# Acute Liver Failure: Review

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**Summary**

Acute liver failure (ALF) is defined as the development of impaired hepatic synthetic function with coagulopathy and the development of hepatic encephalopathy in the absence of underlying liver disease in less than 2 to 3 month time.[1] In the setting of ALF, hepatic encephalopathy may be associated with life-threatening cerebral edema, whereas by contrast this association is absent in patients who have chronic liver failure with encephalopathy. The recovery from the loss of functional liver mass in acute liver injury occurs more readily than in the chronic setting because of the lack of long-standing fibrosis and portal hypertension, and the host's overall better nutritional status. Therefore, if the individual can be supported properly throughout the acute event, and the inciting injury is removed or ameliorated, recovery will follow the rapid regeneration of liver cells. For those in whom spontaneous recovery is not possible, liver transplant may be life-saving. In this review, we outline the causes and clinical manifestations of acute liver failure and discuss current approaches to patient care.

***Abbreviation:*** *ALF- Acute Liver Failure*

***Key words:*** *Acute liver failure, fulminant hepatic failure, cerebral edema, coagulation abnormalities*

## ETIOLOGY AND PATHOGENESIS

Acetaminophen hepatotoxicity was recognized early to be an important cause of fulminant hepatic failure[2] and remains the most common cause. Acetaminophen is metabolized by the cytochrome P450 system with production of an unstable reactive metabolite N-acetyl P-benzoquinoneimine (NAPQI) which is rapidly inactivated by conjugation with glutathione. In over dosage, as glutathione stores are depleted accumulation of the active metabolite causes cell damage. This cell damage can be prevented by sulphydryl donors such as cysteamine, methionine and NAPQI. Fewer patients progressed to grade 4 encephalopathy and the mortality was lower in those cases receiving late N-acetylcysteine (NAC) administration compared with other cases presenting at a similar time after the overdose and with similar prolongation of the prothrombin time.[3]More recently preliminary analysis of a randomized clinical trial of late NAC administration has also shown a lower mortality in the treated cases. Improvements in survival with the later use of NAC, when most of the acetaminophen has been cleared, probably results from mechanisms unconnected with the direct binding of NAC to the reactive metabolite.

Viral hepatitis is the most common cause of fulminant hepatic failure worldwide with fulminant hepatitis B virus the most prevalent variety in many areas. A fulminant course is more common in the presence of co infection of hepatitis D with hepatitis B virus, but may also be related to an enhanced antibody response to the virus. Compared with cases of uncomplicated acute viral hepatitis, those with a fulminant course have a higher anti-HBc titer and more rapid clearance of HBsAg from serum which may lead to antigen-antibody complex deposition in hepatic sinusoids and ischemic necrosis of hepatocytes. Pathogenetic mechanisms of fulminant hepatitis A and E are unknown but significant differences occur in the clinical course and complication rates between the three types. Thus fulminant viral hepatitis A has a shorter duration before the onset of encephalopathy, a lower peak prothrombin time and cerebral edema is less common compared with presumed E where the patients tend to be older, with a slower onset of encephalopathy and a worse mortality.

Idiosyncratic drug reactions are an important cause of fulminant hepatic failure and have been recorded after a wide range of drugs including isoniazid, non-steroidal anti-inflammatory drugs, monoamine oxidase inhibitors, valproate and ketoconazole, but the most common occurring in up to 5% of all cases referred to the Liver Failure Unit follows halothane anesthesia. Liver failure may develop up to 21 days after halothane exposure often in obese women with a history of atopy and previous minor pyrexial reactions to anesthetics.[5]

