Liver transplantation in acute liver failure

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Acute liver failure (ALF) is a GI emergency that continues to be a therapeutic challenge. Aggressive supportive care in an experienced intensive care facility has improved survival rates of patients with ALF. Liver transplantation is considered an important therapeutic option for ALF patients who have poor prognosis. Prognosticating the outcome in ALF is difficult and the decision to transplant needs frequent monitoring and a multidisciplinary approach from an experienced team. For these reasons, patients with ALF are best cared for in an inpatient ICU setting. Early referrals to such tertiary-care centers with the necessary experience and expertise provide the best outcomes for patients presenting with ALF. [Indian J Gastroenterology 2006;25(Suppl 1):S13-S18]

Acute liver failure (ALF) is a broad term that encompasses both fulminant hepatic failure (FHF) and sub-fulminant hepatic failure (or late-onset hepatic failure, subacute hepatic necrosis) that can result from various causes. Common etiologies for hepatic failure are listed in the Table. The most widely accepted definition of ALF includes evidence of coagulation abnormality, usually INR >1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing cirrhosis and with an illness of <26 weeks’ duration. With improved supportive care, the mortality of 97%, once seen in patients who were managed without transplantation, has decreased to 57%. Liver transplantation is the only definitive treatment option and is now considered for many patients with ALF.

Orthotopic liver transplantation (OLT) is now well-established treatment for chronic end-stage liver disease (ESLD) and is indicated with very few exceptions. Technical and technological advances have resulted in high success rates with acceptable morbidity and mortality. However, a successful transplantation procedure alone does not guarantee good long-term outcome. Organ recipients need lifelong immunosuppression to prevent rejection, monitoring to assess organ function, and interventions to prevent side-effects of immunosuppressive medications. Therefore, a patient’s physical, psychosocial and socioeconomic fitness plays a major role in evaluation for transplant candidacy. Despite these restrictions, the use of OLT in chronic ESLD has undergone an exponential increase, resulting in a shortage of donor organs.

The decision to transplant for ALF poses several unique challenges. Issues regarding patient management and decision-making often arise with the onset of the injury or insult. As in most acute liver problems, with the exception of toxic substance consumption, patients present insidiously. This results in loss of precious time needed for detailed evaluation of recipient factors, such as psychosocial and socioeconomic readiness, both of which tend to play a major role in long-term well-being of a transplanted organ. Often the diagnosis is only made after the patient presents with overt symptoms of liver failure with deep jaundice, altered mental status, or even after the development of a comatose state.

Due to the regenerative capacity of the liver, patient survival and recovery is often a balance between the damaged liver and the available functional liver mass. Because of this, patients who have overcome the acute-injury phase in ALF often pose a difficult therapeutic challenge. In these patients assessment of the likelihood of spontaneous recovery is critical in the decision to use OLT and should be made with the pros and cons in mind, such as the need for lifelong immune suppression, associated problems, expense, etc. This decision is often hard to make and requires close monitoring of the patient and evaluation at frequent intervals by a multidisciplinary team. The timing of OLT in FHF is also critical as a delay in the availability of the donor organ may often mean onset of infections or irreversible neurological damage and poor outcome.

Table: Causes of acute hepatic decompensation

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Wilson’s</th>
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<tr>
<td>HELLP syndrome</td>
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<td>Acute fatty liver of pregnancy</td>
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<td>Reye’s syndrome</td>
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<td>Non A to E hepatitis</td>
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<td>Drugs or toxin mediated</td>
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<td>Acetaminophen</td>
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<td>Isoniazid</td>
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<td>Halothane</td>
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<td>Amanita phalloides</td>
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<tr>
<td>Thrombotic/vascular</td>
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<tr>
<td>Budd-Chiari syndrome</td>
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<td>Shock liver</td>
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<td>Auto immune</td>
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<td>Malignancy</td>
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<td>Primary</td>
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<td>Melanoma</td>
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<td>Secondaries</td>
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<td>Trauma</td>
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Common causes of FHF

Drug-related hepatotoxicity is the leading cause for FHF in the United States and accounts for more than 50% of ALF cases. The incidence is approximately 2000 cases per year and includes acetaminophen toxicity (30%) and idiosyncratic drug reactions (13%). Other causes are hepatitis A and B (12%), autoimmune hepatitis, and Wilson disease. Acute hepatitis delta virus (HDV) infection may occasionally be diagnosed in a hepatitis B-positive individual. Although controversial, hepatitis C alone does not appear to cause ALF. Nearly 17% of cases remain of indeterminate etiology.

