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LIVER UPDATE

VOL. 6, NO. 4 / FALL 2005

A PUBLICATION OF THE CENTER FOR LIVER DISEASES AND THE INOVA TRANSPLANT CENTER

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Acute Liver Failure in the United States: The U.S. ALF Study

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Acute liver failure (ALF) is a rare condition in which rapid deterioration of liver function results in altered mentation and coagulopathy in previously normal individuals. United States estimates are placed at approximately 2,000 cases per year.[1] Acute liver failure often affects young persons and carries a high morbidity and mortality. Prior to transplantation, most series suggested less than 15 percent survival. Currently, overall short-term survival with transplantation is greater than 65 percent.[2]

DEFINITION: The most widely accepted definition of acute liver failure includes evidence of coagulation abnormality, usually an INR ≥ 1.5, and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks duration. Patients with Wilson disease or autoimmune hepatitis may be included in spite of the possibility of cirrhosis if their disease has only been recognized for less then 26 weeks. A number of other terms have been used, including fulminant hepatic failure and fulminant hepatitis or necrosis. Acute liver failure is a better overall term that should encompass all durations up to 26 weeks. Terms used signifying length of illness such as hyperacute (< 7 days), acute (7-21 days) and subacute (> 21 days and <26 weeks) are not particularly helpful since they do not have prognostic significance distinct from the cause of the illness. For example, hyperacute cases may have a better prognosis but this is because most are due to acetaminophen toxicity.[5]

ETIOLOGIES: The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion; many cases (~20%) have no discernible cause.[2] The most common cause in the U.S. currently is acetaminophen poisoning which accounts for around 50 percent of all cases each year. The percentage of cases annually has increased over the last several years from 28 to 53 percent this past year. The reasons for so many cases

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Non-Alcoholic Fatty Liver Disease: Hepatic Manifestation of Metabolic Syndrome

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Nonalcoholic fatty liver disease (NAFLD) represents a spectrum from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. NAFLD is increasingly being recognized as the hepatic manifestation of the metabolic syndrome (MS). In the United States, the prevalence of NAFLD has been estimated to be between 3-23 percent. In other parts of the world, prevalence of NAFLD ranges from 9-37 percent. On the other hand, in obese patients undergoing bariatric surgery, the prevalence of NAFLD ranges from 72-93 percent and that of NASH from 12-25 percent. Furthermore, the prevalence of NASH from the autopsy and liver biopsy series has been estimated between 1.2- 6.3 percent.

The natural history of NAFLD is still not entirely clear. In a large cohort of patients with NAFLD, those with NASH were more likely to die of liver-related causes as compared to those with other types of NAFLD. In cohorts of NAFLD patients with paired liver biopsies, about a third of patients showed progression of fibrosis over a follow-up of two to five years. In the same period of time, 9 percent progressed to cirrhosis. Additionally, a number of studies have reported an association between cryptogenic cirrhosis and NAFLD. In one study,

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patients with cryptogenic cirrhosis resembled NASH patients in that they were more likely to be female, obese, or have diabetes. Another line of evidence providing similar support comes from post-transplant follow-up of patients receiving hepatic allografts for cryptogenic cirrhosis. Several studies have demonstrated that recurrence of NAFLD occurs in the hepatic allografts of these patients. All these studies suggest that some patients with biopsy proven NASH can progress to cirrhosis.

Over the past decade, the pathogenesis of NAFLD has been the subject of intense research. Central to the pathogenesis of NAFLD is insulin resistance. Insulin resistance is almost universally demonstrated in patients with NAFLD. Because insulin resistance can be demonstrated in patients with simple steatosis as well as those with NASH, other events are most likely responsible for progression to steatohepatitis to cirrhosis. The above findings have given rise to the "multi-hit" hypothesis. The first "hit" is fat accumulation in the hepatocyte. This is believed to be due to insulin resistance via increased lipolysis and increased delivery of free fatty acids to the liver. Other abnormalities that contribute to fat accumulation include decreased synthesis of apolipoproteins and microsomal transfer protein gene polymorphism, both leading to decreased export of triglycerides out of the liver. Presence of hepatic steatosis is thought to then set the stage for the development of inflammation and liver cell injury that is characteristic of NASH.

There are several factors or second "hits" that have been proposed, including oxidative stress from reactive oxygen species produced in mitochondria and by cytochrome P-450 enzymes. Insulin resistance and obesity, especially central obesity, can also contribute to the hepatocyte injury in NASH via free fatty acids, the levels of which are increased in NASH. Increased levels of free fatty acids can lead to increased ROS production through increased mitochondrial and peroxisomal FFA oxidation. Cytokines, in particular TNF· as well as adipokines (adiponectin, leptin and resistin), have been implicated as potential second "hits". Despite this interesting data, the exact contribution of each pathway to be pathogenesis of NASH remains to be determined.

In managing patients with NAFLD, it is important to establish the diagnosis and to understand the limitations of the currently available data. Diagnosis of NAFLD should be considered in any patient who has abnormal liver enzymes, hepatomegaly, or "bright" liver on ultrasound. It is important to exclude other causes of chronic liver disease especially alcoholic liver disease and HCV infection, both of which can lead to hepatic steatosis. It is also important to remember that liver enzymes are not always a sensitive marker for NAFLD as some patients with NAFLD and normal liver enzymes can have significant liver disease. While most hepatic imaging modalities can detect steatosis, they are unable to distinguish between simple steatosis, NASH or fibrosis.