**COAGULATION ABNORMALITIES**

Studies on the severe abnormalities in coagulation in relation to bleeding stem from the often referred to seminal work of Rake et al on intravascular coagulation in liver failure.[6] Increased susceptibility to bleeding in acute liver failure results from both consumption and lack of synthesis of clotting factors and their inhibitors, as well as a low platelet count. Originally a number of trials to replace depleted clotting factors using fresh frozen plasma and factor IX concentrates to reduce bleeding and heparin to stop intravascular coagulation were carried out by Clark, Gazzard and others with little overall success. Further studies were stimulated as a result of the problems with biocompatibility of artificial liver support. In these Weston et al investigated platelet function and found that platelet aggregation to classical stimuli was impaired and platelet ultra structure was abnormal. Platelet stickiness was found to be increased consistent with activated platelets remaining in the circulation because of lack of clearance by the damaged liver. Factor VIII is involved in platelet adhesion to foreign surfaces and is the only clotting factor found at increased concentrations in fulminant hepatic failure, probably as it originates from vascular endothelial cells. All three components of factor VIII were found by Langley et a/[7] to be at concentrations over three times normal in liver failure, suggesting involvement of factor VIII in the platelet reactions. Difficulties of anticoagulation during extracorporeal circulation in these patients led Sette et al to study heparin clearance and response in liver failure and it was found that there was more rapid elimination of heparin and increased heparin sensitivity which helps explain the basis of this problem. Further confirmation of on-going activation of the coagulation and platelet systems was obtained when highly sensitive assays became available; fibrinopeptide A for thrombin action, fibrinopeptide B 1-42 for plasmin action, thromboglobulin and platelet factor 4 for platelet activation. Plasma levels of all these were higher than normal, but not to the degree seen in true disseminated intravascular coagulation.[8]

Recent studies by Langley et al have concentrated on the role of coagulation inhibitors in the consumptive coagulopathy of liver failure. Anti- thrombin III, is the major inhibitor of coagula- tion and was found to occur at very low levels in patients with acute liver failure. As antithrombin III is a heparin cofactor, it was evaluated supplementation during haemodialysis in liver failure. Antithrombin III levels were normalized, less heparin was administered and losses of platelets were significantly reduced. In the other trial, the effect of anti-thrombin III supplement- ation was assessed in patients with septic shock associated with liver failure. The rationale for this being that intravascular coagulation is most severe in this group of patients and could underlie multiple organ failure. Despite correction of anti-thrombin III levels the high mortality in this group was not improved and it was considered that earlier therapy might have been more successful. Protein C is a potent inhibitor of factor V and VIII and as with other clotting factors was found at low levels in fulminant hepatic failure, suggesting that supplementation might be worthy of study.

The relationship between infection and the coagulation derangement was investigated further from the plasma levels of leucocyte elastase measured by the presence of elastase a1-antitrypsin complexes. Greater release of elastase was found in liver failure patients who had bacterial infection and this correlated with reduced plasma fibrinogen and increased thrombin-antithrombin complexes another sensitive marker of thrombin formation. Thus it is likely that infection with the associated cytokine release is interrelated with activation of the coagulation system.

**ARTIFICIAL LIVER SUPPORT**

Early attempts at liver support at King's included exchange transfusion and pig liver perfusion, which were impractical to perform on a regular basis. The concept of artificial liver support based on haemoperfusion through adsorbents to remove the wide range of toxins accumulating in the circulation is still attractive. Experimental work by Wilson, Dunlop and others led to the clinical use of charcoal haemoperfusion, as pioneered by TMS Chang in Canada. A column of polymer-coated activated charcoal to remove water soluble toxins was developed in association with Smith and Nephew Research. The exciting results in the first patients were reported in the Lancet by Gazzard et al,[9] with 10 of the 22 patients in grade IV encephalopathy treated surviving. Further patients had severe hypotensive episodes, however, which were shown by Weston et al to be related to the formation of platelet aggregates in the extracorporeal circuit. Alternative means of patient treatment were needed and hence the use of polyacrylonitrile dialysis with a high per- meability membrane. After laboratory studies on agents to inhibit the platelet reactions; charcoal haemoperfusion with prostacyclin (PGl2) was started in 1980. Subsequently Gimson et al [10] reported results in 76 patients, with a survival rate of up to 65% in patients treated early, when still in grade III coma. There had been considerable debate about the question of performing a clinical trial of charcoal haemoperfusion over the years; original plans were shelved due to the problems of blood compatibility. This was finally resolved when two clinical trials were performed, five hours versus 10 hours haemoperfusion in patients with grade III and 10hours haemoperfusion versus intensive care alone in patients with grade IV encephalopathy. No significant differences were found in these two groups

in 137 patients entered. Overall survival was good and was related to etiology, being best in acetaminophen overdose and viral hepatitis A and B and worst E hepatitis and adverse reactions to drugs." It was considered that these results were the result of the improving background of intensive care management which masked any earlier benefits of charcoal haemoperfusion.