Acetaminophen or paracetamol overdose is a prominent cause of FHF in Europe, where ALF accounts for 11% of patients receiving OLT. In the developing world, acute hepatitis B virus (HBV) infection dominates as a cause of FHF. Hence, HDV superinfection is much more common. Hepatitis E virus (HEV) infection is associated with a high incidence of FHF in pregnant women and is of concern in pregnant patients living in or traveling through endemic areas. Hepatitis A can present with FHF in less than 1% of patients. FHF can also be caused by other non-hepatotropic viruses, such as Epstein-Barr virus, cytomegalovirus, adenoviruses, and herpes simplex virus, but these are rarer causes of FHF and usually present with distinctive clinical features.

Some of the metabolic syndromes associated with pregnancy may present with ALF. Acute fatty liver of pregnancy is rarely known to present as ALF and liver rupture. ALF, however, is more commonly seen with a metabolic syndrome presenting as hemolysis, elevated liver enzymes, and low platelet count (HELLP), and occurs in 0.1% to 0.6% of all pregnancies and in 4% to 12% of women with severe pre-eclampsia. The etiology of HELLP is uncertain, although vascular endothelial injury appears to play a pivotal role. Maternal morbidity related to HELLP includes disseminated intravascular coagulation (21%), abruptio placentae (16%), acute renal failure (7.7%), pulmonary edema (6%), and subcapsular liver hematoma (0.9%). Delivery is the definitive treatment for HELLP syndrome. Rupture of a subcapsular hematoma is a rare but life-threatening complication and is associated with a mortality rate of 16% to 59%.

The initial presentations of liver complications in HELLP are often misleading. Right upper quadrant or epigastric pain, nausea and vomiting, and headache are often mistaken for gastroenteritis, hepatitis, or cholelithiasis. A high index of suspicion is necessary to make a prompt diagnosis and appropriate intervention. A diagnosis of HELLP should prompt transfer of care to a tertiary medical center as it often necessitates a multidisciplinary approach.

Patients with massive hepatic necrosis or subcapsular hematoma need careful monitoring in an ICU setting with frequent imaging depending on the clinical findings. Cardiovascular instability with evidence of continuing bleeding or a free rupture needs surgical exploration in an emergent setting. There are reports of total hepatectomy performed as a temporary stabilizing procedure followed by successful transplantation, though the initial surgical approach is to attempt aggressive control of bleeding with other available surgical techniques. In situations where conventional surgical approaches have failed, liver transplantation has been successfully used with acceptable mortality (17%) for the management of bleeding and liver failure from massive hepatic necrosis.

Wilson’s disease (WD), an autosomal recessive genetic disorder of copper metabolism (mutation site ATP7B on chromosome 13), affecting approximately one in 30,000 people worldwide, can often present with FHF. The disease is usually fatal by the age of 30 years unless detected and treated. Although in most cases well-timed treatment can solve both hepatic and neurological signs, a few patients fail to respond to therapy. Some require liver transplantation, which can cure the disease by correcting the expression of the genetic defect in the liver.

The pathophysiology in WD includes excessive absorption of dietary copper and faulty excretion due to dysfunction of copper-transporting p-type ATPase due to the gene mutation, resulting in progressive copper accumulation in the hepatocytes. The excess copper is initially bound to metallothionein and distributed evenly throughout the cytoplasm. When the binding capacity of metallothionein is exceeded, copper is partly deposited in lysosomes, leading to hepatic dysfunction. It also leaks out into the blood and is deposited in the brain and other tissues. The common clinical manifestations include chronic liver disease, neurological disease, FHF and hemolysis.

