

MANAGEMENT OF ACUTE LIVER FAILURE IN CRITICAL CARE ANAESTHESIA TUTORIAL OF THE WEEK 251

20TH FEBRUARY 2012

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QUESTIONS

Before continuing, try to answer the following true or false questions. The answers can be found at the end of the article, together with an explanation

1. Concerning acute liver failure (ALF):
 - a. Paracetamol toxicity is the commonest cause of ALF worldwide
 - b. Hyperacute presentations of ALF are associated with poorer outcomes
 - c. Albumin is a good marker of acute liver failure
 - d. All patients with ALF should receive prophylactic antibiotics

2. The following are poor prognostic markers in ALF:
 - a. Prothrombin time > 100 seconds
 - b. Elevated serum ammonia levels
 - c. Underlying aetiology of paracetamol toxicity
 - d. Prolonged period between the onset of jaundice and encephalopathy

3. The following are diagnostic criteria for ALF:
 - a. Absence of chronic liver disease
 - b. Acute transaminitis (ALT/AST)
 - c. Coagulopathy with INR > 1.3
 - d. Evidence of encephalopathy
 - e. Illness duration < 28 days

- d. Concerning the management of neurological complications in ALF:
 - a. Target PaCO₂ is that of low-normal range
 - b. Hypertonic saline is a recognised treatment for cerebral oedema
 - c. All patients should have invasive intra-cranial pressure monitoring
 - d. Sedation and ventilation is recommended for grade 3 encephalopathy and above

INTRODUCTION

Acute liver failure (ALF) is a rare, life-threatening multisystem illness resulting from severe hepatic injury from a variety of potential aetiologies (Figure 1). The potential for multi-organ failure makes ALF an extremely challenging disease to manage. Despite advances in the understanding of the aetiology and pathogenesis of the condition mortality rates remain high. In the most severe cases emergency liver transplantation is the only option.

The Intensive Care Unit has a pivotal role in the management of this condition by providing support for failing organs while allowing time for hepatic regeneration or for pre-optimisation prior to liver transplantation.

This tutorial explores the practical management of ALF in the critical care setting and aims to provide a structured approach to management of these patients.