A number of laboratory studies on the toxins accumulating in liver failure were carried out at the same time as the haemoperfusion work. Fulminant hepatic failure serum was shown to contain substances inhibitory to membrane sodium transport both in leucocytes by Alam and Poston [12,13] and in brain by Seda et al.[14] Membrane ultra filtration (<10 kD) followed by column chromatography on Sephadex G-25 produced four fractions which contained the inhibitory activity. Resin and charcoal haemoperfusion were shown to be complementary in removing these Na+,K+-ATPase inhibitors. Subsequently some of the peaks were shown to cross-react with antibodies to digoxin, an inhibitor of Na+, K•-ATPase, making this radioimmuno-assay useful for monitoring toxin removal in artificial liver support.[15]

**CEREBRAL EDEMA**

The mechanisms involved in the development of hepatic encephalopathy and the associated cerebral edema in acute liver failure remain ill defined. Cerebral edema remains the most common cause of death in fulminant hepatic failure as originally reported from the Unit,[16] although there has been considerable progress in its management. The importance of this complication was first shown in post mortem studies and in an animal model of liver failure, but in 1980 Hanid et al reported the first use of an intracranial pressure monitor in patients with fulminant hepatic failure. Dramatic rises in intracranial pressure were observed, often spontaneous but occasionally precipitated by external events, which importantly preceded clinical evidence of cerebral edema (opisthotonus, pupillary abnormalities, respiratory arrest).

Rises in intracranial pressure occur in up to 80% of cases of fulminant hepatic failure and management rests on maximizing cerebral perfusion pressure and cerebral blood flow, both of which tend to fall as intracranial pressure rises. The patient is nursed flat with minimal stimulation, pC02 maintained at 3·5-4 kPa and core temperature normalized. Attempts to prevent the development of cerebral edema with dexamethasone as used in head injury were unsuccessful. In a large controlled clinical trial Canalese et al [11] showed that cases that did not develop cerebral edema had a 60% survival whereas in those in whom it did develop and who did not receive mannitol survival was 10%. Mannitol therapy was highly effective in reducing a raised intracranial pressure and signific- antly improved survival. This was the first randomized trial in fulminant hepatic failure to show an improved survival with a defined treatment modality and represented an important advance.

Current studies are attempting to investigate the relationship between intracranial pressure, mean arterial pressure, cerebral perfusion pressure and cerebral blood flow as well as less invasive methods to monitor cerebral blood flow. Jugular bulb cannulation with continuous measurement of venous oxygen saturation shows encouraging results as a continuous index of cerebral blood flow.

Parallel laboratory studies were performed to investigate the possible mechanisms involved in the development of cerebral edema. Changes in blood-brain barrier permeability could allow solutes into brain which would give rise to increased water content. Zaki et al [18] showed an increase in blood-brain barrier transport in a rat model of liver failure. Later, ultra structural studies showed that the tight junctions in the cerebral capillaries were intact indicating that the breakdown of the blood-brain barrier was functional rather than structural suggesting vasogenic mechanisms of edema formation are less important. Inhibition of membrane transport would be consistent with a cytotoxic mechanism of cerebral edema. Inhibition of Na+, K+-ATPase activity, a key enzyme of sodium transport, and increased brain water content were found in experiments using the galactosamine rat model of liver failure,[19]although dehydration of the animals limited the degree of edema.

**HOST DEFENSE AND SEPSIS**

It has long been recognized that a significant proportion of the mortality from fulminant hepatic failure can be attributed to the high incidence of sepsis that is so frequently seen. Investigation and documentation of this increased susceptibility to infection has been a topic of much research at the Liver Unit over the years. Studies by Wyke et al showed defective opsonisation of E coli and yeasts by serum of patients with fulminant hepatic failure, the etiology for this defect was ascribed to complement deficiency with components of both the classical and alternative pathways being reduced to below 40% of that found in control serum. Neutrophil adherence was also noted to be significantly impaired by Altin et al and this impaired adherence along with complement deficiency and depressed opsonisation result in an overall significant impairment in host defences against infection. Both the plasma level of fibronectin, an important component of the reticuloendothelial system and in vitro plasma opsonisation activity were found by Imawari et al to be significantly depressed in patients with fulminant hepatic failure and the level of fibronectin correlated with the degree of impairment of opsonisation activity. Significant impairment of Kupffer cell function was elegantly demonstrated by Canalese et al in