The fulminant mode of presentation occurs without clear precipitating cause, and is more common in females. It is frequently associated with hemolytic anemia as hepatocyte necrosis results in the massive release of copper ions into the circulation. Clinical signs include jaundice, hemoglobinuria, and renal failure; in this setting, diagnosis is a matter of extreme urgency since, if the patient is not
promptly considered for liver transplantation, prognosis is uniformly fatal.\textsuperscript{18} WD should be entertained in the differential diagnosis of any patient below the age of 40 presenting with fulminant liver failure.

The diagnosis of fulminant WD can be very difficult as the clinical signs of chronic liver disease and Kayser-Fleischer rings may be absent. Confirmatory biochemical markers such as ceruloplasmin, serum copper and urinary copper excretion are often unreliable and liver histology and copper staining are often misleading. Hepatic copper content, which is considered the gold standard for diagnosis, may be below the diagnostic level, because of massive release of copper from necrotic hepatocytes, biopsy sampling error or non-availability of the results on a timely fashion. The clinical presentation of ALF with deep jaundice and evidence of intravascular hemolysis with hemoglobinuria and renal failure should raise the possibility of WD. Fulminant WD is associated with abnormally low levels of serum alkaline phosphatase. Moreover, due to hemolysis, the serum AST tends to run higher than ALT (ratio over 1:4).\textsuperscript{19}

Without liver transplantation fulminant WD is uniformly fatal.\textsuperscript{18} A suspicion of fulminant WD should prompt immediate transfer of the patient to a hospital with an active liver transplantation program. While awaiting transplant, plasma exchange with fresh frozen plasma replacement has been the most efficient method of removing copper from the circulation – better than hemodialysis, peritoneal dialysis, and hemofiltration, with net copper removal reaching up to 12 mg per session.\textsuperscript{20} With appropriate pre-operative care, patients who have been transplanted in timely fashion have excellent long-term prognosis, with the reported one-year survival ranging from 70%-90% for a condition that is otherwise fatal.\textsuperscript{21}

Acute Budd-Chiari syndrome is an uncommon GI emergency but when it occurs, it is a difficult clinical problem. The condition is characterized by hepatic venous obstruction and in most cases is secondary to an underlying prothrombotic problem.\textsuperscript{22} The presentation can be fulminant, acute, chronic or asymptomatic. Fulminant presentation includes ascites with evidence of liver necrosis, lactic acidosis and early onset of encephalopathy. Medical management mainly includes supportive care for the liver decompensation and ascites. The natural history of the disease has shown 30% early mortality with 5-year survival of 50% in the rest.\textsuperscript{23} Use of surgical options such as portocaval shunt has improved long-term prognosis of surviving patients.\textsuperscript{24,25} Liver transplantation and transjugular intrahepatic portosystemic shunt (TIPSS) placement are treatment modalities that benefit patients who are at risk for high mortality.\textsuperscript{26} In FHF, successful TIPSS helps to get symptomatic improvement and stabilization. Liver transplantation, if available in a timely fashion, is not only life-saving but also provides long-term survival for otherwise fatal presentation of this syndrome.\textsuperscript{27}

Liver trauma when severe may result in acute liver insufficiency. Trauma to the liver is associated with massive bleeding from injury to major vessels and liver tissue. Management includes conventional surgical techniques of debridement, perihepatic packing, deep suturing, partial heptectomy, vascular ligation, or a combination of any of the above. Patients usually have associated injuries from the trauma or suffer from secondary damage to other organs from massive bleeding, shock and resuscitation. Removal of the liver to control bleeding, with the creation of a portosystemic shunt, has been used as a temporary stabilizing measure in the event of severe trauma. This is then followed by OLT.\textsuperscript{28} Results from these drastic measures depend on variables including the primary and secondary injury to other organs and timely availability of a suitable donor liver.

