Management in Acute Liver Failure

Shalimar, Subrat K. Acharya

Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India

Acute liver failure (ALF) is a rare, potentially fatal complication of severe hepatic illness resulting from various causes. In a clinical setting, severe hepatic injury is usually recognised by the appearance of jaundice, encephalopathy and coagulopathy. The central and most important clinical event in ALF is occurrence of hepatic encephalopathy (HE) and cerebral edema which is responsible for most of the fatalities in this serious clinical syndrome. The pathogenesis of encephalopathy and cerebral edema in ALF is unique and multifactorial. Ammonia plays a central role in the pathogenesis. The role of newer ammonia lowering agents is still evolving. Liver transplant is the only effective therapy that has been identified to be of promise in those with poor prognostic factors, whereas in the others, aggressive intensive medical management has been documented to salvage a substantial proportion of patients. A small fraction of patients undergo liver transplant and the remaining are usually treated with medical therapy. Therefore, identification of the complications and causes of death in such patients, and use of appropriate prognostic models to identify those who need liver transplant and those who can be managed with medical treatment is a vital component of therapeutic strategy. In this review, we discuss the various pathogenetic mechanisms and treatment options available. (J Clin Exp Hepatol 2015;5:S104–S115)

Acute liver failure (ALF) can be a fatal complication of acute hepatic injury and occurs unpredictably. It is a rare clinical entity marked by the sudden loss of hepatic function and a severe life-threatening course in a person with no prior history of liver disease. ALF represents a syndrome rather than a specific disease, having multiple causes that vary in course and outcome. ALF is difficult to identify in its early stages, resulting in frequent delays in initiation of treatment. The causes of ALF include viral hepatitis, drug induced and toxin-induced liver damage, metabolic errors, ischemia, and miscellaneous rare causes.

Keywords: ammonia, cerebral edema, LOPA
Received: 24.7.2014; *Accepted:* 26.11.2014; *Available online:* 3.12.2014
Address for correspondence: Subrat K. Acharya, Department of Gastroenterology, All India Institute of Medical Sciences, New Delhi 110029, India.
E-mails: subratacharya@hotmail.com; subratacharya@gmail.com
Abbreviations: AASLD: American Association For the Study of Liver; ALF: Acute Liver Failure; ALFED: Acute Liver Failure Early Dynamic Model; BBB: Blood Brain Barrier; BCAA: Branched Chain Amino acid; CBF: Cerebral Blood Flow; CPP: Cerebral Perfusion Pressure; CVVHD: Continuous Veno-Venous Hemodialysis; FFP: Fresh Frozen Plasma; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; HE: Hepatic Encephalopathy; ICU: Intensive Care Unit; IEI: Icterus Encephalopathy Interval; INR: International Normalized Ratio; IL-1β: Interleukin-1 beta; IL6: Interlekin 6; LOLA: L-Ornithine L Aspartate; LOPA: L-Ornithine Phenyl Acetate; MAP: Mean Arterial Pressure; NAC: N-Acetyl Cysteine; NO: Nitric Oxide; OLT: Orthotopic Liver Transplantation; PCWP: Pulmonary Capillary Wedge Pressure; PEEP: Positive End Expiratory Pressure; PT: Prothrombin Time; SIMV: Synchronous Intermittent mandatory Ventilation; SIRS: Systemic Inflammatory Response Syndrome; SPEAR: Selective Parenteral and Enteral Antibiotic Regimen; TNF-α: Tumor Necrosis Factor alfa; UCD: Urea Cycle Disorder; USALF: United States Acute liver Failure Study Group
http://dx.doi.org/10.1016/j.jceh.2014.11.005

ALF is defined by three criteria: (1) rapid development of hepatocellular dysfunction (jaundice, coagulopathy), (2) encephalopathy, and (3) absence of a prior history of liver disease.[1] However, the interval between onset of acute hepatic injury (jaundice) and onset of liver failure (encephalopathy with or without coagulopathy) in such patients (icterus-encephalopathy interval; IEI) has been described to be between 4 weeks (Indian definition)[2–4] to 24 weeks (AASLD–ALF study group).[5] Further, due to the diverse natural course, ALF has been sub-classified as hyperacute (IEI $\leq$ 7 day), acute (IEI $\leq$ 4 weeks) and sub-acute ALF (IEI $\geq$ 5 week to $\leq$12 weeks) by British authors.[6] Despite these differences in definitions, the central and most important clinical event in ALF is occurrence of hepatic encephalopathy (HE) and cerebral edema which is responsible for most of the fatalities in this serious clinical syndrome. The pathogenesis of encephalopathy and cerebral edema in ALF is unique and multifactorial, and evaluation of these pathogenetic processes provides insight into its effective treatment strategy. Additionally, infection and coagulopathy have been identified to ensue rapidly in these patients - which also determines outcome with resultant management challenge.[7]

COMPLICATIONS AND CAUSES OF DEATH IN ACUTE LIVER FAILURE

The major complications in ALF usually associated with death include cerebral edema, seizures, infections, bleeding due to coagulopathy and renal failure. These events infrequently get further aggravated by electrolyte and acid base imbalance and hypoglycaemia. The complications of ALF vary by region and by etiology.

