Acute liver failure

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Abstract

Acute liver failure (ALF) is a life-threatening condition with many possible causes. In developed countries, common causes include paracetamol overdose, toxin exposure (e.g. mushrooms) and idiosyncratic drug reactions. Viral hepatitis is much more common in developing countries, although must be considered in any location. The clinical syndrome of ALF is remarkably independent of the cause and comprises the following key features: jaundice, encephalopathy with cerebral oedema, coagulopathy, vasodilatory state, renal dysfunction, hypoglycaemia and immune dysfunction. Management of the patient with severe ALF is threefold in aim: (i) prevent further liver damage by treating the underlying cause of ALF where possible; (ii) prevent and treat complications of ALF (e.g. cerebral oedema, shock and infection); and (iii) early referral to specialist centre for consideration of liver transplantation. Despite modern intensive care practices, the mortality of severe ALF remains high. Optimal supportive care aims to extend the period available to source an organ for transplantation and/or to allow full recovery. This article provides a practical approach to the diagnosis and management of critically ill patients with ALF.

Keywords Cerebral oedema; fulminant liver failure; severe acute liver failure

Royal College of Anaesthetists CPD Matrix: 2C00

Learning objectives

After reading this article, you should be able to:

- recognize the key features of severe ALF
- have an approach to the assessment and management of the patient with acute liver failure
- outline the rationale for early referral to a specialist (liver transplant) centre for patients with severe acute liver failure

Liver failure is traditionally classified according to the time between development of jaundice and encephalopathy. This classification is valuable when determining the cause, prognosis and appropriate treatment of severe acute liver failure (ALF). Encephalopathy develops within 1 week of jaundice in hyperacute liver failure, between 1 and 4 weeks in acute liver failure and between 5 and 12 weeks in subacute liver failure. Chronic liver failure involves a more gradual onset of symptoms and signs of liver dysfunction, associated with cirrhosis. The pathophysiology, natural history and treatments differ considerably between chronic liver disease and the acute spectrum of liver disease. Severe ALF is a rare, although life threatening, condition with multiple possible causes and complications. Prognostication models facilitate the early identification of patients with low survival rate. Early referral of these patients to a liver transplant centre should be made. The most popular models are the King's College criteria and the Clichy criteria. However, these may lack sufficient sensitivity and specificity to reliably guide clinical practice. This article will consider the major diagnostic and management issues in patients with ALF.

Key clinical features of ALF

Important details include: previous state of health, history of cirrhosis (to differentiate from decompensated chronic liver disease), family history of liver failure and risk factors for viral hepatitis (intravenous drugs, travel, sexual history, tattoos). Female patients should be asked about the possibility of pregnancy. A thorough drug history (non-prescription, herbal remedies and illicit as well as prescribed therapies) must be obtained. Mushroom ingestion should also be asked about.

After initial resuscitation, patients must be examined for evidence of chronic liver disease (e.g. sarcopenia, gynaecomastia, clubbing, leukonychia, spider nevi, prominent abdominal wall veins, and advanced ascites). Encephalopathy can be graded according to the West Haven criteria (Table 1), but critical care physicians may be more familiar with the Glasgow Coma Scale for describing abnormal conscious states. Whichever approach is utilized, repeated assessment will assist in detecting deterioration. Abdominal examination should evaluate liver and spleen size as well as the presence of ascites. Herpetic skin lesions, tattoos and evidence of needle tracks should be sought on the skin. Eye examination should include looking for Kayser-Fleischer rings which indicate copper deposition in Wilson's disease.

Investigation of ALF

Although the complications of ALF are largely independent of the underlying cause, it is still important to identify the aetiology where possible, as specific therapy may be available. Table 2 lists suggested initial investigations for causes and complications of ALF.

Management of ALF

Treatment of patients with ALF is primarily aimed at preventing or treating complications, to allow time for endogenous hepatocyte regeneration, or for a transplant organ to become available.

Some causes of ALF have specific treatment modalities to minimize further hepatocyte damage (Table 3). Note that patients with severe ALF from causes other than paracetamol or hepatotropic viruses more often present with subacute liver failure and are unlikely to survive without transplantation.[1] Referral to a specialist centre capable of liver transplantation should be undertaken early.

