The Management of Fulminant Hepatic Failure

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**Introduction**

Fulminant hepatic failure (FHF) is a true medical emergency. It is a clinical syndrome characterized by the appearance of sudden marked impairment of liver cell function with hepatic encephalopathy, resulting from acute necrosis or dysfunction of a large portion of liver parenchyma. It is uncommon, but not rare. An estimated 2000 to 2500 deaths per year in the United States are due to FHF. Even with supportive medical care, the mortality rate ranges from 50% to 90%, primarily because of associated cerebral edema, sepsis, and multiorgan failure[1,2,3].

The most frequently recognized causes of FHF are viral hepatitis and hepatic injury due to therapeutic drugs or other hepatotoxic chemicals[2]. Many cases are of unknown or indeterminate etiology. This group may include FHF due to hepatitis B virus mutants[4], hepatitis non-A, non-B, and non-C, or medications and toxins that are not tested for because they are thought to be insignificant. To date, there is no strong evidence of hepatitis C as a cause of FHF[5].

The causes of FHF vary geographically. For example, in the United Kingdom acetaminophen is the primary cause of FHF, while in the United States FHF is largely due to indeterminate causes[6,7,8].

The term fulminant hepatic failure applies to patients who develop hepatic encephalopathy within eight weeks of the onset of illness or jaundice. Subfulminant hepatic failure designates those patients who develop the disease after this time[9]. A two week interval is also used to distinguish between fulminant and subfulminant groups[10]. This distinction is important in terms of assessing etiology, management and prognosis.
Management of FHF

There are multiple goals in the management of FHF. First, it is important to correctly diagnose the condition and distinguish it from diseases with similar presentations, such as drug overdoses and Gram negative sepsis. The initial symptoms of FHF are nonspecific. The disease usually presents with nausea and vomiting, followed by jaundice and the rapid onset of an altered mental status. Other indices of hepatic failure include a prolonged prothrombin time, elevated transaminases and bilirubins, hypoglycemia, and a respiratory alkalosis. Second, it is important to identify the causes of FHF because this has implications for prognosis, therapy, and prevention.

The third goal in the management of FHF is to provide adequate supportive care to the failing liver, as well as to prevent and treat extrahepatic complications of the disease. Finally, it is important to identify prognostic features that portend a poor outcome and indicate the need to proceed to urgent orthoptic liver transplant (OLT).

Patients with FHF should be admitted to a medical intensive care unit, preferably at an institution capable of performing liver transplantation, as this may offer the only cure for certain patients with FHF. If transfer is necessary, it should be performed as quickly and safely as possible to avoid exacerbating cerebral edema.

A team of hepatologists, critical care specialists, anesthesiologists, liver transplant surgeons, and transplant coordinators should assess the patient's medical and neurological status and determine the patient's need for urgent OLT. Every attempt to identify a causative agent should be made. If possible, the agent should be removed, and the patient should be treated appropriately.

Intensive medical and neurological monitoring, including the use of intracranial pressure monitors, and arterial and Swan-Ganz catheters, is essential to a good outcome. If stage 3 or stage 4 hepatic encephalopathy develops, the patient should undergo endotracheal intubation for airway protection and mechanical ventilation.

Blood glucose and electrolyte levels, arterial blood gases, hepatitis A, B, and delta serologies, ceruloplasmin, copper and acetaminophen levels are important for initial diagnosis and management. In addition, bilirubin levels, arterial pH, prothrombin time, and factor V levels are important for prognosis and evaluation for OLT. If there is no obvious contraindication to OLT[3], the patient is placed on a transplant list. If the patient's medical or neurological condition worsens, he or she is advanced on the transplant list.

