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What you need to know about: acute liver failure

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Abstract

Acute liver failure is a rare but important clinical syndrome, with a high mortality rate. Prompt recognition, appropriate management and early referral to a liver transplant centre can lead to good outcomes in these critically unwell patients. This article gives an overview of the key clinical challenges and optimal management of patients with acute liver failure. Acute liver failure is defined and a comprehensive list of aetiologies and suggested investigations is provided. The clinical challenges of sepsis, renal impairment, coagulopathy, hypoglycaemia, haemodynamic instability and cerebral oedema are discussed. Quadruple H therapy, a combination of therapies aimed to reduce cerebral oedema in acute liver failure, is described. A systemic guide to managing patients with acute liver failure is provided, as are indications for referral to a liver transplant centre.

Key words: Acute liver failure; Fulminant liver failure; Intracranial hypertension; Liver transplantation; Quadruple H therapy

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Introduction

Acute liver failure is a rare but important clinical syndrome that often affects young, previously well individuals, with a high mortality rate (Bernal et al, 2013). The incidence of acute liver failure in the developed world is estimated to be between 5 and 10 cases per million people every year (Bower et al, 2007; Bernal et al, 2010). Prompt recognition, appropriate management and early referral to a liver transplant centre can lead to good outcomes in these critically unwell patients (Marundanayagam et al, 2009). This article provides an overview of the key clinical challenges and management of acute liver failure.

Definition

Acute liver failure can be defined as the rapid onset (less than 8 weeks) of severe liver dysfunction in the absence of pre-existing liver disease (Trey and Davidson, 1970). The principal manifestations of acute liver failure are hepatic encephalopathy and deranged coagulation (an international normalised ratio that is higher than 1.5) (Wlodzimirow et al, 2012).

The absence of previously known liver disease differentiates acute liver failure from the more commonly seen syndromes of decompensated cirrhosis and acute-on-chronic liver failure (Figure 1). Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with established cirrhosis. Common manifestations include worsening ascites, hepatic encephalopathy, hepatorenal syndrome and variceal haemorrhage (Mansour and McPherson, 2015). Acute-on-chronic liver failure is an acute deterioration of cirrhosis, resulting in the failure of one or more extrahepatic organ systems (Bernal et al, 2015), and is associated with a higher 30-day mortality than decompensated cirrhosis (41% vs 7%, respectively) (O'Leary et al, 2018).

Liver injury, in the context of multiple organ failure, is common during critical illness (eg in the setting of septic shock or cardiac tamponade). However, this is not generally considered to be acute liver failure, because the initial disease process does not originate in the liver. Definitions of acute liver failure also generally exclude alcoholic hepatitis, malignant infiltration causing liver failure, and hepatic insufficiency after major liver resection.

Aetiology

Paracetamol toxicity accounts for 65% of cases of acute liver failure in the UK (Bernal et al, 2013). Other common causes in industrialised countries include non-paracetamol

