Acute Liver Failure

General

- Acute liver failure (ALF) is usually defined as altered mental status and coagulopathy in the setting of acute hepatic disease; fulminant liver failure is generally applied to patients in whom hepatic encephalopathy develops after eight weeks of the onset of illness; subfulminant hepatic failure is that which occurs after a longer illness.

- There are approximately 2000 cases of ALF annually in the U.S. with previous mortality approaching 80% but with the introduction of orthotopic liver transplantation survival rates have improved to 60-80%.

Etiology

- **Viral (and other infectious causes)** – viral hepatitis accounts for 72% of all cases of ALF, however viral hepatitis leads to hepatic failure in < 1% of cases.
  
  ◊ Hepatitis A – usually a self-limited enteric infection which rarely leads to liver failure (≈ 0.35% of cases); prognosis is generally good for those in whom ALF develops with >60% survival

  ◊ Hepatitis B – may lead to ALF in up to 1% of those infected; prognosis differs for those patients who become seronegative for HbsAg (survival rate of 47%) as opposed to those who remain HbsAg+ (survival rate of 17%).

  ◊ Hepatitis C – rarely causes ALF (≈ 0.1%)

  ◊ Hepatitis D – accounts for <10% of all cases of acute hepatitis, however causes ALF in 5-20% of those infected and more than 50% of cases of ALF due to HBV are coinfected with the delta agent.

  ◊ Hepatitis E – enteric virus similar to HAV with 1-2% incidence of ALF which has a good prognosis

  ◊ CMV, EBV, HSV, Parvo B19, and coxsackieviruses are implicated occasionally

  ◊ Rarer infectious agents that can present with ALF include *Toxoplasma, Leptospira, Candida, Brucella, Mycobacteria*, and...
**Drugs and Toxins** – liver injury may follow the inhalation, ingestion, or parenteral administration of a large number of chemical (e.g. CCL₄), pharmaceutical (acetaminophen, EtOH, inhalant anesthetics), and "natural" hepatotoxins (Amanita and Galerina mushrooms); patients/families must be carefully questioned about occupational exposures, prescribed and OTC pharmaceuticals.

**Vascular** – ALF is most often seen in instances of "shock liver" with severe hypotension and/or LV dysfunction. Sinusoidal obstruction secondary to liver metastases (e.g. gastric carcinoma, breast cancer, small cell lung cancer, leukemic infiltration) can rarely present as ALF, as well as hepatic vein occlusion (Budd-Chiari syndrome) and venoocclusive disease.

**Miscellaneous**

◊ Wilson’s disease – can occasionally present as ALF

◊ HELLP syndrome – severe variant of preeclampsia associated with ALF

◊ Acute fatty liver of pregnancy – occurs in the third trimester, often associated with ALF and preeclampsia; if promptly diagnosed it usually resolves with delivery

◊ Reye’s syndrome – characterized by progressive CNS damage, ALF, and hypoglycemia usually following an URI occurring in children less than 15yoa; mortality 50%; decreased incidence since discovery of association with aspirin use in children.

**Treatment** – despite the introduction of several new therapies, survival rates with medical therapy alone for ALF that progresses to stage 3 or 4 encephalopathy are poor, varying between 10 and 40%, but with OLT survival rates improve to 60-80%. Thus, the current goal of medical management has become not only to support the patient and allow the native liver to regenerate, but also to improve the patient’s condition for possible OLT. Cerebral edema and sepsis are the most common causes of death, and multi-system organ failure is frequently encountered. Specific treatments aimed at the underlying physiological derangements await development (except N-acetyl cysteine); antiviral agents, e.g. interferon, have not proved beneficial.

◊ Encephalopathy – encephalopathy is a universal feature of ALF and once stage 3 or 4 encephalopathy develops the patient is at high
risk for development of cerebral edema and multi-system organ failure. Supportive measures include correction and avoidance of any factor that could aggravate pre-existent encephalopathy, e.g. hypoglycemia, hypoxia, hemorrhage, sepsis, drug toxicity, electrolyte and acid-base disturbance. Lactulose and dietary protein restriction are commonly used measures to treat hepatic encephalopathy; other agents include metronidazole and neomycin.