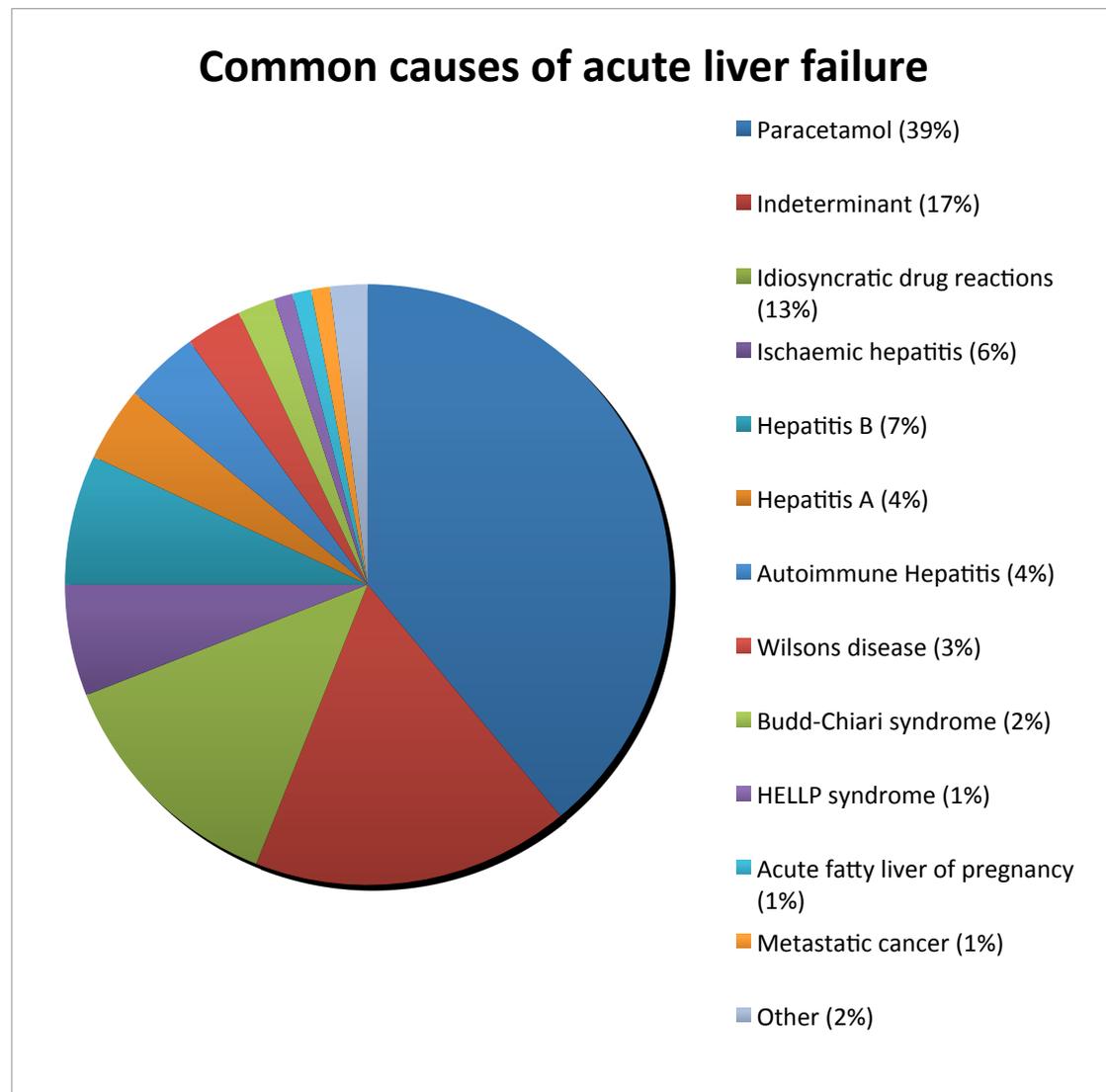


Figure 1. Common causes of acute liver failure in the developed world. Data obtained from United States of America, however this list is representative of the majority of developed countries.

AETIOLOGY AND DEFINITION

Determining the aetiology of ALF is a primary concern in the management of this condition because it can influence management and help to predict outcome. N-acetylcysteine (NAC) for paracetamol (acetaminophen) overdose, delivery of the foetus for HELLP or fatty liver of pregnancy, and treatment with lamivudine in Hepatitis B viral infection are examples of disease-specific therapies. These need to be instigated promptly to guide further management and reduce morbidity and mortality.

ALF is an uncommon condition. In the UK there are approximately 400 cases per year, of which up to 70% of these are secondary to paracetamol (acetaminophen) overdose.

In the developed world paracetamol overdose is the most common cause of ALF, however worldwide, viral aetiologies (Hepatitis A, B and E) and seronegative hepatitis predominate.

There are multiple classifications of ALF. The most widely used classifies ALF by the speed of onset of encephalopathy from when the patient becomes symptomatic. These definitions have prognostic implications and can provide clues regarding potential aetiology.

Table 1. Outcome based on days of symptoms prior to occurrence of encephalopathy

Hyperacute (0-7 days)	Transplant free survival 30%
Acute (7-28 days)	Transplant free survival 33%
Subacute (>28 days)	Transplant free survival 14%

Hyperacute:

In the UK hyper-acute presentations are almost exclusively related to paracetamol toxicity, although contributing stimuli such as ischaemic insults, viral pathogens and toxins have been identified. Although these groups show the greatest degree of coagulopathy, cerebral oedema and encephalopathy they also have the highest rates of spontaneous recovery.

Acute:

This type of presentation is commonly seen with viral aetiologies (e.g. Hepatitis B). It is associated with a moderate spontaneous survival rate but a slightly higher rate of transplantation when compared to hyperacute presentations.

Subacute:

A protracted course of acute liver failure is associated with a significantly higher mortality and the aetiology is often more frequently non-paracetamol drug-related. This type of presentation is difficult to distinguish from acute on chronic liver failure so a careful history and investigation are vital.

Diagnosis

The diagnosis of ALF is made with reference to the specific criteria listed below. However, the clinical picture is dominated by coagulopathy and encephalopathy.

1. Absence of chronic liver disease
2. Acute hepatitis (elevation in AST/ALT) accompanied by elevation in INR >1.5
3. Any degree of mental alteration (encephalopathy)
4. Illness less than 26 weeks duration

Investigations

Serum biochemistry

Bloods should be sent for serological tests to try and ascertain the cause of the ALF (Table 2).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) will be acutely elevated reflecting hepatocellular damage. Serum bilirubin will also be elevated with levels exceeding 300 $\mu\text{mol/l}$ indicating severe disease.

Serum albumin has a half-life of approximately 20 days and is therefore a poor marker of acute hepatic failure.