The role of liver biopsy in NAFLD in routine clinical practice has not been fully established. A liver biopsy can confirm the diagnosis and exclude other causes of liver disease. Additionally, a liver biopsy is currently the only technique to differentiate between simple steatosis and NASH, a distinction that has prognostic significance. However, a liver biopsy does carry a small risk of morbidity and mortality and is expensive.

A number of serum markers of fibrosis are being developed to replace liver biopsy. However, their use in patients with NAFLD has not been established. A reasonable approach to a patient suspected of NAFLD in clinical practice is consider a liver biopsy in patients who evidence of metabolic syndrome and in those who have persistently elevated liver enzymes despite optimal management of the associated metabolic conditions such as obesity, diabetes, or hyperlipidemia. Regimens used for treatment of patients with NAFLD are summarized in the table below.

In summary, NAFLD is a common cause of chronic liver disease. Most patients with NAFLD have conditions associated with the metabolic syndrome (i.e., obesity, diabetes, and hyperlipidemia) and NAFLD is now considered the hepatic manifestation of the metabolic syndrome. Although a large number of agents have been used for treatment of NAFLD, there are currently no proven effective treatments. Nevertheless, interventions improving insulin resistance are promising and prospective studies are currently underway.

Treatment Intervention	Studies (N)	Patients(N)	Outcomes
Interventions Targeting Components of the Metabolic Syndrome:			
Medical Weight Loss	5	3-39	Enzymes
Surgical Weight Loss	4	15-104	Enzymes, Histology
Lipid Lowering Agents	7	3-46	Enzymes
Thiazolidinediones	4	10-30	Enzymes, Histology
Metformin	2	7-20	Enzymes
Interventions Targeting Oxidative Stress and Cytoprotection:			
Vitamin E	4	11-49	Enzymes, Histology
Other Antioxidants	4	1-169	Enzymes
Ursodeoxycholic Acid (UDCA)	5	1-166	Enzymes*

** A recent RCT of UDCA 13-15 mg/kg/d for 48 weeks showed similar efficacy to placebo.*

▶ *ALF STUDY, from page 1*

occurring remain unclear. In a series of 275 patients with ALF due to acetaminophen liver injury,[3] unintentional overdoses accounted for 131 (48 percent) cases, intentional (suicide attempts) 122 (44 percent), and 22 (8 percent) were of unknown intent. In the unintentional group, 38 percent took two or more acetaminophen preparations simultaneously and 63 percent used narcotic-containing compounds. Overall, 178 subjects (65 percent) survived, 74 (27 percent) died without surgery and 23 subjects (8 percent) underwent liver transplantation; 71 percent were alive at three weeks. Susceptible acetaminophen patients have concomitant depression, chronic pain, alcohol or narcotic use and/or take several preparations simultaneously. Further education of patients, physicians and pharmacies might help to limit these unfortunate cases.[4]

THERAPY: All patients with clinical or laboratory evidence of moderate to severe acute hepatitis should have immediate measurement of prothrombin time and careful evaluation for subtle alterations in mentation. If the prothrombin time is prolonged by ~4-6 seconds or more (INR ≥ 1.5) and there is any evidence of altered sensorium, the diagnosis of ALF is established and hospital admission is mandatory. Since the condition may progress rapidly, with changes in consciousness occurring hour-by-hour, early transfer to the intensive care unit is preferred once the diagnosis of acute liver failure is made. Antidotes are given if acetaminophen poisoning is suspected and for mushroom poisoning. Pregnancy-related liver disease is managed with delivery of the fetus. If transplantation is an option, then any patient with encephalopathy should be considered for transfer to a transplant center. Those in a transplant center are usually listed for transplantation when coma grade 2 is reached. Patients often deteriorate rapidly.

OUTCOMES: Even in the modern era of transplantation, nearly one-third of patients succumb to ALF. The cause of death is frequently infection, renal failure or cerebral edema, a unique pathophysiology associated solely with ALF. Because of its rarity, ALF has been difficult to study in depth and very few controlled therapy trials have been performed. As a result, standards of intensive care for this condition have not been established.[5] There are no accepted treatments for the overall condition. Centers vary as to whether lactulose, prophylactic antibiotics or intracranial pressure monitors are used. Success in predicting outcomes has been limited. Etiology is one of the best guides, with those with acetaminophen, hepatitis A or shock having good outcomes (~65% survival without transplantation) and those with idiosyncratic drug reactions, hepatitis B or indeterminate cause have poor outcomes (~20% spontaneous survival).

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Faculty Presentations at International Meetings

- Gene Expression of Adipokines in the Adipose Tissue of Obese Patients with Insulin Resistance and NAFLD: 7th International Conference on Cytokines and Chemokines. World Congress of Gastroenterology, Montreal, CA. 2005
- Natural History of Non-alcoholic Steatohepatitis. American College of Gastroenterology. Honolulu, HI. 2005

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- J Ong, R Collantes, A Pitts, L Martin, M Sheridan, Z Younossi. High Rates of Uninsured Among Hepatitis C Positive Patients. Clin Gastroenterol 39(9):826-830, 2005
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Clinical Trials

- Clinical research protocols for patients with Non-Alcoholic Fatty Liver Disease and obesity including a combination regimen for NASH patients after bariatric surgery
- Clinical research protocols for treatment of Hepatitis C including combination of new regimens using novel oral protease inhibitors
- Clinical research protocols for treatment of Hepatitis B including the use of novel oral nucleotide analogues