

Management of acute liver failure

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Key points

Multiple organ failure is common in acute liver failure.

Early adequate resuscitation may improve outcome.

Patients progressing to grade III and grade IV encephalopathy should be managed by tracheal intubation and artificial ventilation.

Serum sodium should be maintained between 140 and 150 mmol litre⁻¹.

Early referral to a specialist centre is advised.

Acute liver failure (ALF) is a devastating syndrome that triggers a cascade of events, leading to multiple organ failure and often death. A previously normal liver may fail within days or weeks; and despite recent advances in intensive care and organ support, mortality rates remain high. In those patients with high grades of encephalopathy, the chances of survival are less than 20% with medical management alone. Early deaths in ALF are often caused by cerebral oedema or cardiovascular collapse, whereas late deaths tend to result from sepsis and multiple organ failure. Liver transplantation is the only current definitive treatment in those failing supportive medical management. However, hepatic assist devices are currently under investigation to provide liver support as a 'bridge to transplantation' or during recovery of the native liver.

Definition and classifications

ALF is a syndrome defined by the occurrence of encephalopathy, coagulopathy and jaundice in an individual with a previously normal liver. Several classifications of ALF have been described, based on the temporal relationship between the onset of jaundice and the appearance of encephalopathy or other symptoms. In 1970, Trey and Davidson defined fulminant hepatic failure as 'a potentially reversible condition, the consequence of severe liver injury, in which encephalopathy developed within 8 weeks of the appearance of first symptoms, in the absence of pre-existing liver disease'. This definition, which is still in use today, makes several important observations about ALF:

- it is reversible in a proportion of patients;
- it is of rapid onset;
- it develops in patients without pre-existing liver disease; and
- it is characterized by the presence of hepatic encephalopathy.

Further refinements of this definition have occurred. In 1993, O'Grady and colleagues developed the King's classification, which is commonly used in the UK. According to this

classification, ALF can be subclassified as hyperacute, acute and subacute if encephalopathy develops within 7 days, 8–28 days and 5–26 weeks, respectively, after the onset of jaundice. This classification (based on a time scale) is important, as it has prognostic implications and provides clues to the aetiology of the liver failure. Subacute fulminant hepatic failure is associated with a poorer prognosis. It has a different aetiology to hyperacute liver failure (HALF), which in the UK is almost entirely caused by paracetamol poisoning.

Aetiology

There is wide geographical variation in the aetiology of ALF. In the UK, the most common cause is paracetamol overdose, followed by seronegative or non-A–E hepatitis where no identifiable cause is found. Other rarer causes include idiosyncratic drug reactions and Wilson's disease. The majority of cases worldwide are caused by hepatotropic viruses. All primary hepatotropic viruses (A–E) have been reported to cause ALF and prognosis is dependent on aetiology, age and the presence of comorbidities.

Clinical features

Clinical presentation of ALF depends upon the severity of the liver injury, which is determined by the cause of the initial liver insult and the rate at which the syndrome subsequently develops. Clinical features range from non-specific mild symptoms, (nausea, vomiting and abdominal discomfort) to confusion, agitation and coma. The diagnosis can be made when supportive information from liver biochemistry and coagulation studies becomes available. Once the diagnosis is confirmed, a formal assessment of the encephalopathy score is essential, graded as follows:

- I. Slow mental function
- II. Inappropriate behaviour
- III. Permanent somnolence
- IV. Coma

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Overall, the mortality is higher in patients who progress to grade III and grade IV encephalopathy, where cerebral oedema is a contributing factor to the higher death rates. Cerebral oedema is estimated to occur in up to 80% of patients with ALF. It is more prominent in patients with HALF and ALF, probably because of a lack of time for the equilibration of osmotic gradients within the brain induced by liver failure. In a post-mortem series of ALF, 30% of patients with cerebral oedema had evidence of cerebellar tonsil and temporal lobe herniation, which were the likely causes of death. However, the risk of cerebral oedema as a cause of death in ALF appears to be decreasing, possibly as a result of improved resuscitation and early supportive care.

Clinical signs of elevated intracranial pressure (ICP) such as hypertension, bradycardia, increased muscular tone with abnormal posturing and impaired pupillary light reflexes tend to occur late and thus do not provide a reliable guide for early therapeutic intervention. Similarly, radiographic imaging is not sensitive enough to detect cerebral oedema and elevated ICP. Direct ICP monitoring provides real-time information, allowing earlier detection of elevated ICP. ICP measurements, in combination with data on cerebral oxygenation obtained indirectly by oxygen extraction from jugular bulb sampling, allow for closer monitoring and appropriate interventions (Fig. 1).