**Management considerations**

Though the precipitating etiology may be varied, one of the common features of ALF is an unpredictable clinical course and progression. For this reason, hospital admission is recommended for all patients with acute onset of moderate to severe hepatitis with elevation of coagulation parameters (PT higher than 4-6 seconds of normal baseline; INR $\geq 1.5$). An altered sensorium heralds a diagnosis of ALF, and early transfer to the ICU is indicated.\textsuperscript{29}

Careful history and clinical examination may shed light on etiologies that may respond to antidote therapies such as N-acetylcysteine (NAC) for acetaminophen or paracetamol overdose, penicillin for *Amanita* mushroom poisoning, immune suppression for autoimmune hepatitis, anti-copper therapy for WD, and antiviral therapy for herpes simplex virus infection. As the progression of encephalopathy is variable, frequent neurologic examinations, avoidance of drugs that may alter the sensorium further, and supportive care are mandatory. Rapidity of progression of hepatic encephalopathy (HE) directly correlates with poor prognosis. Uncontrolled cerebral edema (38%-81%),\textsuperscript{30} intracranial hypertension, ischemic injury to the brain, and uncal herniation are the common causes of death associated with HE and FHF.\textsuperscript{31} Progression of HE symptoms may need endotracheal intubation.
for airway protection. However, intubation requires sedation, making evaluation of the mental status impossible. This makes it necessary to consider placement of epidural intracranial pressure (ICP) monitor to evaluate the cerebral perfusion pressure. Though the utility of ICP monitoring in ALF is controversial, it is a useful tool to determine the cerebral perfusion. A cerebral perfusion pressure (CPP) of >60 mmHg is crucial for maintaining neurologic function. Some centers consider a perfusion pressure <40 mmHg for 2 hours or greater as a contraindication for OLT. Strategies used to maintain adequate CPP include use of vasopressors to maintain mean arterial pressures, and controlled hypothermia. These approaches are controversial and the benefits need further validation. Experience with ICP monitoring has shown dramatic changes in pressure with maneuvers such as endotracheal suction, changing positions or moving a patient, and with ventilatory dyssynchrony. Experienced ICU supportive care measures such as elevating the head to 30° and minimizing stimulation become extremely important in this setting.

Ileus is an expected complication in ALF. Lactulose has shown no benefit and often results in worsening of an existing ileus. Short-acting benzodiazepines and mannitol are beneficial. Intubation also helps improve some of the ventilatory and oxygen-delivery problems that are associated with cardiovascular and hemodynamic changes associated with ALF by providing a means to increase the F\textsubscript{2}O\textsubscript{2} for better oxygen delivery to the tissues.

Coagulopathy is an integral part of ALF. As most patients have associated dysfunction, administering fresh frozen plasma (FFP) to correct elevated prothrombin time adds to the fluid overload problem. The accepted recommendations are to reserve the use of FFP or consider recombinant activated factor VII only to facilitate invasive procedures such as liver biopsy, placement of ICP monitors, or for clinical evidence of bleeding. When pro-coagulant measures listed above are not used, the prothrombin time serves as an excellent indicator to monitor the progression of the ALF. Platelet transfusions are required only for bleeding symptoms or at the time of invasive procedures if the platelet count is <50 x 10\textsuperscript{9}/L. Platelet transfusion prophylaxis is used only if the platelet count is <20 x 10\textsuperscript{9}/L.

Hemodynamic derangements in ALF are caused by several mechanisms that are incompletely understood. However adequate management of hemodynamics is important to maintain organ perfusion, especially to protect the brain and renal function. Placement of pulmonary artery catheter may aid in assessing the volume status, which usually is quite tenuous due to several factors such as decreased oral intake due to mental status change, transudation of fluid into the extravascular space, GI blood loss, and decrease in vascular resistance due to peripheral shunting. Most patients will require fluid resuscitation initially. Fluid replacement with colloid (such as albumin) is preferred to crystalloid; all solutions should contain dextrose to maintain euglycemia.

Acute renal failure is a frequent association with ALF, either as a part of the syndrome such as in WD or as a result of hemodynamic changes and fluid shifts associated with ALF. Renal failure often contributes to mortality and is considered a poor prognostic sign. If renal failure develops despite attempts to protect the kidney, patients should be supported with dialysis. Continuous venovenous hemodialysis (CVVHD) has been shown to provide a better outcome than intermittent dialysis in patients with ALF. Anecdotal reports have suggested a role for hepatectomy as a ‘last-resort’ attempt to help stabilize the hemodynamics in some desperately ill patients with ALF awaiting liver transplantation.