**Stages of acute hepatic encephalopathy:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Confused or altered mood</td>
</tr>
<tr>
<td>2</td>
<td>Inappropriate behavior or drowsiness</td>
</tr>
<tr>
<td>3</td>
<td>Stuporous but arousable, markedly confused behavior</td>
</tr>
<tr>
<td>4</td>
<td>Coma, unresponsive to painful stimuli</td>
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- **Cerebral edema** – complicates stage 4 or late stage 3 encephalopathy in 50-85% of patients with ALF and is the leading cause of death in these patients. Clinical signs of cerebral edema occur when the intracranial pressure (ICP) exceeds 30mmHg; the earliest signs are systolic hypertension and increased muscle tone that progresses to decerebrate posturing. Several modalities have been used to prevent and treat cerebral edema in ALF but few have confirmed benefits.

  ◊ ICP monitoring: uncontrolled data supports use of ICP monitoring to allow for early detection and aggressive treatment of cerebral edema, however no significant change in outcome has been found.

  ◊ Osmotic diuretics: mannitol has been shown to improve survival in randomized controlled trials. Usually given at a dose of 1 g/kg that can be repeated after 4-6 hours if plasma osmolality does not exceed 320mOsm/L.

  ◊ Barbiturates – no randomized controlled trials but widely accepted as an effective treatment of elevated ICP.

  ◊ Hyperventilation – has not been shown to be effective in cerebral edema associated with ALF.
Positioning – there are conflicting data but it is generally recommended that patients’ heads be elevated to 30 degrees above horizontal.

Charcoal hemoperfusion – does not confer survival in randomized controlled trials.

Corticosteroids – several randomized trials have reported that corticosteroids are not beneficial as either prophylaxis or treatment of cerebral edema associated with ALF.

- **Infection** – bacterial and fungal infections are extremely common in patients with ALF. In a prospective study of 50 patients evidence of bacterial infection was found in almost 90% and fungal infection in 32%. Data indicate that prophylactic antibiotics are useful to lower infection rates but are of questionable significance in terms of overall survival.

- **Coagulopathy** – and hemorrhage are extremely common in ALF secondary to consumption and inadequate synthesis of clotting factors as well as frequent thrombocytopenia. Infusion of FFP has not been shown to be beneficial in a randomized controlled trial; plasma exchange may be beneficial but this has yet to be determined in controlled trials.

- **Hemodynamic abnormalities and tissue hypoxia** – ALF is associated with several circulatory abnormalities including a low SVR; blood is shunted away from active tissues and oxygen extraction and consumption are decreased with subsequent anaerobic metabolism and lactic acid production. Tissue hypoxia also contributes to multi-system organ failure. The hemodynamic effects of microvascular vasodilators, such as prostacyclin and N-acetyl cysteine, and vasopressors (norepinephrine) have been evaluated in patients with ALF.

  - Prostacyclin and N-Acetyl cysteine – in an uncontrolled trial, alone or in combination, induced an enhancement of oxygen consumption, suggesting an improvement in the microvascular hemodynamics. Effects on overall outcome have yet to be determined.

  - Vasopressors – use of norepinephrine in patients with ALF was found to be probably harmful in an uncontrolled study.

- **Hepatic regeneration** there has been investigation in the use of agents that regulate liver regeneration. However, a randomized trial of insulin and glucagon
in 18 patients found no evidence of enhanced hepatic function with the use of these agents.

- **Extracorporeal liver assist devices (ELAD)** – "liveralysis" consisting of mammalian hepatocytes that provide metabolic function for the patient with liver failure; ELAD has shown promise in past randomized trials and is now undergoing a multicenter randomized trial. ELAD has many potential clinical uses. ELAD could be used as a bridge to OLT, or if liver function could be supported until hepatic regeneration has taken place to sustain life, liver transplantation or death could be averted.

- **Orthotopic Liver Transplantation** (OLT) has emerged as the most important advance in the therapy of ALF, with survival rates of 60-80%; there is still some clinical controversy as to how best to determine which patients truly require and/or would benefit from OLT. Two selection criteria include the London and Clichy criteria, however these criteria are useful for identifying patients who should not be considered for OLT.

**References**: *Mayo Clin Proc* 1998; 78: 765-71  
*Seminars in Liver Disease* 1996; 16: 369-78  
*Harrison's Principles of Internal Medicine, 14th Edition*