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West Haven grading of hepatic encephalopathy

Grade	Salient symptoms and signs
1	• GCS 14–15 • Mild confusion • Euphoria; anxiety • Word finding difficulties • Decreased attention NB: this grade of encephalopathy may be extremely subtle
2	• GCS 12–15 • Inattention • Moderate confusion e.g. disorientation to time, place or person • Disinhibition; inappropriate behaviours • Lethargy • Asterixis • Slurred speech • Hypo- or hyper-reflexia
3	• GCS 8–12 • Drowsy but rousable • Marked confusion • Marked behavioural abnormalities e.g. paranoia, delusions, aggression • Asterixis • Ataxia
4	• GCS 3–7 • Pupillary abnormalities • Loss of airway reflexes

NB: Assessment of encephalopathy grade should be made after the best attempt to exclude other causes of delirium & altered conscious state e.g. hypoglycaemia, sepsis, intracranial haemorrhage.

Table 1

Investigations in ALF

Blood tests	FBE (high white cell in inflammation, platelets low or normal, anaemia in bleeding) Blood film (e.g. haemolytic anaemia in autoimmune disease & Wilson's disease) U&E (renal impairment) LFT (usually high ALT & AST, initially normal bilirubin and GGT & ALP) Lipase Coagulation studies (including INR, PT, APTT, fibrinogen, functional studies if available) Ammonia Paracetamol level (and other toxicology screen depending on history and examination) Alcohol level βHCG ABG & lactate Caeruloplasmin (plasma levels are low in Wilson's disease)
Serology	HAV, HBV, HDV, HEV EBV, CMV, HSV, VZV Parvovirus B19
Auto-immune investigations	ANA, ANCA, AMA Anti-LKM, anti-SM
Radiology	Hepatic ultrasound with doppler of vessels (esp. Hepatic vein: Budd Chiari syndrome) CXR (ARDS, pneumonia, line and tube placement)
Other	12 lead ECG (toxidromes, arrhythmia from electrolyte abnormality, myocardial ischaemia) EEG (if seizures suspected)

FBE: full blood examination, WCC: white cell count, U&E: urea and electrolytes, LFT: liver function tests, ALT: alanine transaminase, AST: aspartate transaminase, GGT: gamma glutamyl transpeptidase, ALP: alkaline phosphatase, INR: international normalized ratio, PT: prothrombin time, APTT: activated partial thromboplastin time, G&H: group and hold, βHCG: beta human chorionic gonadotrophin, ABG: arterial blood gas, HAV: hepatitis A virus, HBV: hepatitis B virus, HDV: hepatitis D virus, HEV: hepatitis E virus, EBV: epstein barr virus, CMV: cytomegalovirus, HSV: herpes simplex virus, VZV: varicella zoster virus, ANA: antinuclear antibody, ANCA: anti-neutrophil cytoplasmic antibody, Anti LKM: anti liver kidney microsomal antibody, Anti SM: antiSmith antibody, CXR: chest X-ray, ARDS: acute respiratory distress syndrome, ECG: electrocardiograph, EEG: electro-encephalograph.

Table 2

N-Acetylcysteine

Intravenous administration of N-acetylcysteine (NAC) improves survival in paracetamol-induced ALF. The time elapsed between paracetamol intake and commencement of NAC correlates with outcome. Immediate commencement of NAC infusion is recommended even in the initial absence of evidence for overdose. NAC is an inexpensive and effective therapy if paracetamol is implicated, and a harmless treatment if paracetamol ingestion is later ruled out. Patients who may have overdosed on slow release paracetamol preparations should be discussed with a toxicologist, as standard treatment algorithms may not apply. Additionally, there is evidence to support the benefit of NAC in non-paracetamol induced hepatic failure, where haemodynamics and oxygen delivery may be enhanced.[2] The decision to stop NAC in a patient with severe ALF should be made by hepatologists in conjunction with the treating intensivist.

Management of encephalopathy and cerebral oedema

Cerebral oedema occurs in many patients with high-grade encephalopathy, and brainstem herniation is a common cause of death in ALF. Neurological injury occurs because of severe cerebral swelling causing refractory intracranial hypertension. The pathophysiology of ALF associated cerebral oedema is complex, but the accumulation of ammonia and other metabolic toxins, as well as the loss of cerebral autoregulation resulting in cerebral hyperaemia,[3] are the likely two main drivers.

Ammonia is a waste product of nitrogen metabolism and undergoes detoxification via the urea cycle. Most of this detoxification occurs in the liver and hyperammonaemia is therefore a key feature of severe ALF. Ammonia crosses the blood brain barrier and causes neuroexcitation, disruption to many crucial neuronal metabolic processes and astrocyte swelling. Ammonia concentrations of more than 117 μmol/L are highly associated with the development of severe cerebral oedema and dangerous

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