Neurological Complications of FHF - Hepatic Encephalopathy and
Cerebral Edema

Hepatic encephalopathy and cerebral edema represent two different neurological complications of acute liver failure. Although both conditions can present with similar symptoms -- altered mental status and decorticate and decerebrate posturing -- they each have different natural histories and management goals. Careful observation is necessary to detect the onset and progression of hepatic encephalopathy. Hypoxemia, hypoglycemia, sepsis, hypokalemia, and gastrointestinal bleeding exacerbate hepatic encephalopathy and should be identified and treated. A trial of oral or rectal lactulose can help reduce high levels of ammonia, although these medications are not as effective in FHF as they are in the treatment of hepatic encephalopathy associated with chronic liver disease.

Benzodiazepine receptor antagonists, such as flumazenil, have been reported to temporarily improve hepatic encephalopathy[11]. Sedatives should be avoided except for those drugs needed for intubation and management of severe psychomotor agitation. Such agitation, which may worsen intracranial pressure (ICP), can be treated with short acting benzodiazepines like midazolam and lorazepam.

Cerebral edema is the leading cause of death in patients with FHF. It occurs in 75% of patients with stage 4 hepatic encephalopathy[12,13]. Cerebral edema and hepatic encephalopathy may present simultaneously -- making it difficult to distinguish between these two diseases. Traditional signs of increased ICP such as hypertension, bradycardia, increased muscle tone leading to decorticate rigidity and posturing, abnormal pupillary reflexes and brainstem respiratory patterns, are unreliable in FHF[14]. Head CT is also an unreliable way to diagnose and follow ICP in FHF. However, it is indicated to exclude structural lesions including intracerebral hemorrhage, as well as for ICP monitor placement[15].

Intracranial Pressure Monitoring and FHF

Direct monitoring of ICP helps to diagnose and manage cerebral edema in FHF[16]. Most centers install intracranial monitors at the onset of stage 4 coma or rapidly progressing stage 3 coma. Epidural transducers are safer to place than subdural and parenchymal transducers, although they are less sensitive[17]. Prior to ICP monitor placement, the prothrombin time should be corrected to within five seconds of normal limits. ICP monitor placement must also be checked with a CT scan.

ICP monitoring offers many advantages. It allows for rapid and appropriate therapy of cerebral edema, and allows physicians to avoid and correct factors that can temporarily elevate the ICP[3,18].
monitoring also assists in the management of intracranial pressure during surgery. The ICP should be maintained at less than 20 mmHg. Sustained elevations of ICP greater than 40 mmHg are strongly associated with poor neurological recovery even after OLT[19]. Cerebral perfusion pressure (CPP), which is the mean arterial blood pressure minus the ICP, should be maintained above 50 mmHg in order to avoid cerebral ischemia.

The sequential management of intracranial hypertension includes correction of factors that increase ICP such as fever, hypoxemia, hypercapnia, arterial hypertension, and psychomotor agitation. Elevating the head to 20 degrees may be helpful[20]. Prophylactic hyperventilation will not prevent an increase in ICP[21]. However, once cerebral edema is present, even a moderate reduction in pCO2 to 25 to 30 mmHg is helpful in decreasing the ICP. Excessive hyperventilation may lead to cerebral vasoconstriction and actually produce ischemia.

An intravenous mannitol bolus may be of benefit when there are sustained elevations in ICP. Usually this is between 25mmHg and 60 mmHg. Mannitol is also helpful when the serum osmolarity is less than 310 mosm / L. Mannitol may be used several times to treat repeated surges in ICP[22].

Hyperventilation and mannitol often fail to control the intracranial hypertension. The next step is to use an intravenous infusion of barbiturates. The goal is to place the patient in a barbiturate coma[23]. Because of the loss of thermoregulatory, pupillary, and other brainstem reflexes in deep barbiturate coma, the patient should never be declared brain dead when under this medication.

A CPP of less than 40 mmHg for more than two hours is considered a contraindication to urgent OLT. However, a cerebral perfusion scan should be performed before this decision is made. Under certain circumstances, many patients with FHF and resistant intracranial hypertension, may survive and recover with OLT.

