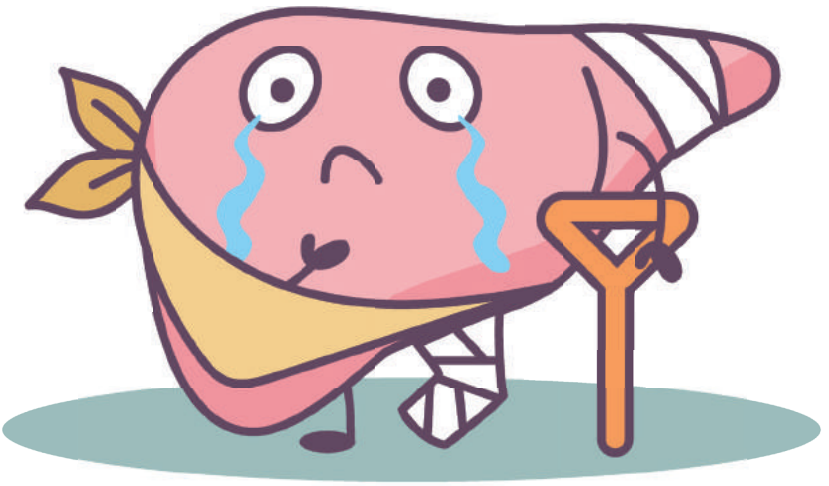
MANAGEMENT OF ACUTE LIVER FAILURE IN ADULTS



GODFREY AZZOPARDI

ABSTRACT

Acute Liver Failure is a medical emergency characterised by cerebral oedema and non-convulsive seizures. Patients with fulminant hepatic failure need urgent workup for liver transplantation. In the meantime, a multimodal approach must be adopted to decrease the incidence of death from neurological complications.

INTRODUCTION

Acute liver failure is a rare, life-threatening condition. Often it occurs in young, previously healthy individuals. Management of these patients is extremely challenging. In view of the fact that experience in management outside specialised centres is limited, consideration for transfer to a tertiary centre with a facility for liver transplantation should be taken as early as possible. Management guidelines facilitate the standardisation of critical care management of these patients amongst different specialities, thereby promoting a smoother and more efficient continuity of care.

CLASSIFICATION OF ACUTE LIVER FAILURE

Liver failure is a triad of jaundice, coagulopathy and encephalopathy.

The O'Grady System classifies acute liver failure as:

1. Hyperacute: encephalopathy occurs within 7 days of the onset of jaundice;
2. Acute: encephalopathy occurs within 8 to 28 days of the onset of jaundice;
3. Subacute: encephalopathy occurs between 29 days to 12 weeks of the onset of jaundice.

PRESENTATION

Acute liver failure presents with acute, severe hepatitis, followed by coagulopathy (high INR) and encephalopathy. These patients typically lack the clinical and radiological signs associated with chronic liver disease, namely hepatomegaly, ascites, clubbing, leukonychia, caput medusa, spider naevi, gynaecomastia and cirrhosis. Paracetamol overdose is the commonest cause of fulminant hepatic failure in developed countries, whereas viral hepatitis is the commonest cause worldwide. The development of cerebral edema is the main cause of morbidity and mortality in patients with acute liver failure.

PATHOPHYSIOLOGY OF CEREBRAL OEDEMA IN ACUTE LIVER FAILURE

1. HYPERAMMONAEMIA

Ammonia, a normal by-product of protein metabolism, is detoxified by the liver to urea. In liver failure, failure of hepatic ammonia metabolism leads to hyperammonaemia. In the brain, ammonia is converted to glutamine. In acute liver failure, this acute rise in intra-cerebral glutamine increases the osmotic pressure in astrocytes, leading to cerebral oedema. In chronic liver disease, the accumulation of intracerebral glutamine is more insidious. Hence, astrocytes have time to equilibrate to these osmolar changes and cerebral oedema does not occur.

2. MASSIVE SYSTEMIC INFLAMMATORY RESPONSE

This leads to cerebral vessel vasodilatation and increased vessel permeability. This promotes the shift of intravascular fluid to the interstitial space, thereby leading to cerebral oedema. In chronic liver disease, the systemic inflammatory response is much less pronounced.

INVESTIGATIONS OF ACUTE LIVER FAILURE

All patients presenting with acute, severe hepatitis of uncertain aetiology should undergo screening for viruses, autoimmune antibodies and toxins, including serum ethanol and paracetamol levels, and have a Doppler ultrasound of their liver. Patients with established acute liver failure should have 6 to 8 hourly blood tests, namely full blood count, serum electrolytes, renal profile, clotting profile, liver enzymes including serum albumin, serum ammonia and arterial blood gases. Serum phosphate levels should be monitored daily as phosphate is consumed during liver regeneration leading to hypophosphataemia. Since these patients are susceptible to infections, they should have regular blood, urine and sputum cultures.