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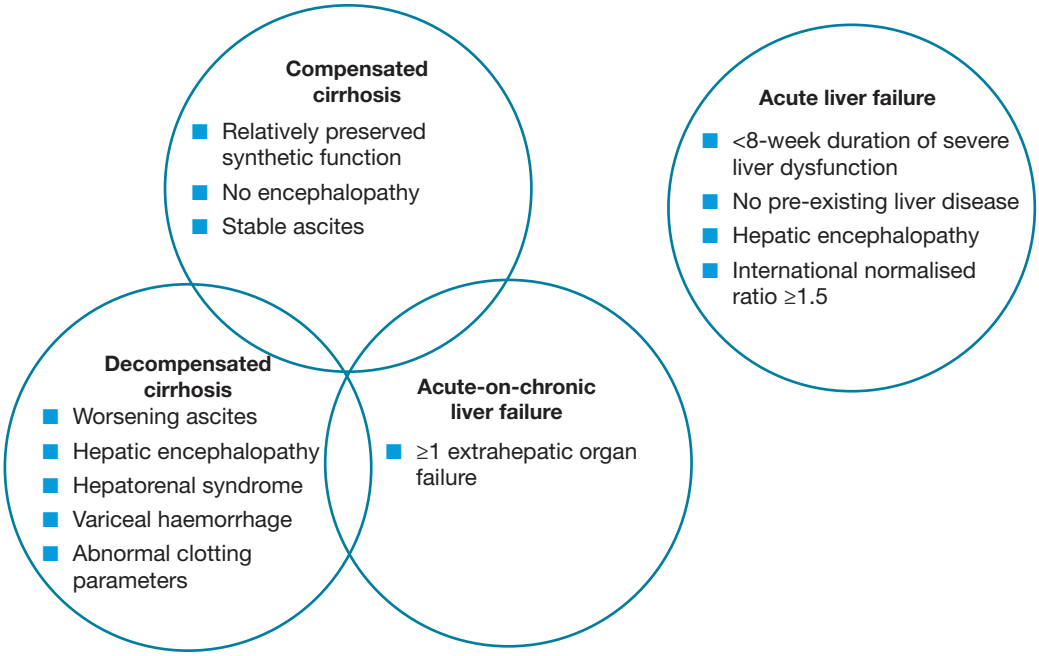

Figure 1. Relationships between different liver-related disorders.

drug-induced liver injury, hepatitis B and autoimmune hepatitis. In developing countries, viral hepatitis (mainly A, B and E) is the main cause of acute liver failure (Stravitz and Lee, 2019). For 15% of adult cases, a specific aetiology cannot be identified (Lee, 1994). Establishing the cause of acute liver failure is important to guide treatment and predict transplant-free survival. The majority of patients experiencing a paracetamol overdose survive acute liver failure without needing a liver transplant, while patients with acute liver failure triggered by other causes (eg drug-induced liver injury and hepatitis B) have a much lower transplant-free survival rate (65% vs 24% respectively) (Stravitz and Lee, 2019). Table 1 shows the major causes of acute liver failure and, where appropriate, specific treatments to minimise further hepatocyte damage.

Assessment

A thorough history is vital to establish the cause of acute liver failure. Given the presence of hepatic encephalopathy, details must often be obtained from relatives and the patient's general practitioner. A history of previous liver disease almost always differentiates acute liver failure from decompensated cirrhosis. It is essential to compile a comprehensive drug history that details all prescription, over-the-counter, herbal and illicit drugs taken in the preceding 6 months. Ingestion of mushrooms should be specifically enquired after. Social history should include alcohol intake, recent travel, sexual history and any contact with unwell individuals.

Following initial resuscitation, hepatic encephalopathy can be graded using the West Haven criteria (Table 2) or the Glasgow Coma Scale. Stigmata of chronic liver disease should be sought (eg spider naevi, ascites, gynaecomastia), and liver and spleen size estimated. Skin should be checked for herpetic lesions and eyes for Kayser-Fleischer rings. Table 3 details the investigations that should be implemented for patients with suspected acute liver failure.

Key clinical challenges

The key clinical challenges of acute liver failure include cerebral oedema with intracranial hypertension, haemodynamic instability, lactic acidaemia, coagulopathy, infection, hypoglycaemia and renal failure; these should be identified and treated early. The majority of patients will require urgent admission to the intensive care unit.