Due to reticuloendothelial dysfunction, patients with ALF are susceptible to infections particularly involving the respiratory and urinary tracts. Attention to standard infection control precautions, along with a high index of suspicion and repeated surveillance cultures, help avert or facilitate prompt treatment of this problem. Some institutions initiate elective broad-spectrum antimicrobial prophylaxis. Continued use of antibiotics however may promote fungal overgrowth and invasive fungal infections, which are then associated with a high mortality.

Transplant indications

Orthotopic liver transplantation remains the only definitive therapy for patients who are unable to achieve regeneration of sufficient hepatocyte mass to sustain life following injury or insult. Given limited organ availability and potential complications of surgery and lifelong immunosuppression, accurate evaluation of ALF is an essential goal. The prognosis of FHF varies with the underlying etiology and other factors. Prognostic scoring systems, although derived from data on relatively large numbers of patients, still have shortcomings in accurate predictions for ALF, likely due to the variable etiology and thus variable potential for recovery. It is clear that there is no single prognostic indicator or even...
scoring system that can determine outcome with reliable accuracy. As a result, decision to list a patient for transplantation is difficult and is based on overall acuity and progression, taking into consideration many clinical and biochemical parameters.

The parameters that are helpful in assessing the prognosis can be categorized as static and dynamic. Static parameters include patient age, race, gender, and etiology of the disease. Among static parameters, age and etiology have shown a correlation with patient survival. Survival rates in patients between the ages of 10 and 40 years is between 30% and 35%, whereas survival rate in patients older than 40 years of age or younger than 10 years of age is poor, less than 10%. While drug-induced and cryptogenic FHF have the worst prognosis, hepatitis A and acetaminophen toxicity have the best survival. Hepatitis B and D survival rates are in between the two listed above. Patients with FHF caused by WD or malignancy rarely survive.

Important dynamic parameters useful in predicting the outcome of FHF include degree of hepatic encephalopathy, prothrombin time, factor V level, serum bilirubin, serum creatinine, alpha-fetoprotein level, arterial pH, and arterial ketone body ratio. The degree of encephalopathy is also a strong predictor of outcome. Other variables that can be sometimes helpful include CT scanning of the liver, and cytokine and phosphate levels.

The Model for End-stage Liver Disease (MELD) score, now widely used to predict mortality among patients with chronic liver disease who are under consideration for liver transplantation, cannot currently be recommended as applicable to ALF. Using both static and dynamic variables, important information regarding prognosis can be gained to estimate the probability of spontaneous recovery. These carefully defined criteria for judging prognosis are valuable but need to be continuously re-evaluated and revised based on advances in the management and supportive care of FHF.

All patients with ALF who fail to show clinical and biochemical improvement with appropriate intensive care management are evaluated for transplantation. The decision to transplant should depend on the status of the patient upon availability of the organ. Contraindications for transplantation in ALF include extrahepatic malignancy, uncontrolled extrahepatic sepsis, multi-system organ failure, irreversible brain damage, or unresponsive cerebral edema with sustained elevation of ICP >50 mmHg and a decrease in CPP to <40 mmHg.

The survival rate in ALF with appropriate intensive care measures has increased to >60%. The post-transplant short-term survival rates for ALF are as high as 80%-90%. This is remarkable as transplant is offered to patients who have little other chance of survival with conservative management only. Timely availability of an allograft is one of the major factors that determine transplant outcomes. In the largest US study, only 29% of patients received a liver graft, while 10% of the overall group (1/4 of patients listed for transplantation) died on the waiting list. Other series have reported death rates of those listed for transplant as high as 40%. This was despite the fact that patients with ALF receive priority listing status (UNOS Status I). Developing prognostic indicators for early identification of patients who would benefit from liver transplantation and developing bridging devices that would provide artificial liver support are two avenues that would help improve patient survival.

Living-donor transplant may address the shortage of organ availability, but the outcome of using partial grafts in an acute setting has not been fully evaluated. Moreover there are several ethical concerns that need to be addressed while evaluating a living donor in the setting of ALF.

**References**

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