MANAGEMENT OF ACUTE LIVER FAILURE

1. ORTHOTOPIC LIVER TRANSPLANT

Without liver transplantation, the prognosis is very poor in acute liver failure. Hence a hepatologist should be involved immediately,

even if the patients do not seem sick enough initially. These patients deteriorate very fast and may miss the therapeutic time window for surgery. There are no universal, exclusion criteria for liver transplantation. However, many specialised centres agree that patients who are very unstable (overt septic shock with multi-organ failure), have uncontrolled seizures or signs of impending brainstem herniation (fixed, dilated pupils or posturing movements) or have malignancies outside the liver will not benefit from liver transplantation.

The American Society for Study of Liver Diseases has recommended the King's College Criteria in assessing the need for liver transplantation in patients with acute liver failure. According to the King's College Criteria, cases of paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. pH < 7.3; or
2. INR > 6.5, serum creatinine > 300 μmol/L and Grade III/IV encephalopathy.

According to the King's College Criteria, cases of non paracetamol-induced acute liver failure should be referred for liver transplantation if they have:

1. INR > 6.5; or
2. Any 3 of the following: (a) age < 10 years or > 40 years; (b) aetiology - non-A, non-B hepatitis or idiosyncratic drug reaction; (c) duration of jaundice before encephalopathy > 7 days; (d) INR > 3.5; and (e) serum bilirubin > 300 μmol/L.

2. NEUROLOGICAL MANAGEMENT

The two most common neurological complications associated with acute liver failure are brain oedema and non-convulsive seizures. Intracranial haemorrhage due to coagulopathy is rare, but devastating when it occurs. All patients admitted with acute liver failure should have regular (30 minutes to 1 hourly) neurocharting. New, focal neurological deficits are more consistent with intracranial haemorrhage and warrant urgent CT brain. Symmetrical neurological deterioration with no focal deficits is more consistent with cerebral oedema. EEG is warranted in cases of neurological deterioration which cannot be explained by CT brain findings to exclude non-convulsive seizures, which would require treatment with intravenous anticonvulsants.

Brain oedema manifests clinically as severe confusion, somnolence and coma. Hence, all patients exhibiting any of these symptoms benefit from protective measures to restore cerebral perfusion, namely:

a. Measures to decrease brain oedema[1] including:
   i. Hyperosmolar therapy with hypertonic saline or mannitol aiming for serum osmolarity of 310-320mOsm/L;
   ii. Renal replacement therapy to lower serum ammonia to < 60 μmol/L even in the absence of renal failure, as ammonia is cleared by dialysis;
   iii. Intubation and hyperventilation, aiming for $PaCO_2$ (arterial partial pressure of carbon dioxide) of 35mmHg. Cerebral blood flow is directly related to $PaCO_2$ up to certain limits. Hence, by decreasing $PaCO_2$, cerebral blood flow is reduced. Therefore, patients with clinical manifestations of intracranial hypertension benefit from intubation and controlled, mechanical ventilation even if their Glasgow Coma Scale > 8 and they are still able to protect their airway
   iv. Hypothermia, aiming for a core temperature of 35°C as this leads to cerebral vessel vasoconstriction and subsequent reduction of intracranial pressure.
b. Measures to promote cerebral venous drainage, namely head of bed elevation 30°, maintaining the head of intubated patients in the neutral position and avoiding any constrictive ties around the neck to fix the endotracheal tube.

3. CARDIOVASCULAR SUPPORT

Patients with acute liver failure typically have high cardiac output states and vasoplegia. Noradrenaline is the vasoconstrictor of choice to counteract the vasoplegia. Restrictive fluid measures are usually desired to avoid worsening of cerebral oedema. These patients are prone to infections and septic shock as they are immunocompromised. Therefore, in case of non-improving clinical picture, broad spectrum antibiotics and antifungals should be considered early.

4. MANAGEMENT OF COAGULOPATHY

Coagulopathy is not corrected unless INR > 6 as it is a useful prognostic marker. Beyond this level, transfusion of fresh frozen plasma is indicated due to increased risk of spontaneous intracranial bleeding.

5. METABOLIC HOMEOSTASIS

Hypoglycaemia is common in acute liver failure as the hepatic glycogen stores are depleted. In such cases, hypertonic dextrose infusions should be used. 5% dextrose should be avoided as it worsens cerebral oedema.

6. N-ACETYLCYSTEINE INFUSION

In paracetamol overdose, hepatotoxicity occurs due to depletion of the hepatic glutathione stores. N-Acetylcysteine replenishes this hepatic glutathione. N-Acetylcysteine is also beneficial in non-paracetamol-induced acute liver failure as it has anti-oxidant properties and improves haemodynamics. In both cases, N-Acetylcysteine infusion should be commenced immediately and continued until discharge from intensive care or liver transplantation is performed.

CONCLUSION

A multimodal approach to the management of acute liver failure addresses the individual pathophysiological processes that occur in this condition. It improves chances of survival in patients awaiting liver transplantation and dramatically reduces the risk of death from neurological complications.

REFERENCE

1. Warrillow S, Bellomo R. Intensive Care Management of Severe Acute Liver Failure. In: Vincent JL (Editor) Annual Update in Intensive Care and Emergency Medicine. London: Springer; 2015. p. 415-430.