Cardiovascular changes of ALF are similar to those observed in septic shock and are characterized by hypotension and low systemic vascular resistance in association with a high cardiac output. These changes are often exacerbated by superadded infection and intravascular volume depletion secondary to the preceding nausea and vomiting.

Oliguric renal failure is common in ALF. It occurs in up to 75% of cases caused by paracetamol overdose and 30–50% of those from other causes. The presence of renal failure in association with ALF is usually an indicator of poor prognosis. An exception to this is paracetamol overdose, where renal failure independent of ALF has a good prognosis and rarely, if ever, leads to chronic renal impairment.

Adaptive and non-adaptive immunity are both impaired in patients with ALF. This immunosuppression is manifest by a decrease in complement synthesis from the failing liver, Kupffer cell dysfunction and abnormalities in neutrophil adhesion and superoxide production. These defects lead to impaired opsonization against bacteria and yeasts, a decrease in endotoxin clearance and an overall increased susceptibility to infection. Bacteriologically proven infection occurs in up to 80% of ALF patients, and major sepsis is a principle contributor to death in 20%. Causative pathogens include *Staphylococcus aureus* (70% of gram-positive sepsis) and *Escherichia coli* (most common cause of gram-negative sepsis). Fungal infection occurs in about 30% of patients and is virtually always caused by *Candida albicans*. It should be noted that pyrexia and leucocytosis are unreliable markers of infection in ALF, as they are absent in one-third of infected patients.

Management

Patients with abnormal liver function tests and coagulopathy should be admitted to a high-dependency unit. All patients with encephalopathy should be referred to a specialist unit.

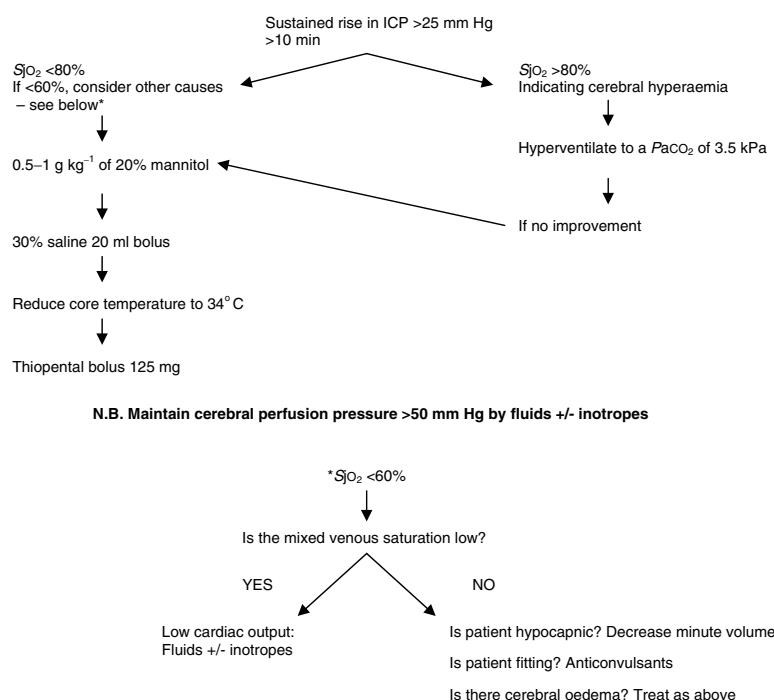


Fig. 1 Algorithm for the management of elevated intracranial pressure (ICP) and abnormal jugular oxygen saturations (SjO_2) in acute liver failure.

Recommended guidelines for referral after paracetamol hepatotoxicity are given in Table 1. Cases of non-paracetamol-induced liver failure should at least be discussed with specialist units even in the absence of encephalopathy. Multidisciplinary input from the hepatologist, intensivist and transplant surgeon is crucial, as the progression of multiple organ dysfunction can be rapid.

Monitoring and investigations

A central venous catheter should be considered in any ALF patient with hypotension, acidosis or renal failure. Patients with renal failure should also have a urinary catheter. Baseline arterial blood gas and lactate measurements are useful in determining the prognosis. Lactate concentrations above 3 mmol litre⁻¹ after adequate resuscitation (at about 12 h after admission) have a similar sensitivity and specificity for death as the King's College Hospital (KCH) criteria (Table 2). Full blood count, clotting and biochemistry screen should be checked at least every 12 h and blood glucose concentrations monitored every 2 h. If a clear history for paracetamol hepatotoxicity is lacking, immunological, microbiological and toxicology screen should be performed.