Renal failure often accompanies ALF and the patient's initial presentation may be that of an acute kidney injury (AKI). In addition, hypoglycaemia, hyponatraemia and metabolic acidosis are commonly present.

Coagulation

A deranged prothrombin time is used in the diagnosis of ALF and it is also used as a prognostic indicator for the consideration of emergency liver transplantation.

Table 2: Investigations required in ALF

Blood Tests

Full Blood Count

Serum electrolytes

Ammonia

Ceruloplasmin

Alpha-1 antitrypsin

Antinuclear antibody

Pregnancy test

HIV antibody

Herpes Simplex virus IgM & DNA

EBV IgG / IgM

Liver Function Tests

INR & partial thromboplastin time

Arterial blood gas and pH

Paracetamol & Salicylates levels

Amylase, lipase

Ant smooth muscle antibody

Serum ferritin, iron, transferrin

Hepatitis serology

CMV IgG/ IgM

Radiological tests

Hepatic Doppler Ultrasound

Radiology

The principle investigation utilised is hepatic Doppler ultrasound to exclude chronic liver disease in the form of varices or a nodular liver. This technique can also assess for intra-abdominal malignancy, which is a contraindication to liver transplantation. Hepatic vein patency is also assessed to exclude Budd-Chiari syndrome.

Liver Biopsy

Acquiring histological data is unlikely to change the therapy being provided. However, it may provide information about specific viral aetiologies or information that would preclude a liver transplant e.g. metastatic malignancy or lymphoma. Therefore the role of liver biopsy in the management of ALF patients is determined by the attending liver specialist and has to be balanced against the risk of performing such a procedure in these coagulopathic patients.

Management

The management of ALF in the ICU setting is discussed below, focusing on each of the systems affected.

Neurological

ALF and cerebral oedema

Acute hepatic damage prevents the liver from metabolising ammonia, a by-product of normal protein metabolism, to the less-toxic compound urea. In ALF arterial ammonia levels are grossly elevated and an alternative pathway is used for ammonia detoxification. Glutamine synthase metabolises urea back to glutamine and this results in increased accumulation of glutamine within cerebral astrocytes. The astrocytes subsequently swell secondary to this cerebral osmotic disturbance leading to cerebral oedema and intracranial hypertension.

This is the most accepted hypothesis for the pathogenesis of cerebral oedema, although it is regarded as a multi-factorial pathology. Inflammatory mediators and disrupted cerebral auto-regulation, resulting in increased cerebral blood flow, are contributing factors.

Ammonia levels have been reported as being a substantive prognostic marker in ALF.

Simple neuro-protective measures should be implemented:

- Elevate head to 30 degrees to improve cerebral perfusion pressure (CPP)
- The patient should be appropriately sedated to prevent stimuli from rising intracranial pressure (ICP)
- Avoid of hypotension. This may require use of vasoactive drugs
- Prevent hypoxaemia
- Target PaCO₂ 4.7 – 5.2 kPa (low normal range)
- Tight glycaemic control with blood glucose target between 4 and 10 mmol/l

Mannitol (0.25 – 0.5g/kg) is used to treat intracranial hypertension associated with cerebral oedema. However, mannitol is associated with marked reductions in blood pressure through decreases in systemic vascular resistance (SVR) and a poorly understood acute vasodilatory effect. Boluses of hypertonic saline can be utilised with similar benefits, without the haemodynamic side effects. Doses of 1-2ml/kg of 5% Saline may be given, ideally via a central line, targeting a serum sodium concentration of between 145-155 mmol/l.

Hepatic encephalopathy

As the clinical course of ALF progresses, hepatic encephalopathy becomes the predominant feature. Caused by the livers inability to remove toxic substances from the body, hepatic encephalopathy is a clinical diagnosis and is graded as shown in table 3.

Table 3. Grades of Encephalopathy

Grade 1	Altered mood, impaired concentration and psychomotor function, rousable
Grade 2	Drowsy, inappropriate behaviour, able to talk
Grade 3	Very drowsy, disorientated, agitated, aggressive
Grade 4	Coma, may respond to painful stimuli

It is generally accepted that all patients who show evidence of grade 3 encephalopathy or above will require sedation and mechanical ventilation for airway protection, given the associated reduction in GCS with high-grade encephalopathy. Mechanical ventilation facilitates the use of sedation and analgesia that can reduce cerebral metabolic demand and cerebral blood flow as well as minimising intracranial pressure rises associated with agitation and painful stimuli. This will, of course, have a beneficial effect on intracranial hypertension.