Table 1. Aetiology of acute liver failure

Possible aetiology of acute liver failure	Example		Specific therapies
Paracetamol	Over-the-counter analgesia, cold and flu medications		N-acetylcysteine
Other drugs	Beta-lactams Isoniazid Non-steroidal anti-inflammatory drugs		Withdraw causative agent
Toxins	Amanita mushrooms		High dose penicillin or silibinin/silymarin
Viral hepatitis	Hepatotropic	Hepatitis B virus Hepatitis A virus Hepatitis E virus	Appropriate antivirals where applicable: ■ Nucleoside analogues, eg lamivudine ■ Aciclovir (herpes simplex virus) ■ Ganciclovir (cytomegalovirus)
	Non-hepatotropic	Herpes simplex virus Cytomegalovirus Varicella zoster virus Epstein–Barr virus	
Vascular	Budd–Chiari syndrome (hepatic vein thrombosis)		■ Anticoagulation ■ Revascularisation procedures (eg catheter directed thrombolysis, balloon angioplasty or stent insertion into hepatic vein)
Inherited metabolic disorders	Wilson's disease		Chelating agents (eg penicillamine, zinc) Plasmapheresis
Pregnancy-related	Acute fatty liver of pregnancy		Delivery of fetus
Autoimmune diseases			Immunosuppression (eg high-dose steroids)

Table 2. West Haven grading for hepatic encephalopathy

Grade	Correlating Glasgow Coma Scale	Signs and symptoms
1	14–15	Mild confusion, shortened attention span, euphoria, anxiety, impaired performance of addition, altered sleep
2	12–15	Moderate confusion, inappropriate behaviour, lethargy, asterixis
3	8–12	Drowsy but responsive to verbal stimuli, marked confusion, ataxia
4	3–7	Coma: unresponsive to verbal or physical stimuli

Cerebral oedema and intracranial hypertension

Cerebral oedema in acute liver failure can lead to intracranial hypertension, which can progress to cerebral herniation and death. Although the incidence of intracranial hypertension in patients with acute liver failure has decreased in the last 20 years, the mortality rate in those who develop intracranial hypertension remains high, with Bernal et al (2013) reporting a 55% mortality rate. Two key driving factors for cerebral oedema in acute liver failure are the accumulation of metabolic toxins, especially ammonia, and the loss of cerebral vascular autoregulation, leading to hyperaemia (Raghavan and Marik, 2006).

Ammonia is a toxic waste product of protein metabolism that is mostly detoxified in the liver via the urea cycle. Therefore, hyperammonaemia is a key complication of severe liver dysfunction. Ammonia crosses the blood–brain barrier, and high concentrations cause neuroexcitation and astrocyte swelling through the accumulation of glutamine and increased oxidative stress (Scott et al, 2013). Very high ammonia levels (>150 µmol/litre) in acute liver failure are associated with severe cerebral oedema and intracranial hypertension

Table 3. Investigations in patients with acute liver failure

	Test	Comment
Arterial blood	Arterial blood gas	Baseline $PaCO_2$ before mechanical ventilation, acid–base disturbances
	Ammonia	Raised levels predictive of severe cerebral oedema
Haematology	Full blood count	Thrombocytopaenia, anaemia in bleeding, raised white cell count in infection or inflammation
	Blood film	Haemolytic anaemia in Wilson's disease and autoimmune diseases
	Coagulation studies, including prothrombin time, international normalised ratio, activated partial thromboplastin time, fibrinogen	
	Thromboelastography or rotational thromboelastometry, if available	
	Group and hold	
Serum biochemistry	Urea and electrolytes	Renal impairment, hyponatraemia
	Calcium, phosphate and magnesium levels	Electrolyte derangement
	Albumin level	
	Liver function tests (alkaline phosphatase, alanine transaminase, bilirubin, gamma glutamyl transpeptidase)	
	Serum lactate	
	Lipase	Concurrent pancreatitis
	C-reactive protein	Concurrent infection
Viral hepatitis serologies	Hepatitis A, B, D or E	
	Epstein–Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus	
Autoimmune investigations	Antinuclear antibody, anti-neutrophil cytoplasmic antibody, antimitochondrial antibodies	
	Anti-liver kidney microsomal antibody, anti-Smith antibody	
Microbiology	Urine, blood and sputum cultures	
Toxicology	Paracetamol level	
	Alcohol level	
Radiology	Liver ultrasound with Doppler of vessels	Hepatic vein occlusion in Budd–Chiari syndrome
	Chest X-ray	Pneumonia, acute respiratory distress syndrome, following tracheal intubation or central line placement
	Computed tomography of the brain	Cerebral haemorrhage
Other	Blood glucose concentration	Hypoglycaemia
	Beta human chorionic gonadotrophin in all women	
	Caeruloplasmin	Low in Wilson's disease
	12-lead electrocardiograph	Arrhythmias secondary to electrolyte disturbances, myocardial ischaemia, toxidromes

(Clemmesen et al, 1999). Astrocyte adaptation in chronic hyperammonaemia may explain why significant cerebral oedema is rare in decompensated cirrhosis (Wakim-Fleming, 2011).