**Infections and FHF**

Infection is a common early complication of FHF, and a significant cause of death in these patients[24]. Management is aimed at prevention and prompt treatment of infection. Frequent examinations for skin abscesses, sinusitis, dental infections, peritonitis, and meningitis, as well as strict aseptic nursing techniques with regular intravenous catheter changes, are required. Daily surveillance blood, urine, sputum, and catheter cultures are especially important during the first week. Regular chest radiographs are also necessary. Because
infections can strike early in the course of FHF, and because they have a high associated mortality, there should be a low threshold for beginning empirical broad spectrum antibiotics. There is growing evidence that the use of prophylactic antibiotics leads to a decrease in bacterial infections, fewer deaths, and shortened hospital stays[25]. Prophylactic antibiotics may also increase the number of successful OLTs[26]. Catheterized patients receiving parenteral nutrition are at a high risk of fungal superinfection, and early treatment of fungal infection is also mandatory.

Coagulopathy and FHF

The coagulopathy of FHF is often complicated by thrombocytopenia due to bone marrow suppression[27] and low grade DIC[28]. The coagulopathy may be silent or present as a spontaneous and fatal intracranial bleed. The prothrombin time, and factor V and VII levels, are all reliable indicators of hepatic synthetic function [6,29]. Correction of the coagulopathy is essential before any invasive procedure can be performed. Vitamin K is administered to ensure adequate stores. Fresh frozen plasma transfusions may effectively correct mild to moderate coagulopathy. Exchange plasmapheresis rapidly and effectively corrects severe coagulopathy.

When coagulopathy coexists with DIC, it is often difficult to interpret the coagulation tests. It is best to avoid heparin, and instead use epsilon-aminocaproic acid or cryoprecipitate transfusions.

Respiratory Complications of FHF

There are many respiratory problems which can complicate FHF. These include respiratory depression, hypoventilation, aspiration, pneumonia, ARDS, intrapulmonary hemorrhage, and intrapulmonary shunts. Oxygen supplementation, treatment of infections, and endotracheal intubation and mechanical ventilation are important. Under these circumstances, the addition of PEEP may have deleterious effects on cerebral edema, hemodynamic stability, and hepatocyte regeneration[30].

A high cardiac output state with low systemic vascular resistance is seen in FHF. The clinical picture is similar to sepsis. After adequate fluid replacement and invasive cardiac monitoring, the cautious use of inotropes and vasoconstrictors may be helpful.

Renal Failure and FHF

Renal failure develops in more than 50% of patients with acute liver failure[31], and is a major cause of mortality in patients with subfulminant hepatic failure. Typically the renal failure is secondary to
hepatorenal syndrome. Renal failure is sometimes due to acute tubular necrosis or drug toxicity. Management requires correction of hypovolemia and hypotension with fluid and albumin. Nephrotoxic agents such as aminoglycosides and contrast dyes should also be avoided.

Hemodialysis or continuous arteriovenous hemofiltration may be indicated for the management of severe metabolic acidosis, hyperkalemia, or fluid overload. Hemodialysis may be difficult in the setting of hypotension and coagulopathy. Dialysis may also worsen cerebral edema. Hepatorenal syndrome can be reversed by OLT. Thus, the development of renal failure in FHF should not preclude transplantation [32].

Metabolic Abnormalities and FHF

Hypoglycemia is commonly seen in FHF. Blood glucose levels should be monitored and hypoglycemia should be treated with a 10% dextrose solution. A 50% dextrose solution should be used if the blood glucose level is less than 60 mg/dL. Other electrolyte abnormalities include hyponatremia, hypokalemia, hypomagnesemia and hypophosphatemia. FHF patients are extremely catabolic, hence the need for early nutritional supplementation [3].

Specific Therapies in FHF

Specific therapies are only available for a limited number of causes of FHF. In FHF secondary to acetaminophen poisoning, oral N-acetylcysteine is administered in order to restore the glutathione stores. Recent evidence suggests that there may be advantages in starting N-acetylcysteine beyond 15 hours following ingestion of acetaminophen, and even as late as 36 hours following the event [34,35]. FHF due to herpes zoster or CMV may be treated with acyclovir or ganciclovir.

