ELSEVIER

Acute Liver Failure and Liver Assist Devices

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ABSTRACT

Survival of patients presenting with acute liver failure (ALF) has improved over the past decades due to earlier disease recognition, advances in supportive measures, intensive care, and liver transplantation. Liver assist devices may have a role in future care of patients with ALF, bridging them to recovery or to transplantation. A multidisciplinary team approach to the care of patients with ALF is critical for achieving good patient outcomes.

Acute liver failure (ALF) is the loss of hepatic synthetic function with associated coagulopathy and hepatic encephalopathy without underlying liver disease developing in <8–12 weeks.[1] Hepatic encephalopathy and hyperammonemia in patients with ALF can be associated with life-threatening cerebral edema.

PATHOGENESIS

The pathogenesis of the liver injury is largely etiology dependent.[2] Hepatocellular injury causes cell damage or cell death, the latter by necrosis, apoptosis, or both.[3] Cellular glutathione is reduced, increasing susceptibility to oxidative injury and impairing the cells' ability to conjugate and detoxify substances. Liver progenitor cells are present mainly in the portal regions, so injury to the portal zone severely inhibits the regenerative response. The central zone of the hepatic lobule is more susceptible to ischemic injury. Toxic exposures differ in their site and severity of injury in the liver owing to differences in the metabolism of central compared with portal hepatocytes.[4]

ETIOLOGIES AND SPECIFIC THERAPIES

The etiologies of ALF are the single most important determinants of outcome[2] and differ in frequency in different geographic locations.[2,5]

Toxic Injuries

Acetaminophen is the most common cause of ALF.[2] ALF due to acetaminophen ingestion typically requires ingestion of ≥4 g and often >10 g of the drug. Less amounts of acetaminophen can cause ALF in the setting of alcohol use or underlying liver disease.[6] Acetaminophen is metabolized by hepatocyte microsomal cytochrome enzymes to a toxic metabolite that is detoxified by conjugation with glutathione. Glutathione depletion that results from its use for detoxification and other effects of the toxic metabolite cause liver injury. N-acetylcysteine (NAC) helps replenish glutathione stores.[7] Recovery without transplant occurs in as many as 80% of patients with ALF due to acetaminophen with timely NAC therapy.[2,7] NAC is now available as an intravenous (IV) preparation,[8] which is more costly but preferable in the setting of ALF because absorption is not an issue.[9] Reactions to IV NAC include allergic responses or cardiac dysrhythmia. These are rare but may be related to the rate of NAC infusion and are typically reversible with antihistamines or drug discontinuation.

Amanita poisoning from the heat-stable toxin in the mushroom *Amanita phalloides* and *Amanita virosa* causes gastrointestinal symptoms followed by liver injury, ALF, and secondary injury to other organ systems.[10] Mortality approaches 10%–30%. Treatment with silibinin or high dosages of penicillin G early on may ameliorate the hepatic injury by blocking hepatocyte uptake of the toxin.[11]

Other drugs and herbal compounds may cause ALF. The site within the liver that is affected determines in part the probability of recovery from the injury. Many of these injuries are idiosyncratic; however predisposition to developing severe drug-induced liver injury owing to individual differences in drug metabolism are possible.[12] One of the most common examples of this is isoniazid.

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0041-1345/–see front matter
doi:10.1016/j.transproceed.2011.01.109

Viral Hepatitis

A small percentage of patients with viral hepatitis A, B (HBV), and E (HEV) infection develop ALF.[2,5] There are no specific therapies for hepatitis A or E, but there are antiviral agents that inhibit HBV replication. Retrospective studies from India and the US ALF Study Group (W.M. Lee, personal communication) failed to demonstrate any risk reduction for developing ALF;[13] however, the use of antiviral agents for acute HBV to suppress the virus in a patient awaiting liver transplant may reduce the risk of posttransplantation recurrence. Coinfection or superinfection with hepatitis D virus (HDV) worsens the clinical course of acute HBV infection. Outbreaks of HBV and HDV have been reported in association with injection drug use.[14,15] HEV infection is rarely fatal; however, in pregnant patients in India with acute HEV infection liver failure and death occured in up to 20%.[16] In contrast, high mortality with HEV during pregnancy was not seen in other geographic regions.[17] Other viral causes for ALF include herpes simplex virus, varicella zoster virus, cytomegalovirus, and rarely Epstein-Barr virus.[2,18,19] For herpes simplex virus and cytomegalovirus infections with associated liver failure, acyclovir and ganciclovir may be used for lowering viral load, but there are limited data about outcomes for patients with ALF from these infections.

