Acute Liver Failure: An Update

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Abstract

Acute liver failure is a serious medical emergency resulting from various insults that liver sustains. In our setting, viral etiology is the commonest cause. The syndrome results in significant liver damage leading to hepatic encephalopathy, coagulopathy and several other serious clinical consequences. Sepsis, cardio vascular failure and renal failure can result in multi system organ failure and fatal consequences. Management requires identification of etiologic agent as soon as possible. Nursing care in intensive care unit (ICU) setting is recommended. Attention towards correction of electrolyte imbalance, coagulopathy, encephalopathy and systemic complication along with judicious use of antibiotics help in obtaining a favorable outcome. Transplant remains the ultimate management.

Key words: Liver failure, acute.

Introduction

Acute liver failure (ALF), also called fulminant hepatic failure was described as a specific and unique entity in the United States in the early 1950’s. Exact definition remains a matter of discussion. This syndrome of severe impairment of liver function leading to hepatic encephalopathy, coagulopathy and jaundice may result in cerebral edema which is the most common cause of death, and was first described in 1969. The condition can be a catastrophic illness as it can rapidly progress to coma and death because of multi organ dysfunction, especially in children. Mortality had approached nearly 100%, but more recently, and with the advent of liver transplantation in the more developed countries, the survival rate has improved to 70%. In under developed countries, however, fulminant hepatic failure (FHF) can be a devastating disease due to lack of advanced critical care support and liver transplantation. Recent classification of ALF broadly separates this condition into hyper-acute, acute and sub-acute, based on time interval between the development of jaundice and encephalopathy. An interval of less than 7 days is hyper-acute, 8-28 days is acute and 29 days to 12 weeks is sub-acute.

Etiology

In western world, most cases of ALF had been related to drug overdose, specifically paracetamol which has been much more prevalent in United Kingdom and United States but not in Spain and Germany. In under developed countries; the viral etiology of ALF has been most frequent and hepatitis A has been noted as a frequent cause of FHF in Pakistan. Hepatitis B related ALF has
also been reported and recovery is more likely in this case\(^6\). Hepatitis E has been found in epidemic form in various parts of Pakistan\(^9\) and phylogenetically distinct hepatitis E has been found in different epidemics in various parts of Pakistan at different times\(^3,10\). In Pakistan, hepatitis E has been noted to be endemic\(^11\) and high in-hospital mortality has not only been reported from Pakistan\(^2\) but also from Europe\(^3\). Mortality has been particularly high in case of pregnant women who develop hepatitis E\(^12,21\).

### Table 1: Distribution of causes of ALF in various parts of world.

<table>
<thead>
<tr>
<th>Study</th>
<th>ACM</th>
<th>HAV</th>
<th>HBV</th>
<th>Drug</th>
<th>Shock</th>
<th>Undetermined</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina 1996-2001</td>
<td>0</td>
<td>8</td>
<td>22</td>
<td>14</td>
<td>0</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Denmark 1973-1990</td>
<td>19</td>
<td>2</td>
<td>31</td>
<td>17</td>
<td>3</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>France 1972-1990</td>
<td>2</td>
<td>4</td>
<td>32</td>
<td>17</td>
<td>?</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>India 1987-1993</td>
<td>0</td>
<td>2</td>
<td>31</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>62</td>
</tr>
<tr>
<td>Japan 1992-1999</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>UK 1993-1994</td>
<td>73</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

ACM=acetaminophen

The delta hepatitis, associated with hepatitis B infection, leading to ALF has been reported from India\(^16\). The Indian studies have also noted viral etiology to be the commonest cause of ALF\(^7,18\). Apart from viral etiologies, other conditions leading to ALF include typhoid fever\(^17\), shock and other undetermined factors (Table-1).

### Clinical features

Large studies have reported a median interval of 6 days between the onset of illness and encephalopathy and a median interval of 2 days between the onset of jaundice and encephalopathy\(^20\). Symptoms generally lead to coma, while most cases also have elevated serum creatinine of 2 mg/dl or greater and acidosis on admission with pH of less than 7.30\(^1\). Nearly half the patients also have a culture positive infection\(^21\).