Patients with FHF due to the Budd Chiari syndrome may benefit from portal vein decompression with mesocaval or mesoatrial shunts. Patients with FHF from autoimmune hepatitis may benefit from a trial of steroids. Amanita Phalloides hepatotoxicity may benefit from the administration of silibinin, which is a flavinoid-alcohol, or penicillin G, which interferes with the uptake of alpha-amanitin into hepatocytes. This is useful up to 48 hours after ingestion of the toxin [36].

Other therapies suggested for FHF have included steroids, which have no effect on mortality or cerebral edema, and may further compromise the immune system [37,38], and prostaglandins, whose initial benefit [39] in the treatment of viral induced FHF has not been borne
Hepatic Support in FHF

Recent research in hepatic failure has focused on the concept of hepatic support. This theory is based on the concept that if the liver fails to clear an unidentified substrate extrahepatic organ function deteriorates. Thus, it is postulated that if the liver could be supported for a short time, then extrahepatic organ dysfunction might not occur and the liver might recover. However, initial trials with techniques such as human cross-circulation, plasma exchange[41], plasmapheresis, and charcoal hemoperfusion[42] have shown no significant survival benefit.

The more recent development of the Extracorporeal Liver Assist device (ELAD)[43,44] or Bioartificial Liver (BAL)[45], is similar in technique to hemodialysis and uses liver cell lines placed in hollow perfusable cartridges. Despite improvements in biochemical and clinical parameters, a recent trial failed to show an improvement in the clinical outcome[46]. There are a total of 4 out of 8 cases of patients managed successfully with either human or porcine Extracorporeal Liver Perfusion (ECL) support, bridging the period of FHF until OLT could be performed[47,48]. Both direct hepatocyte transplantation[49,50], and the use of hepatic growth factors are promising approaches to hepatic support in FHF, but have yet to be developed sufficiently before they are applied clinically.

Orthoptic Liver Transplantation in FHF

Liver transplantation is the only proven therapy for FHF. In the United States, the major cause of FHF leading to OLT was unknown or indeterminate, followed by viral hepatitis[51,52]. Patients with FHF undergoing OLT are more likely to be on mechanical ventilation, and have shorter waiting periods for transplantation. They also have lower rates of patient and graft survival than patients with nonfulminant disease[51,52]. Survival after OLT depends more on the functional status of the recipient than on the recipient's age, the donor's age, the cause of FHF, or the pretransplantation laboratory values. In the setting of FHF, marginal donors may be used, and OLT may be performed across blood groups.

The timing of OLT depends on accurate and sensitive prognostic criteria to determine the likelihood of spontaneous recovery. Some of these criteria include the stage of hepatic encephalopathy, levels of factor V[29] and etiology of the FHF. Perhaps the most frequently used criteria are those proposed by the King's College Group[6]. These criteria were compiled from a large retrospective study and tested in a
prospective trial. They are capable of identifying individuals with a less than 20% chance of surviving without liver transplantation.

Variations on liver transplantation include auxiliary liver transplantation, partial liver transplantation, and xenotransplantation. In auxiliary liver transplantation, the liver graft is placed in the right upper quadrant beside the native liver. If the native liver recovers function, immunosuppression can be withdrawn and the heterotopic graft will undergo rejection and atrophy[53,54]. A partial liver transplantation from a living relative involves implantation of the left lateral lobe of the liver. It has been used for children and even young adults with FHF. Porcine liver xenotransplantation has been attempted as a bridge until an appropriate human liver was available. Death occurred at less than 48 hours, due to rejection[55].

Conclusion

Improved survival for patients with FHF depends on many factors. Earlier referrals to specialized medical centers, prevention of hepatitis through vaccines, greater supplies of donor organs, and improved hepatic support systems will all lead to better outcomes. Innovative modalities to treat the complications of FHF may be the most important factors to improve the morbidity and mortality of this serious disease.

Comments

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References

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