Coagulopathy

As the liver synthesises both anticoagulant and procoagulant factors, the failure of hepatic function can increase the risk of both bleeding and thrombosis. Bleeding occurs in around a fifth of patients with acute liver failure, although most episodes are not clinically serious (eg diffuse upper gastrointestinal ooze and mild bleeding from vascular access sites) (Warrillow et al, 2019). Although rare, spontaneous intracranial haemorrhage can be devastating.

An increased international normalised ratio is a hallmark of acute liver failure and often increases clinician concern regarding risk of bleeding. However, evidence suggests that there is only a limited association between the international normalised ratio and bleeding episodes, while thrombocytopaenia and hypofibrinogenaemia are much more predictive of bleeding; maintaining a platelet count >75x10^9/litre and a fibrinogen concentration of at least 1.5 g/litre is recommended (Warrillow et al, 2019). An improving international normalised ratio, in the absence of clotting factor replacement, indicates hepatic regeneration and is associated with recovery.

Thrombosis is uncommon in acute liver failure, affecting 10% of patients, with over half of episodes occurring several days after emergency liver transplantation (Warrillow et al, 2019).

Haemodynamic instability

The haemodynamic profile of acute liver failure is clinically similar to septic shock; increased levels of pro-inflammatory cytokines result in vasodilation and capillary leak. The redistribution of fluid into the interstitium, abnormal external losses and poor oral intake result in relative hypovolaemia. A high proportion of patients will require vasopressor support to maintain adequate blood pressure.

Lactic acidaemia

Hypovolaemia and vasodilation in acute liver failure reduce oxygen tissue delivery, while microcirculatory disturbances reduce oxygen use by tissues, resulting in increased lactate production. As the majority of lactate clearance also normally takes place in the liver, the combination of increased lactate production and reduced lactate clearance in acute liver failure results in a lactic acidaemia.

Infection

Serious infection is an important cause of death in acute liver failure. Gram-positive and Gram-negative bacteria and fungal infections are all common in acute liver failure, and may originate from the patient's own flora or the hospital environment.

Hypoglycaemia

Hypoglycaemia occurs in acute liver failure as a result of reduced hepatic gluconeogenesis and depleted glucagon stores. Blood glucose concentration should be checked at least every 4 hours, with a target of 6–10 mmol/litre.

Renal failure

Renal failure complicates acute liver failure in 70% of cases, requiring renal replacement therapy in 30% of patients (Tujios et al, 2015). Renal failure can result from the cause of the liver insult (eg paracetamol is also directly nephrotoxic at high concentration), or from pre-renal hypovolaemic and distributive shock. Clinical challenges in acute renal failure include electrolyte disturbances and fluid overload. Uraemia is rare as a result of loss of urea cycle function in severe liver failure, and clinicians should not delay the initiation of renal replacement therapy just because the urea concentration remains low.

Management

The overall aim in managing patients with acute liver failure is to treat and prevent complications while allowing sufficient time for hepatic regeneration or liver

transplantation. Almost all patients with acute liver failure will require early admission to the intensive care unit. The cause of liver failure should be sought so that specific treatments, such as N-acetylcysteine for paracetamol toxicity, can be commenced early (Table 1). A systematic guide to managing patients with acute liver failure is provided in Table 4.