If the encephalopathy score deteriorates to grade III/IV, elective tracheal intubation and artificial ventilation are indicated with the patient nursed at 20 degrees head-up position. Progression of haemodynamic instability and multiple organ failure can be rapid, and arterial pressure should be monitored invasively in these patients. A pulmonary artery catheter or other means of measuring cardiac output is also recommended. ICP monitoring should also be considered if facilities and expertise are available. If cerebral oedema is suspected, a retrograde jugular bulb catheter should be inserted to assess cerebral oxygenation. Coagulopathy should be corrected before insertion of ICP bolt or in the presence of bleeding.

Cardiovascular and fluid management

Patients with ALF often require aggressive fluid resuscitation at presentation to correct commonly associated hypovolaemia. There is a tendency to avoid excessive sodium in patients with chronic liver disease, and this is often translated into the care of patients with ALF. The overzealous use of 5% dextrose in the early stages of resuscitation results in severe hyponatraemia. This may in itself result in encephalopathy or seizures, and there is evidence that cerebral oedema is more prominent in hyponatraemic patients. The need for inotropic support is common. Inoconstrictors such as norepinephrine are used preferentially in the early stages, as the usual pattern is of vasodilatation with a high cardiac output. Early enteral feeding is recommended. Gut decontamination and lactulose have no proven role in the management of ALF encephalopathy.

Respiratory management

Intubation of the trachea is recommended in patients with grade III/IV encephalopathy. This is not usually indicated for

Table 1 Referral guidelines for paracetamol hepatotoxicity

Day 2	Day 3	Day 4
Encephalopathy	Encephalopathy	Encephalopathy
INR >3.0	INR >4.5	Increase in INR from day before
Creatinine >200 µmol litre ⁻¹	Creatinine >200 µmol litre ⁻¹	Creatinine >250 µmol litre ⁻¹
Arterial pH <7.30	Arterial pH <7.30	-
Hypoglycaemia	-	-

Day (2, 3 and 4), day after overdose.

INR, international normalized ratio.

Table 2 King's College Hospital prognostic criteria (originally devised as prognostic criteria to predict patient survival without liver transplantation but now used as selection criteria for potential liver transplant recipients)

Paracetamol hepatotoxicity	Non-paracetamol hepatotoxicity
Arterial pH <7.30 (7.25 if given <i>N</i> -acetyl cysteine)	Prothrombin time >100 s
or	or
All three of the following:	Any three of the following:
• Prothrombin time >100 s	• Unfavourable aetiology (seronegative or drug-associated fulminant hepatic failure)
• Creatinine >300 µmol litre ⁻¹	• Jaundice >7 days before encephalopathy
• Grade III encephalopathy	• Age <10 or >40 yr
	• Prothrombin time >50 s
	• Serum bilirubin >300 µmol litre ⁻¹

hypoxaemia but for control of carbon dioxide and protection of the airway. Intrapulmonary shunting is uncommon in ALF compared with chronic liver disease. Physiotherapy and respiratory lavage should be used with caution because of the risk of inducing cerebral herniation. ICP monitoring provides reassurance while performing tracheal toilet. Hyperventilation is generally not recommended unless there is suggestion of cerebral hyperaemia; otherwise, the aim is to maintain normocapnia.

Renal management

Up to 75% of patients with ALF have acute renal failure and require renal replacement therapy. Continuous haemofiltration has proven advantages over intermittent haemofiltration in terms of haemodynamic and ICP stability. Bicarbonate-buffered replacement fluid is preferable to either lactate or acetate-containing fluids. Lactate metabolism is often impaired in ALF, resulting in its accumulation and failure to correct acid-base deficit.

CNS management

If ICP remains above 25 mm Hg for longer than 10 min, mannitol 20% (0.5–1 g kg⁻¹) is administered over 20 min. Mannitol should be avoided in patients with oliguria without renal replacement therapy; but if the patient is undergoing haemofiltration, twice the administered volume of mannitol should be removed. Hypertonic saline (30%) is an alternative osmotic agent to mannitol. Serum sodium concentrations should be maintained between 145 and 150 mmol litre⁻¹ with hypertonic saline. The maintenance of a high serum osmolality early in ALF reduces the incidence of

intracranial hypertension. If ICP is labile, ensure adequate sedation and reduce patient interventions to prevent surges in ICP. The routine use of neuromuscular blocking drugs is not recommended, as they are associated with neuromyopathy and infection.

