Acute liver failure (ALF) is a clinical syndrome characterized by sudden loss of hepatocyte function due to a large spectrum of etiologies in previously normal individuals. In India, acute viral hepatitis is leading cause for ALF, with hepatitis E being the most common followed by hepatitis B. In western countries, drug induced hepatotoxicity, mostly due to acetaminophen (paracetamol) overdose, is the leading cause of ALF. Sepsis and cerebral edema with encephalopathy are two most common complication of ALF leading to death. Sepsis occurs due to altered immunity and loss of opsonic activity in serum. Cerebral edema is caused by alteration in permeability of blood-brain barrier. ALF carries grave prognosis with mortality rate varying from 30–40% with intensive care and liver transplantation to around 70% in countries like India, where facilities for liver transplantation are limited. Early identification of etiology and institution of specific therapy, if any, can be life saving in patients with acute liver failure. Newer advances in form of temporary liver support systems hold a bright promise in bridging the crisis period till recovery or liver transplantation.

INTRODUCTION
ALF is defined by occurrence of coagulopathy (INR > 1.5) and onset of encephalopathy with in 26 weeks of acute liver insult due to any etiology, in absence of any pre-existing liver disease. Patients with pre-existing Wilson disease, vertically-acquired HBV, or autoimmune hepatitis may be included in this definition in spite of the possibility of cirrhosis, if their disease has only been recognized for <26 weeks. In children, signs and symptoms of encephalopathy are slow to occur and are difficult to recognize, leading to a growing consensus for defining ALF in children in presence of severe coagulopathy (INR > 2) alone, in addition to standard definition. ALF has traditionally been sub-classified on basis of duration of disease into hyperacute/fulminant (<7 days), acute (7-21 days) and subacute (>21 days and <26 weeks) liver failure. But, Indian as well as western studies have failed to show any prognostic significance of this classification and its use is no longer recommended. Outcome of acute liver failure remains dismal, especially in developing countries like India due to limited availability of intensive care units and liver transplantations. Most of the published studies are from tertiary care centers having good intensive care facilities but limited or no facilities for liver transplantation. These studies report a mortality rate of 60-70%; which would be much higher in population overall, as not all patients with ALF have access to ICU care. In western countries, centers with facilities for liver transplantation report, much lesser though still unacceptably high, mortality rate of around 30-35%. Cerebral edema and sepsis contributes towards majority of deaths. Respiratory failure and renal failure also contributes significantly towards mortality in patients with ALF. Coagulopathy, if identified and corrected timely, do not lead to death per se.

King’s college hospital criteria (Table 1) and Ph < 7.30 are two most commonly accepted and well validated prognostic criteria for assessing survival in patients with ALF. Other factors which have been evaluated, either alone or in various combinations, include age, duration of disease, elevated serum creatinine, encephalopathy grade, and prothrombin time elevation, decreased cases, while patients with clinical presentation suggestive of viral hepatitis but without any identifiable viral marker constitute 15 to 47 % of the cases in different studies. Hepatitis E remains the leading etiology (23 – 41% of the cases). Acute hepatitis B infection contributes significant number of ALF cases (11-27%). Acetaminophen has been implicated in very few cases in causation of ALF in India. On the other hand, acetaminophen is single most common etiology responsible for ALF in western countries (30-35% in USA and 60% of cases in Europe). Non-acetaminophen drug toxicity is next common etiology followed by viral hepatitis. Females constitute more than half of the cases worldwide, irrespective of etiology of ALF. In a study by Khuroo and Kamili, ratio of male to female was 1:1.6 with higher prevalence of females in HEV (79.7%) than those in the non-E group (47.5%). Twenty-five to 30 per cent of the women patients are pregnant, whereas the frequency of pregnancy among women in the general population at any time in India is 3%. The prevalence of HEV in pregnant women with ALF was 95.8% as against 41.2% in non-pregnant women (P < 0.001).

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Acute Fulminant Hepatic Failure

Table 1: King’s College Hospital Criteria for poor prognosis in Acute Liver Failure

<table>
<thead>
<tr>
<th>Acetaminophen-induced disease</th>
<th>Arterial pH &lt; 7.3 (irrespective of the grade of encephalopathy) or Grade III or IV encephalopathy, and Prothrombin time &gt; 100 seconds, and Serum creatinine &gt; 3.4 mg/dl</th>
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<tr>
<td>All other causes of fulminant hepatic failure</td>
<td>Prothrombin time &gt; 100 seconds (irrespective of the grade of encephalopathy) or Any three of the following variables (irrespective of the grade of encephalopathy): 1. Age &lt; 10 years or &gt; 40 years 2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions 3. Duration of jaundice before onset of encephalopathy &gt; 7 days 4. Prothrombin time &gt; 50 seconds 5. Serum bilirubin &gt; 18 mg/dl</td>
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factor V level, the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Gc globulin (vitamin D binding protein, a liver-derived component of the actin-scavenging system). In a study by Ostapowicz et al. ALF due to acetaminophen, hepatitis A, shock liver, or pregnancy-related disease showed > 50% transplant-free survival, while all other etiologies showed < 25% transplant-free survival. Other less validated factors include alpha-fetoprotein levels, factor VIII, adrenal insufficiency and cytokine levels.

PATHOGENESIS OF ACUTE LIVER FAILURE

Acute liver failure is characterized by massive necrosis of hepatocytes and hence loss of synthetic and metabolic functions. Deficiency of clotting factors synthesized by liver, factors II, V, VII, IX, and X, account for the prolonged prothrombin time and partial-thromboplastin time observed. Hypoalbuminemia contributes towards loss of intravascular volume and interstitial edema. Impaired metabolism leads to accumulation of toxic substances, including benzodiazepines-like substances, leading to hepatic encephalopathy. Impaired gluconeogenesis and impaired hepatic uptake of insulin leads to hypoglycemia.