Table 4. A systematic guide to managing patients with acute liver failure

Definition	Acute liver failure: ■ Presence of hepatic encephalopathy (may be mild) ■ Coagulopathy (abnormal prothrombin time or international normalised ratio) ■ Jaundice to encephalopathy <8 weeks ■ No previous history of liver disease
Airway	■ Intubate if Glasgow Coma Scale score is <8 or West Haven grade III or IV encephalopathy
Respiratory	■ Target oxygen saturations 92–96% ■ If intubated, target partial pressure of carbon dioxide ($PaCO_2$) 4.5–5.0 kPa (33–37 mmHg), or that achieved by patient before intubation
Circulation	■ Target mean arterial pressure ≥65 mmHg. If mean arterial pressure <65 mmHg, consider fluid bolus or commence noradrenaline infusion

Neurological	■ Check neurological observations twice hourly
	■ If intubated, keep head at 30° and neutral position
	■ Check arterial ammonia level
	■ If acute change in neurology, urgent computed tomography scan of the brain to exclude cerebral haemorrhage
	■ If high grade hepatic encephalopathy and ammonia >80mmol/litre, consider quadruple H therapy:
	  ■ Hyperventilation: Target a $PaCO_2$ at the lower end of normal (4.5–5.0 kPa or 33–37 mmHg) or that achieved by patient before intubation. Adjust mechanical ventilation to achieve necessary minute ventilation
	  ■ Hypernatraemia: Target sodium concentration 145–155 mmol/litre Commence 5–10 ml/hour 20% saline via central venous catheter
	  ■ Haemo(dia)filtration: continuous veno-venous haemofiltration or continuous veno-venous haemodiafiltration
	  ■ Hypothermia: Target temperature 35°C

Endocrinology	■ Check blood glucose concentration at least every 4 hours ■ If glucose is <6 mmol/litre, start concentrated dextrose infusion (eg 25%) via central venous catheter. Target a blood glucose concentration of 6–10 mmol/litre
Renal	■ Check arterial blood gas for pH, sodium and potassium concentrations every 4 hours ■ Assess fluid balance twice daily ■ If metabolic acidosis (pH <7.2), hyperkalaemia, severe hyponatraemia or fluid overload is present, commence renal replacement therapy (continuous veno-venous haemofiltration or continuous veno-venous haemodiafiltration) ■ Check $PO4^+$ daily and correct hypophosphataemia if required
Gastrointestinal	■ Commence proton pump inhibitor ■ Commence enteral feeding
Haematology	■ Check international normalised ratio (do not correct if there is no clinically significant bleeding) ■ Check fibrinogen; target >1.5 g/litre ■ Check platelets; target >$75x10^9$/litre
Infectious diseases	■ Check white cell count and C-reactive protein ■ Daily blood, sputum and urine cultures ■ Check invasive lines for signs of infection ■ Daily chest X-ray ■ If clinical concern of infection, start antibiotics and antifungals. Control source if possible

Airway

If the Glasgow Coma Scale score is reduced, the patient should be intubated to minimise risk of aspiration, airway obstruction or hypoventilation. Hypoxia and hypercapnia will both worsen cerebral oedema.

Breathing

An elevated partial pressure of carbon dioxide in arterial blood ($PaCO_2$) leads to cerebral vasodilatation, which exacerbates cerebral oedema and must be avoided in patients with acute liver failure. Targeting a lower $PaCO_2$ by mild hyperventilation is neuroprotective, through attenuation of cerebral vasodilation and associated hyperaemia (Stravitz et al, 2007). Intubated patients must be ventilated sufficiently to target a $PaCO_2$ on the lower end of normal ($PaCO_2$ 4.5–5.0 kPa or 33–37 mmHg) or that achieved by the patient before intubation (whichever is lower). Hypoxia must be avoided.

Circulation

Hypovolaemia should be treated with intravenous fluids or blood products if secondary to bleeding. Peripheral vasodilatation can be treated with a noradrenaline infusion titrated to maintain a mean arterial pressure of 65 mmHg.