ICP monitoring

The role of ICP monitoring devices in ALF is controversial. Although such devices allow titration of inotropic support to maintain desirable cerebral perfusion pressures (CPP), the benefits need to be weighed against the risks of their use in this population of coagulopathic patients.

Respiratory

A grade 3 or 4 encephalopathy is often an indication for intubation and ventilation in order to protect the airway. Complications of liver disease, such as intra-abdominal hypertension (IAH) secondary to bowel oedema or ascites, pleural effusions, acute lung injury and acute respiratory distress syndrome also have the potential to compromise a patient's respiratory function and may lead to the requirement for ventilatory support.

Patients receiving mechanical ventilation are at risk of ventilator acquired pneumonia but additional measures undertaken to protect against intracranial hypertension, for example, heavy sedation and reduced bronchial suction, may increase the likelihood of pulmonary sepsis further.

This risk is compounded by a degree of immune compromise associated with ALF. This is secondary to the inability to mobilise cellular components of the immune system and a diminished acute phase and complement response.

High levels of positive end expiratory pressure (PEEP) should be avoided if possible because they may increase hepatic venous pressure and ICP.

Cardiovascular

The majority of ALF patients admitted to ITU are intravascularly depleted secondary to a combination of insensible losses, vomiting and reduced oral intake. Reduced systemic vascular resistance is characteristic in ALF. This may result in hepatic hypoperfusion despite a sometimes elevated cardiac output. These changes are confounded by poor lactate clearance due to hepatic impairment to cause profound hyperlactataemia.

Fluid resuscitation is an important early management step. No definitive guidance exists for the type of fluid to be utilised, although there are a few important considerations. Any external lactate load is unacceptable and therefore Hartmann's or lactated Ringer's solutions should be avoided. In addition, 5% Dextrose solutions lack suitable volume expanding properties and result in hyponatraemia that can worsen cerebral oedema. Targeted fluid resuscitation is advisable because overloading the intravascular space may also worsen cerebral oedema, which can ultimately lead to brainstem herniation and death.

Hypotension that persists despite fluid resuscitation will require inotropic support. In the presence of decreased systemic vascular resistance vasopressors such as norepinephrine, dopamine or vasopressin can be used.

Renal

Acute kidney injury (AKI) is common in the setting of ALF, especially if associated with paracetamol toxicity. AKI can be secondary to direct nephrotoxic effects of drugs or associated with raised intra-abdominal pressure, hepatorenal syndrome and acute tubular necrosis (ATN) due to profound hypovolaemia and hypotension.

Renal replacement therapy (RRT) should be provided early in the course of AKI complicating ALF to prevent worsening acidosis and fluid overload. Continuous veno-venous haemodialysis (CVVHD) is preferred over intermittent haemodialysis due to the associated haemodynamic instability of the latter method.

Hepato-renal syndrome

Although generally a feature of liver cirrhosis, a rapidly progressive form is commonly seen in the ITU setting and in the context of ALF. The progressive rise in cardiac output and reduction in SVR results in reduced total vascular resistance and, ultimately, a decline in renal perfusion. The end result is reduced glomerular filtration rate (GFR) and sodium excretion. The pathological basis for this phenomenon is thought to be associated with the accumulation of vasoactive substances such as endotoxin, which are usually cleared in the liver.

Hepato-renal syndrome is a condition that is often irreversible and may be rapidly fatal.

Anaesthesia considerations

The sedating agent of choice is propofol. It is favoured for its relatively short half-life, whereas benzodiazepines can have a protracted sedating effect in the context of acute hepatic impairment. In addition, propofol is thought to provide protection against the intracranial seizure activity that is thought to complicate the higher grades of encephalopathy. As with any other ventilated patient, the concomitant use of opioid analgesics can reduce the doses of anaesthetic agents required with resulting improvements in cardiovascular stability.

Nutrition

ALF is a catabolic state and nutritional support should be instigated as soon as feasibly possible. Enteral and parenteral routes are both accepted methods of delivery. Protein intake should not be restricted and dietary laxatives (e.g. lactulose) should be administered to speed the evacuation of nitrogenous waste.

Due to the loss of hepatic glycogen stores with diminished gluconeogenesis and hyperinsulinaemia, hypoglycaemia often complicates ALF. Infusion of 10% Dextrose solutions may be required, at least until feeding is established. Therapy aimed at blood glucose above 3.5mmol/l is recommended^[4].