Patients who have ingested paracetamol, the onset of encephalopathy is generally quicker and has a median period of one day from the onset of jaundice to the onset of encephalopathy\(^1\). Median dose of paracetamol ingested has been 13.2 g/day and these patients are generally young women and have markedly elevated aminotransferase levels\(^1\).

Hepatic encephalopathy (HE) is a common neurological feature of ALF. Although its pathogenesis is multifactorial, it centers on failure of the liver to remove toxic, mainly nitrogenous, substances from the circulation. Blood ammonia levels increase but do not correlate with the depth of coma or the prognosis\(^1,22\).

These patients develop confusion, delusions, delirium, uncooperative behavior, drowsiness and fits before slipping into coma\(^21\).

Cerebral edema is another serious consequence of ALF in higher grades of HE and leads to increase in intracranial pressure and brainstem herniation which is the most common cause of death in these cases\(^1,20\). Cerebral edema occurs due to accumulation of osmolytes such as glutamine, particularly in astrocytes, with subsequent osmotic uptake of water in the cells, this being augmented by changes in cerebral blood flow and disruption of blood-brain barrier\(^23\). Features of systolic hypertension, increased muscle tone, myoclonus (decerebrate posturing), dysconjugate eye movements and loss of papillary reflexes ultimately lead to respiratory arrest from brainstem herniation.

### Diagnosis

Clinical presentations include jaundice, lethargy, confusion, disorientation and rapidly progressing encephalopathy, which may lead to coma. The laboratory studies generally show markedly deranged liver function tests, significantly prolonged prothrombin time, various metabolic, fluid, electrolyte and acid base abnormalities. The diagnostic workup of acute liver failure cases is shown in Table-2.

### Table 2: Possible work up for ALF patient.

<table>
<thead>
<tr>
<th><strong>Hematology</strong></th>
<th>Hemoglobin, WBC, platelets, PT, blood group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemistry</strong></td>
<td>LFT, glucose, creatinine, sodium, potassium, bicarbonate, chloride, calcium, phosphorus.</td>
</tr>
<tr>
<td><strong>Virology, microbiology</strong></td>
<td>Anti HAV, HBsAg, HBcore IgM, anti HCV, anti HDV, anti HEV, anti HGV</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td>Blood, urine, sputum and stool cultures</td>
</tr>
</tbody>
</table>

### Others

- Chest x-ray, ECG, ABG, FDP, drug levels

It is important to distinguish ALF from decompensated chronic liver disease, as ALF requires intensive and aggressive management due to chances of potential reversibility. Chronic liver disease has long history, hard liver, splenomegaly and other signs of chronic liver disease like spider angiomata. Serological markers often are available to make the diagnosis.

### Management

Patients with ALF need management in the intensive care unit. General measures include correction of fluid, electrolyte and acid base abnormalities. They should have intravenous fluid with supportive care and a nasogastric tube should be inserted for lavage or feeding. Nutritional support is given through enteral or parenteral route along with measures to improve the encephalopathy. Barrier nursing should be practiced. Administration of lactulose either as enema or by nasogastric tube to ensure...
3-4 loose stools per 24 hours help in the reduction of ammonium production\textsuperscript{22}. 

**Complications**

Various complications develop in acute liver failure patients that need critical and intensive care management. These include fluid, electrolyte acid-base disorder, coagulopathy, multi organ dysfunction, infection and cerebral edema (Table-3).

**Table 3: Complications of ALF and their management.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>Reduce protein by mouth, phosphate enema twice daily, no sedation, lactulose</td>
</tr>
<tr>
<td>Cerebral oedema</td>
<td>Intravenous mannitol, avoid hyperthermia, monitor ICP</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>100 ml 50% glucose if blood glucose falls below 3 mmol/l, infusion 10-15% dextrose, check hypokalemia</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>10% calcium gluconate i.v.</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Dopamine infusion, hemofiltration, hemodialysis</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>Intubation, ventilation, oxygen, maintain normal blood gases</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Albumin, fresh frozen plasma, vaso-constrictors</td>
</tr>
<tr>
<td>Infection</td>
<td>Frequent cultures, prophylactic antibiotics (see test), specific antibiotics later</td>
</tr>
<tr>
<td>Bleeding</td>
<td>No arterial puncture, PPI, H\textsubscript{2} block, sulcralfate, fresh frozen plasma and platelets</td>
</tr>
</tbody>
</table>

Management of cerebral edema is of prime importance for which mannitol infusion is recommended, however, the role of intravenous steroids has been questionable at best\textsuperscript{30}. Management of infection requires aggressive antibiotic therapy and is beneficial as nearly half of the patients have infection which is a major contributor to the deterioration of encephalopathy\textsuperscript{23}.

