitis patients. However, as currently practiced in the United States, transplantation is rarely used as a treatment for acute alcoholic hepatitis.

Secondly, in regard to the long-term outcomes of transplanted patients, there is concern about a return to alcohol abuse. Data regarding recidivism in transplanted patients shows a return to heavy alcohol use in approximately 10–15%. Therefore, most transplant centers enforce a policy where alcoholic patients need to be abstinent for at least 6 months prior to consideration for candidacy. This holds true for substance abuse in transplant patients with viral hepatitis as well.

G&H Is there any new research in this area that may change the way alcoholic hepatitis patients are treated?

TM Dr. Mathurin and his colleagues from Lille, France, have recently analyzed data from more than 500 alcoholic hepatitis patients they have treated with corticosteroids during the past 15 years. Their data, which has been accepted for publication in *Hepatology*, shows that measurement of 5 variables at the time of diagnosis (age, albumin, creatinine, bilirubin, prothrombin time) and 1 variable measured after 1 week of corticosteroid treatment (change in bilirubin level) is better than DF, MELD, or change in bilirubin level alone in predicting which patients will respond to corticosteroids and which patients are unlikely to respond. I believe this model, called the Lille Model, will change the way corticosteroid treatment is used in alcoholic hepatitis. According to these investigators, up to 40% of patients with alcoholic hepatitis are resistant to corticosteroid treatment. An area for future research is the development of effective treatment for these patients.

Suggested Reading

McCullough AJ, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. *Am J Gastroenterol*. 1998; 93:2022-2036.

Mathurin P. Is alcoholic hepatitis an indication for transplantation? Current management and outcomes. *Liver Transpl*. 2005;11(11 Suppl 2):S21-S24.

Kulkarni K, Tran T, Medrano M, et al. The role of the discriminant factor in the assessment and treatment of alcoholic hepatitis. *J Clin Gastroenterol*. 2004;38: 453-459.

Rongey C, Kaplowitz N. Current concepts and controversies in the treatment of alcoholic hepatitis. *World J Gastroenterol*. 2006;12:6909-6921.

Morgan TR, McClain CJ. Pentoxifylline and alcoholic hepatitis. *Gastroenterology*. 2000;119:1787-1791.

Louvet A, Naveau S, Abdelnour M, et al. The Lille Model: a new tool for the therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology*. 2007. In press.