Metabolic

ALF may result from underlying metabolic liver diseases in adults; however, these are less predominant than in children, where they are the most common etiology. In children, metabolic disorders–associated ALF include galactosemia, tyrosinemia, mitochondrial disorders, and fatty acid oxidation defects among others. Many of these are cured by liver transplantation. In adults, Wilson disease (WD), an autosomal recessive inherited disorder of copper metabolism, accounts for ~5% of all patients with ALF.[20,21] Liver failure due to WD differs from other causes of ALF, because advanced hepatic fibrosis or cirrhosis is present at the time of presentation. ALF due to WD is typically accompanied by a nonimmune hemolytic anemia, an alkaline phosphatase–bilirubin ratio of <4, ALT-AST ratio <2, elevated serum copper >200 μg/dL, and 24-hour urine copper that can be >1,000 μg.[22] Kayser-Fleischer rings, copper deposits in the cornea, are present in ~30%–50% of patients diagnosed with WD in the setting of ALF.[20,22] Transplantation is life saving for these individuals, but treatments to lower copper levels may help stabilize the patient while awaiting tansplantation.[23,24]

ALF can occur during and following pregnancy. Acute fatty liver of pregnancy (AFLP) is due to metabolic disruption in fatty acid metabolism in the fetus that causes maternal-fetal distress.[25,26] AFLP occurs typically in the third trimester with marked elevation of liver tests and is frequently associated with preeclampsia. AFLP may progress rapidly to jaundice and ALF. Fatty liver can be detected by ultrasound, but liver biopsy is the standard for diagnosis. Delivery of the fetus is necessary for maternal and fetal survival; however, the use of plasma exchange has improved outcomes with reduced hospital stays and prevention of multiorgan failure syndrome in a small group of patients with AFLP.[27] Another cause of ALF in pregnancy, HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome also occurs mostly in preeclamptic patients in their last trimester.[28] Delivery of the fetus is the only known treatment.

Vascular

Acute vascular obstruction of the liver or hepatic ischemia can cause ALF. Acute obstruction of the hepatic veins or Budd-Chiari syndrome is recognized by hepatomegaly, ascites, and demonstration of hepatic venous thrombosis by imaging or angiography. Acute decompression with transhepatic intrahepatic portosystemic shunt[29] or surgical portosystemic shunt procedure[30] may prevent further hepatic injury. Transplantation may become necessary if liver failure progresses.[29–32] Budd-Chiari syndrome is frequently associated with hypercoaguable states.[32]

Ischemic hepatitis, or "shock liver," results in central zonal injury and typically occurs after hypotension. Treatment of the underlying condition that led to the ischemic injury is critical for recovery.[33,34]

Autoimmune

Autoimmune hepatitis (AIH) may rarely present with ALF. Up to 30% of patients with acute presentations of AIH test negative for typical serum markers for AIH.[34] Some patients may respond to high-dose steroid treatment. Liver biopsy may help identify those individuals with AIH and negative serologies or confirm the diagnosis in others; transjugular liver biopsy may be performed in those with significant coagulopathy or ascites.

ASSESSING THE NEED FOR LIVER TRANSPLANTATION

The Kings College criteria remains the standard as to whether or not a patient with ALF will die.[35] Other studies have attempted to look at etiology-specific indices or have tried to use other additional serum-based tests to help predict survival.[36–38] Although these may be used adjunctively with the Kings College criteria to help predict death or recovery, the best decision can be reached by the transplant team by following the patient's clinical course and disease progression. Patients with advanced-stage coma and progressive coagulopathy are likely to need active intervention for survival. Once a decision is made that the patient is unlikely to survive without transplant, assessment for transplant should begin. Social and psychiatric history, history of any active infection or malignancy, or other contraindications to transplantation must be rapidly assessed to the best of the team's ability. Patients must undergo surveillance for infection even if antibiotic and antifungal prophylaxis is used, and their neurologic, hemodynamic, and pulmonary status must be assessed frequently.