Treatment of cardiovascular, pulmonary and renal complications is of paramount importance and consistent intensive care is required (Table-3). Hemodialysis may be required in patients of renal failure. Gastric acid suppression is accomplished with H-2 receptor blockers or proton pump inhibitors\textsuperscript{26}. Paracetamol overdose should be treated with N-acetylcysteine administration. Transcatheter arterial steroid injection therapy (TASIT) via the hepatic artery to reduce hepatic macrophage activity in patients with severe acute hepatic failure has been tried with some success\textsuperscript{24}.

Transplantation has been used for treatment of ALF with great success\textsuperscript{25} in patients meeting certain criteria (Table-4). Use of live-related transplantation has been used in fulminant hepatic failure in many countries, especially in pediatric cases\textsuperscript{1,26}. Improvement in surgical technique, optimal timing and better post operative care are important in survival\textsuperscript{25}. Donor livers are hard to find and many patients die waiting for liver graft.

**Table 4: King’s college hospital criteria for liver transplantation in acute liver failure\textsuperscript{25}**

<table>
<thead>
<tr>
<th>Acetaminophen (paracetamol)</th>
<th>pH &lt; 7.30 (irrespective of grade of encephalopathy) or Prothrombin time &gt; 100s (INR &gt; 7) and serum creatinine &gt; 300 umol/l in patients with grade III or IV encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-acetaminophen patients</td>
<td>Prothrombin time &gt; 100s (INR &gt; 7) (irrespective of grade of encephalopathy) or Any three of the following variables (irrespective of grade of encephalopathy)</td>
</tr>
<tr>
<td>Age &lt; 10 or &gt; 40 years Aetiology: non-A-E hepatitis, 'viral' hepatitis no agent identified, halothane hepatitis, idiosyncratic drug reaction duration of jaundice before onset of encephalopathy &gt; 7 days prothrombin time &gt; 50s (INR &gt; 3.5) serum bilirubin &gt; 300 umol/l</td>
<td></td>
</tr>
</tbody>
</table>

**Auxiliary liver transplantation, hepatocyte transplantation and Bio-artificial Liver support measures, including albumin dialysis have been used with some success\textsuperscript{26,27}. Molecular Absorbent Recycling System (MARS) has been used as a "bridging procedure" for transplantation\textsuperscript{28} and survival is dependent on availability of transplant\textsuperscript{25}.

**Prognosis**

Patients with grade 3 or 4 encephalopathy have overall survival of 20% without transplantation\textsuperscript{1}. Patients with viral etiology have a better survival. Unfavorable clinical signs are small liver, ascites, prolonged prothrombin time, elevated creatinine, sepsis, hypoglycemia and decerebrate rigidity\textsuperscript{29,30}. Model for End Stage Liver Disease (MELD) score of > 30 predicts mortality in patients with acetaminophen toxicity\textsuperscript{31} and non-acetaminophen induced FHF\textsuperscript{31}. The Acute Liver Failure Early Dynamic (ALFED) model uses four variables including arterial ammonia, serum bilirubin, international normalised ratio and hepatic encephalopathy > grade II. This model was found to be superior to the King’s College Hospital criteria and the MELD score\textsuperscript{32}. Co-existance of other diseases worsens the prognosis. Cerebral edema, bleeding, infection, respiratory, circulatory and renal failure, hypoglycemia and pancreatitis are common causes of death. Survival depends considerably on optimal post operative care after transplant.
The future

Despite advances in our understanding, ALF remains a cause of significant mortality because of the absence of curative medical therapy. Hence, only emergency liver transplantation is reliably life-saving. There is an urgent need for better understanding of the pathogenesis of ALF caused by different causes, of genetic susceptibility, development of validated prognostic indicators. Management of this form of severe liver disease may be helped by the success of liver support devices\textsuperscript{33}, including application of stem cells\textsuperscript{34} which are under investigation at this time.

References