Infection

Patients with ALF are prone to infection from Gram negative and Gram positive bacteria and fungi. However, the role of prophylactic antimicrobial drugs is an area of contention. It is therefore important to implement general measures to reduce the likelihood of infection, have a high index of suspicion of infection and use appropriate targeted anti-microbial agents early.

The normal systemic features of infection may be absent in patients with ALF and therefore extra vigilance is required.

Patients being considered for liver transplantation may benefit from prophylactic antibiotics because sepsis can prevent the proposed procedure.

Coagulation

The liver synthesises all the coagulation factors apart from factor VIII. Abnormal synthesis of these factors in addition to deficient protein C and anti thrombin III and coexistent sepsis mean that severe coagulopathy and low grade DIC are common in ALF. However, clinical significant bleeding is uncommon. The routine use of fresh frozen plasma (FFP) to correct coagulopathies should be discouraged. FFP will mask the trends in the prothrombin time that can be used as a prognostic marker. In addition, if given in excess of targeted fluid requirements, FFP administration can potentiate cerebral oedema through increases in intravascular volume. Thrombocytopenia should also not be routinely corrected.

The obvious exception to the rule is the administration of such products in patients who are actively bleeding or as cover for invasive procedures.

N-acetylcysteine

N-acetylcysteine (NAC) is a proven effective therapy for paracetamol hepatotoxicity and should be administered as soon as possible following the overdose as guided by treatment nomograms.

It is widely accepted that given that NAC is a relative innocuous substance and the reported pro-coagulant properties of this treatment are negligible.

NAC should be administered in all cases of ALF, especially where the underlying aetiology is unclear. However, survival benefits have only been shown in paracetamol related hepatotoxicity.

Liver Transplantation

Detailed analysis of liver transplantation is beyond the scope of this tutorial, however it remains the only effective therapy for ALF patients who fail to recover spontaneously. There have been large studies deriving data on ALF patients but no single predictive scoring system has been successfully derived due to the wide variety of aetiologies. However, the Kings College Hospital Criteria (Table 4) is probably the most widely used with the most diagnostic accuracy. Contraindications to liver transplantation include irreversible brain damage, accelerating inotrope requirements, uncontrolled sepsis and severe respiratory failure. In the UK approximately 600-700 liver transplants are undertaken each year. However, ALF is a rare indication, accounting for approximately 10% of cases.

Specialist Liver units

It is important that cases of patients presenting with ALF are discussed with a specialist unit at the earliest opportunity. This is especially important for patients who are potential candidates for liver transplantation.

Table 4: Kings College Hospital criteria for liver transplantation in acute liver failure

Paracetamol (acetaminophen) overdose

- pH <7.3 (irrespective of encephalopathy)
- Or all of the following:
- Grade III-IV encephalopathy
 - Creatinine >300umol/litre
 - Prothrombin time >100 seconds (INR >6.5)

Non-paracetamol aetiology

- Prothrombin time >100 seconds
- Or any 3 of the following:
- Age <10 years or >40 years
 - Prothrombin time >50 seconds
 - Bilirubin >300umol/litre
 - Time from jaundice to encephalopathy >2 days
 - Non-A, non-B hepatitis, halothane or drug-induced acute liver failure
-

Summary

Acute liver failure is a rare multisystem disease. Overall survival with medical treatment alone is 10-40% ^[4]. The prognosis depends largely on the aetiology and is best following paracetamol overdose, Hepatitis A, ischaemic hepatitis or pregnancy-related disease. Independent of aetiological factors, the management of these patients in the ITU setting maximizes their survival potential and can provide the pivotal support required whilst allowing hepatic regeneration or hepatic transplantation to occur.

ANSWERS TO QUESTIONS

1.
 - a. **F** (viral aetiologies predominate worldwide)
 - b. **F** (subacute presentations have the worst prognosis)
 - c. **F** (albumin's half life is too long for it to be a responsive marker)
 - d. **F** (although patients being considered for transplantation may benefit from this intervention)

2.
 - a. **T** (contained within Kings College criteria for liver transplantation)
 - b. **T** (considered main pathogenesis of cerebral oedema)
 - c. **F** (this has a better prognosis than many other causes)
 - d. **T** (this describes a subacute presentation)

3.
 - a. **T**
 - b. **T**
 - c. **F** (INR >1.5)
 - d. **T** (any grade of encephalopathy)
 - e. **F** (subacute liver failure is encephalopathy >28 days after symptoms start)

4.
 - a. **T**
 - b. **T**
 - c. **F** (due to risk of insertion in coagulopathic patients)
 - d. **T**

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