Cerebral edema has been documented to be the most common cause of mortality. In India 58% of ALF patients have cerebral edema at the time of hospitalization. The mortality rate of patients with cerebral edema has been reported as 82%, compared to 44% among patients without cerebral edema.[2] Older studies from the UK reported that overt features of cerebral edema increase in frequency with increasing grades of HE. However, with advent of intracranial pressure estimation, it is now clear that most patients with ALF at the time of hospitalization have some degree of cerebral edema and need careful monitoring.[8] Recent data suggest that cerebral edema is less frequent now than in former years, but this may reflect earlier admission to hospital and better intensive care unit care.[9]

Infection is a common complication in ALF that has been documented across the globe.[10] An incidence of infection has been reported as high as 90% has been reported in the initial series from UK; the causative organisms being bacteria in 80% of cases and fungal infections in 32%.[10] The predominant organisms are Gram-positive bacteria and the most common site of infection is respiratory tract. In more recent reports, the predominant organisms reported are Gram-negative.[10,11]

Renal failure has been described in 40%–80% of patients in western series, and is associated with a poor prognosis. It occurs more frequently in acetaminophen induced ALF (70%) and less frequently in ALF due to other causes (30%) in western series, suggesting that there may be a toxic effect of acetaminophen on renal tubules.[10] Renal failure is reported in 10% of patients from India.[12]

Gastrointestinal bleeding is reported in 7–20%.[2,8] However gastrointestinal bleed has rarely been implicated as the cause of death and usually occurs as a terminal event associated with other complications.

These complications may occur at presentation, or may develop subsequently. They may occur in isolation or in combinations. Management of each complication is important as it influences the ultimate outcome. Encephalopathy and cerebral edema are common presenting features over which other complications like infections, renal failure and gastrointestinal bleed may supervene, perpetuating the brain edema and consequent death. Therefore it is important to understand the pathophysiologic drivers of encephalopathy. Intervention at the level of these pathogenetic mechanisms, along with specific therapy of complications, forms the mainstay of medical management of ALF.

PATHOGENETIC DRIVERS

The underlying pathogenesis of encephalopathy, consequent cerebral edema and raised intracranial hypertension (ICT) in ALF is complex and has been extensively studied. Ammonia has been implicated as the major neurotoxin in ALF.[13] In addition, Systemic Inflammatory Response Syndrome (SIRS) and loss of autoregulation of cerebral blood flow have been implicated as other important pathogenetic events in accentuating encephalopathy and cerebral edema in ALF.[14]

Role of Ammonia

In animal models as well as in patients with ALF, marked swelling of astrocytes has been documented. In animal models of ALF, expression of various astrocytic proteins has been reported.[13] Astrocytes are specialized neuroglial cells, initially considered as passive supporters of the neuronal framework, which are now recognized to play crucial roles in brain metabolism, maintaining the blood brain barrier, modulating synaptic transmission, and neural inflammation. Changes in astrocytes are documented to be due to hyperammonemia in ALF. Astrocyte swelling due to increased brain water and alteration in the functional property of the astrocyte causes encephalopathy and cerebral edema resulting in intracranial hypertension, which often results in brain herniation, the most important mechanism of death in ALF.[15] The source of circulating ammonia is primarily derived from glutamine metabolism in the intestinal epithelium.[7] Intestinal epithelium undergoes rapid turnover and uses glutamine as a source of energy. Intestinal epithelium contains glutaminase as well as glutamine synthase, and glutaminase converts glutamine to glutamate and ammonia. Some amount of ammonia is also generated by the urease activity of gut flora and renal production (kidney also contains glutaminase and glutamine synthase).[9] The circulating ammonia to some extent is excreted by the kidney, used by the muscles to re-synthesise glutamine (muscle also has glutamine synthase and glutaminase), but predominantly is converted to urea (Kreb's urea cycle present in periportal hepatocytes) as well as glutamine (by glutamine synthase present in perivenous hepatocytes) in the liver. Brain also contains glutamine synthase as well as glutaminase. Therefore, brain can synthesise glutamine from ammonia as well as metabolise glutamine to glutamate and ammonia.[16] Thus, ammonia is predominantly metabolized in the liver and is converted to urea and glutamine. The enzymes for a complete urea cycle are exclusively localized in the liver. Urea is water soluble and is excreted in urine which is the major pathway for ammonia disposal. Thus, the ability of liver to metabolise ammonia is grossly compromised in ALF resulting in hyperammonemic state, which exerts deleterious effects contributing to HE.[16]

The neurotoxic effect of ammonia in ALF

1. Alteration in Cell (Astrocyte) volume regulation
2. Alteration in cerebral energy homeostasis
3. Alteration in astrocytic and neuronal protein expression effecting its structure and functions
4. Oxidative and nitrosative stress