patients with fulminant hepatic failure using clearance of micro aggregated albumin.[20] Impaired Kupffer cell function was associated with encephalopathy and a significant improvement in function at 48 hours was seen in those patients who survived. By contrast hepatocyte dysfunction was equally impaired in patients with acute hepatic necrosis with and without encephalopathy, highlighting the possible importance of the relationship between Kupffer cells and hepatocytes in the etiology of encephalopathy. Fibronectin replacement in patients with fulminant hepatic failure was studied by Hughes et al, this resulted in an increase in in vitro plasma opsonisation activity, however, clearance of micro aggregated albumin remained unchanged as did oxygen consumption, suggesting that other factors are responsible. The incidence of infection in patients with fulminant hepatic failure has recently been reported by Rolando et al,[21] showing a 80% infection rate in patients with fulminant hepatic failure, of great interest was the finding that infecting organisms were gram positive in 50% of cases and were nosocomial in nature. Further work by Rolando et al has also indicated a surprisingly high incidence of fungal infection in fulminant hepatic failure, occurring in 30% of patients.

**HEMODYNAMIC**

The hemodynamic and cardiovascular disturbances of fulminant hepatic failure have long been an interest of the Liver Unit. Weston et al described a frequent incidence of cardiac dysrythmias and electrocardiographic abnormalities in patients with fulminant hepatic failure, malignant arrhythmias being more frequent in patients with hypoxia, acidosis and hyperkalaemia. Macroscopic cardiac abnormalities were found in 64% of patients at necropsy, these comprising scattered peticheal hemorrhages, pericardia effusions and fatty pale ventricles. The pathophysiology of the hypotension seen in fulminant hepatic failure was first investigated by Trewby et al. In this paper it was shown that the hypotension of fulminant hepatic failure was related to peripheral vasodilatation rather than primary myocardial failure, and that volume loading frequently resulted in an increase in cardiac output and a resultant increase in mean arterial pressure. Trewby et al also noted the presence of low pressure pulmonary edema in fulminant hepatic failure, this finding being frequently associated with the presence of severe cerebral edema raising the possibility of neurogenic pulmonary edema in patients with fulminant hepatic failure. Work by Bihari and Gimson resulted in detailed study and further investigation of the hemodynamic pathophysiology of fulminant hepatic failure, with the identification of pathological supply dependency for oxygen in such patients. Significant differences between survivors and non-survivors was noted, with lower systemic vascular resistance indices, oxygen extraction ratio and higher blood lactates in non-surviving patients.[22] Only in survivors was the in vivo P50 related to the oxygen extraction ratio. In addition it was noted that mixed venous lactate correlated with systemic vascular resistance index, mean arterial pressure and oxygen extraction ratio.[23]These data suggest that in patients with fulminant hepatic failure there is a disturbance of the microcirculation resulting in a tissue oxygen debt that is greater in patients that fail to survive. The use of prostacyclin, a microcirculatory vasodilator in such patients results in an increase in oxygen uptake, with the possibility of lessening or reversing the covert tissue oxygen debt. More recently the effects of vasopressin agents have been studied. Although these agents improve mean arterial pressure they have a detrimental effect on peripheral oxygen extraction ratio and oxygen consumption result-ing in tissue hypoxia and this effect on peripheral oxygen uptake can be reversed by the use of prostacyclin in addition to vasopressin agents. The etiological events that result in a tissue oxygen debt in patients with fulminant hepatic failure are poorly understood but relate to the development of interstitial edema, white cell and platelet plugs and functional arteriovenous shunts. Cytokines are almost certainly important mediators resulting in these microcirculatory changes. Recent work by Sheron et al has shown raised levels of cytokines in fulminant hepatic failure with interleukin-6 (a marker of endothelial activation) correlating with hypotension, cerebral edema, systemic vascular resistance index, oxygen extraction ratio, oxygen consumption and pH.