Impaired regulation of cytokine regulation results in systemic proinflammatory state. Levels of tumor necrosis factor, prostaglandin E2 and thromboxane are raised in patients with ALF. This proinflammatory state leads to subclinical intravascular coagulation and low grade fibrinolysis resulting in thrombocytopenia and DIC like state. Impaired vascular permeability leads to aggravation of hypoalbuminemia, interstitial edema and increased leakage of cytokines in tissues resulting in enhanced oxygen demand with resultant hypoxia at tissue level. All these factors result in cerebral edema and decrease in intracranial cerebral perfusion pressure and hence precipitate hepatic encephalopathy.

Altered immunity, due to impaired cytokine metabolism, results in loss of cell mediated as well as humoral immunity. Bacterial and fungal sepsis is common in ALF and endotoxemia leads to septic shock like state.

Acute hepatic failure, even in absence of infection, has been postulated to be associated with adrenal insufficiency because of its pathophysiological similarity with septic shock. In liver disease, low levels of high density lipoproteins (HDL) have been postulated to be responsible for decreased synthesis of cortisol, leading to adrenal insufficiency. Some other factors, which are common to liver disease and sepsis, contributing to adrenal insufficiency are increased levels of endotoxin and proinflammatory cytokines, which suppress corticotrophin releasing hormone and adrenocorticotropic hormone levels; inactivation of cortisol to cortisone; and peripheral resistance to action of cortisol.

MANAGEMENT

Initial evaluation of ALF has to be extensive to confirm the diagnosis, ascertain etiology and institution of specific therapy, establish prognosis and referral for liver transplantation, if indicated and available. Any patient with clinical features suggestive of acute hepatitis should immediately undergo evaluation for altered mental status and prothrombin time. Prolongation of prothrombin time with INR > 1.5 and slightest evidence of altered sensorium establishes the diagnosis of ALF and admission becomes mandatory. As ALF progresses very rapidly, rigorous monitoring of mental status and early admission in ICU is highly recommended.

History should include ingestion of any drug especially acetaminophen and possible exposure viral infection. Past history for presence of predisposing factor for chronic liver disease should be elicited. Physical examination must include any stigmata of chronic liver disease. Inability to palpate the liver or even to percuss a significant area of dullness over the liver can be indicative of decreased liver volume due to massive hepatocyte loss.

An enlarged liver may be seen early in viral hepatitis or with malignant infiltration, congestive heart failure, or acute Budd-Chiari syndrome.

Initial laboratory investigations include routine blood chemistries including Prothrombin time/INR, serum electrolytes, glucose, AST, ALT, alkaline phosphatase, total bilirubin, albumin, renal function tests, arterial blood gas, complete blood count, blood type and screen, pregnancy test (females) and ammonia levels (arterial if possible). Other investigations to ascertain etiology consist of viral hepatitis serologies (anti-HAV IgM, HBSAg, anti-HBC IgM, anti-HEV, anti-HCV), acetaminophen level, toxicology screen, ceruloplasmin level and autoimmune markers (ANA, ASMA, Immunoglobulin levels), whenever indicated according to clinical features.

Therapy for ALF consist of general supportive measures, specific therapies for some of the etiologies, liver transplantation and other methods of temporary liver support.

General supportive ICU care (Table 2) includes management of raised intracranial pressure, correction of coagulopathy, prevention and aggressive treatment of infection, pulmonary and
renal dysfunction and reversal of metabolic derangements.

For raised ICP, apart from measures listed above, hypothermia, hyperventilation and hypertonic saline have also been used less commonly at some centers. Corticosteroids have also been used but have failed to show any evidence of benefit. If an ICP monitor is placed, key parameters to follow are both ICP and CPP. ICP should be maintained below 20-25 mm Hg if possible, with CPP maintained above 50-60 mm Hg. N-acetylcysteine, the standard antidote for acetaminophen overdose, has recently been suggested to be beneficial in other forms of ALF, possibly through its effects on hemodynamics in multiorgan failure and its renal protective actions.¹

**Specific therapies** have to be instituted for acetaminophen poisoning, autoimmune hepatitis and mushroom poisoning (Table 3).

**Liver transplantation** has improved the outcome of ALF. Orthotopic liver transplant has traditionally been preferred over living donor transplantation, because of time constraints for evaluating donors and ethical concerns. But, living donor transplant is being increasingly used to overcome donor organ shortage. Indications for liver transplantation vary slightly in different countries and are summarized in Table 4. Contraindication for liver transplantation in ALF include extrahepatic malignancy, multi-system organ failure, irreversible brain damage, refractory raised ICP with sustained elevation of ICP > 50 mmHg and a decrease in central perfusion pressure to < 40 mmHg.¹

Liver support systems are used in patients who have contraindication for liver transplantation or for whom liver tissue is not available. Liver support systems can be non-biological detoxification systems or they can be cell based systems. Cell based systems are more complicated and costly, but have advantage of providing metabolic as well as detoxification support. Emerging liver support therapies include hepatocyte transplantation and liver tissue engineering on 2-D or 3-D synthetic extracellular matrix.¹

**CONCLUSION**

ALF is a rapidly progressing and life threatening medical emergency. ALF due to Acetaminophen, shock, and hepatitis A have more
favorable outcome than other etiologies. Key to survival is early institution of specific therapy and liver transplantation.

Facilities for intensive care and liver transplantation needs to strengthened on urgent basis to improve outcome of ALF in India.

REFERENCES