Deep intravenous anaesthesia with thiopental is reserved for patients unresponsive to the osmotic agents. Subclinical seizures and overt seizures are difficult to recognize in ventilated and sedated patients, but they should be suspected in those with an elevated ICP and a low jugular oxygen saturation (SjO_2), reflecting an increased oxygen consumption by the brain. Anticonvulsants used in this setting have been shown to decrease ICP and to improve SjO_2 . There is some evidence that moderate hypothermia ($32\text{--}33^\circ\text{C}$) in humans reduces ICP and improves cerebral blood flow. However, further studies are required, as induced hypothermia has also been associated with worse outcome in patients with head injuries.

Specific therapies

Where appropriate, a specific antidote should be administered as soon as possible. In cases of paracetamol overdose, *N*-acetyl cysteine (NAC) should be commenced at the earliest opportunity, regardless of blood results and paracetamol concentrations, as early treatment has great impact on the subsequent outcome. Improved outcome has been shown when NAC is administered even more than 24 h after paracetamol overdose. After the loading dose of NAC 150 mg kg^{-1} , the infusion is continued at the recommended maintenance dose of 100 mg kg^{-1} until the INR (international normalized ratio) improves to less than 2.0. There is growing evidence that NAC administration may be clinically beneficial in non-paracetamol-induced ALF, though the mechanism of action of NAC in this situation is unclear. In these cases, the usual loading and maintenance dose recommended for paracetamol overdose applies.

Prophylactic antimicrobials with broad-spectrum coverage of gram-positive and gram-negative activity including an anti-fungal (e.g. piperacillin with tazobactam and fluconazole) should be administered on admission, as this halves the incidence of infective episodes when compared with commencement at the time of suspected infection. However, this benefit must be balanced against the risk of developing multi-resistant pathogens.

Liver transplantation

Orthotopic liver transplantation (OLT) is the definitive treatment in ALF patients who meet the criteria for transplantation. Patient selection is based on the KCH prognostic criteria (Table 2), which have a positive predictive value for ICU death without transplantation of 0.98 and a negative predictive value of 0.82. Other criteria using factor V concentrations have also been validated. The 1-yr and 5-yr survival of patients undergoing OLT for ALF is about 20% lower than elective cases for cirrhotic patients. These differences reflect the severity of illness and the lack of choice in donor graft selection. Auxiliary liver transplantation is an alternative option in which a partial liver graft is placed while awaiting the

native liver to regenerate. The main advantage of this procedure is the potential to withdraw immunosuppression at a later date. Despite initial enthusiasm, the procedure has not been used extensively because of poor initial function with the partial graft and the failure of long-term regeneration and withdrawal of immunosuppression in the majority of patients. Recently, living related donation for ALF has been used in some countries with some success, especially in children.

Absolute contraindications to OLT include overwhelming sepsis, refractory hypotension, acquired immunodeficiency syndrome and uncontrolled intracranial hypertension with suspected permanent neurological damage. Once a patient has been selected to undergo OLT, their suitability for transplantation must be reviewed regularly because of the progressive nature of the disease.

Hepatic assist devices

The development of an effective hepatic assist device has been ongoing for over 40 yrs. The methods can be either biological or non-biological. The ultimate aim is to provide full hepatic support on an extra-corporeal circuit. To date, these approaches have met with limited success. Non-biological methods that have been successfully used for renal failure (haemofiltration, haemodialysis and plasmapheresis) have been adapted for ALF. The molecular adsorption and recirculation system (MARS) is an adaptation of haemodialysis in which blood is dialysed against 20% albumin solution. It supports the excretory function of the failing liver by removing albumin-bound toxins. MARS has been shown to improve encephalopathy, renal function and haemodynamic parameters in patients with acute-on-chronic liver failure. However, its efficacy in the management of ALF has yet to be studied in a randomized control trial, and these approaches are limited by the absence of provision of metabolic and synthetic function. Several bio-artificial devices are currently undergoing phase II assessment, with some improvement in biochemical and clinical parameters, although further evaluation and randomized trials are needed. The key issues to be considered are safety and choice of cellular component (human hepatocytes, tumour cell lines or xenogenic).

Key references

- Allen J, Hassenein T, Bhatia S. Advances of bioartificial liver devices. *Hepatology* 2001; **34**: 447–55
- Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol induced acute liver failure: a cohort study. *Lancet* 2002; **359**: 558–63
- Jalan L, Damink S, Deutz N, Lee A, Hayes P. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet* 1999; **354**: 1164–8
- Lee W. Acute liver failure. *N Engl J Med* 1993; **329**: 1862–72
- Williams R. Classification and clinical syndromes of acute liver failure. In: Lee W, Williams R (eds) *Acute Liver Failure*, 1st edn. Cambridge: Cambridge University Press, 1997; 1–9

See multiple choice questions 30–32.