**HEPATIC REGENERATION**

Liver regeneration is ultimately responsible for survival in liver failure, but the processes involved are only recently beginning to become elucidated at the molecular level. This was confirmed in in vivo experiments in partially hepatectomised rats by Yamada et al.[15] Injection of fulminant hepatic failure serum at the time of maximal DNA synthesis inhibited the incorporation of 3H- thymidine into hepatic DNA. These effects were greater with sera from patients with fulminant hepatic failure because of hepatitis and adverse reactions to drugs compared with patients with fulminant hepatic failure caused by acetaminophen overdose and hepatitis A and B. The inhibitory activity was associated with a less than 10kD fraction of serum and this could be further resolved into two fractions by gel chromatography corresponding to approximate molecular weights of 2 kD and 5 kD.

The isolation and purification of a highly potent human hepatocyte growth factor (hHGF) was recently reported by workers from Japan.[26] High concentrations of this factor were found in sera of patients with fulminant hepatic failure, particularly in those who died. This suggests that the poor liver regeneration in certain groups of

patients is not caused by lack of this stimulatory factor. In which case identification of the inhibitory factors found at King's is of even greater importance.

**RECOMMENDATIONS FOR TREATMENT**

The previous sections have given a selected overview of the main areas of therapeutic study and have led to certain generalizations about overall treatment strategies for fulminant hepatic failure. All patients with grade 3 or 4 hepatic encephalopathy should receive dextrose infusion and Hz-receptor blockers as originally described by the late Brian Macdougall. Intermittant positive pressure ventilation to maintain PaC02 at 4-4·5 kPa should be started and the patient nursed with 10° head up position. Mannitol, 20% solution, should be given for episodes of cerebral edema detected either by clinical criteria or intracranial pressure monitoring and supplemented by haemofiltration if renal failure is present. Machine driven dialysis should be avoided and continuous arteriovenous haemofiltration is the preferred renal replacement therapy. Close microbiological surveillance will reveal septic episodes and dictate the appropriate antibiotic policy. Finally, in those cases in whom the prognostic criteria indicate a survival of less than 10%, orthotopic liver transplantation remains the best chance of prolonged survival.

**THE FUTURE**

The mechanisms of hepatocellular necrosis and attempts to prevent this process will be of prime importance. Preliminary studies from Toronto on the use of PGE 1 infusion as a hepatoprotective agent have been encouraging start to this approach, but await formal trials. When events at the sinusoidal level and cellular level which lead to cell death are better understood, more rational treatment strategies could then be developed.

The concept of circulating toxins that are not cleared by the failing liver and are responsible for the end organ damage of fulminant hepatic failure has a long history. Nevertheless, recent anecdotal reports of significant improvements in intracranial pressure and hemodynamic in patients with fulminant hepatic failure in whom the liver is removed some hours before orthotopic liver transplantation have raised the possibility that the necrotic liver itself is releasing toxic substances with systemic effects on organ function and microcirculatory blood flow. Identification of these substances and attempts to remove them by extracorporeal devices or by neutralization with monoclonal antibodies will be of key importance, as well as earlier removal of the necrotic liver in patients selected for liver transplantation.

Because of the high frequency of clinically significant bacterial and fungal sepsis during fulminant hepatic failure the possibility of prophylactic treatment has been raised. Systemic parenteral and enteral decontamination regimes have been shown to be of use in critically ill patients in intensive care units. A trial is currently in progress to assess the benefit and side effects of prophylactic parenteral and enteral decontamination.

The future investigation of the haemodynamics of fulminant hepatic failure requires elucidation and investigation of agents involved in the control of the microcirculation, such as the endothelins, endothelium-derived relaxant factor, thromboxanes and prostacyclin. Improved understanding of the role of these agents and their interaction with tumor necrosis factor and the interleukins will allow greater manipulation of the microcirculation. Compounds to promote nutritive microcirculatory flow could be administered and detrimental agents removed with appropriate monoclonal antibodies. Such a strategy would limit tissue hypoxia and hence the multiple organ damage that is so frequently seen in fulminant hepatic failure and results in such an increase in mortality.

In recent years there has been much study of the mechanisms of control and initiation of liver cell regeneration. Identification of hepatic stimulatory substances and inhibitors of regeneration and investigation of the ability of the surviving hepatocytes to respond to these stimuli will all yield important results.

Hepatocyte transplantation and heterotopic liver transplantation to tide the patient over a period of severe hepatocellular dysfunction, with the patient retaining their own liver, is also another promising area for future investigation.

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