Disability

Severe cerebral oedema in patients with acute liver failure can result in refractory intracranial hypertension and death. A combination of therapies, known as quadruple H (haemodiafiltration, hypernatraemia, hypothermia and hyperventilation) therapy (quad H), may reduce severe cerebral oedema in patients with acute liver failure (Warrillow and Bellomo, 2014).

Haemo(dia)filtration

Hyperammonaemia is highly associated with severe cerebral oedema and intracranial hypertension (Clemmesen et al, 1999). Arterial ammonia can be reduced to safe levels using continuous renal replacement therapy (Slack et al, 2014), and so this should be commenced early in acute liver failure patients with hyperammonaemia (Warrillow et al, 2020).

Hypernatraemia

Hypernatraemia can reduce cerebral oedema by encouraging the movement of water out of the brain (Warrillow and Bellomo, 2014). A sodium concentration of 145–155 mmol/litre should be targeted (eg using an infusion of 5–10 ml/hr 20% sodium chloride via a central venous catheter).

Hypothermia

Mild hypothermia (33–35°C) can reduce cerebral oedema in acute liver failure by reducing ammonia production and CNS uptake, as well as reducing neuro-excitation (Chatauret et al, 2002). However, a randomised control trial of 46 patients with acute liver failure and a high risk of intracranial hypertension found that mild hypothermia at 33–34°C did not confer a benefit, when compared to management at 36°C, in the prevention of intracranial hypertension or in overall survival (Bernal et al, 2016). Avoidance of fever remains essential, and targeting a core temperature of 35°C appears to be a safe and pragmatic means of achieving this. Renal replacement therapies can be highly effective in lowering core body temperature, especially if the inbuilt heating mechanism can be switched off; otherwise, external cooling devices can be applied.

Hyperventilation

As explained in the section of breathing within this article, mild hyperventilation targeting a $PaCO_2$ at the lower end of normal ($PaCO_2$ 4.5–5.0 kPa or 33–37 mmHg) can reduce the risk of cerebral oedema. Hyperventilation to lower levels of $PaCO_2$ is not recommended, except as a temporising measure or rescue therapy for severe intracranial hypertension that is refractory to other measures.

Other

The patient's head should be at 30° and in a neutral position, with no tight ties around the neck in order to optimise venous drainage. Hypoxia and hypoglycaemia must be avoided. Deep sedation (eg with propofol) and muscle relaxants can also help reduce intracranial pressure if cerebral oedema develops despite other measures.

Endocrinology

Blood glucose levels should be checked a minimum of every 4 hours, and more often if they are low. A blood glucose target of 6.0–10 mmol/litre is reasonable. Hypoglycaemia should be treated aggressively with a concentrated dextrose infusion (eg 25%). Hypotonic 5–10% dextrose solutions should be avoided as these can cause hyponatraemia and exacerbate cerebral oedema.

Fluids, electrolytes and renal support

Over two-thirds of acute liver failure patients will develop acute kidney injury. Continuous renal replacement therapy should be commenced early in acute liver failure patients with high-grade hepatic encephalopathy, even in the absence of acute kidney injury. Continuous renal replacement therapy, such as veno-venous haemodiafiltration, avoids the cardiovascular and metabolic instability often encountered during intermittent modes of renal replacement therapies (Hall and Fox, 2006). Continuous renal replacement therapy improves metabolic acidosis by clearing non-volatile acids, correcting electrolyte disturbances and allowing an even fluid balance to be maintained.

Gastrointestinal support

Proton pump inhibitors should be commenced to reduce risk of stress ulcers and upper gastrointestinal bleeding. Early nutrition is important and should be commenced via a nasogastric tube if the patient is intubated or nil by mouth.

Haematological support

A raised international normalised ratio is not significantly associated with bleeding in acute liver failure and should not be corrected with clotting factors, unless the patient is actively bleeding or undergoing a high-risk invasive procedure. Central lines and access for continuous renal replacement therapy can be safely inserted by experienced clinicians, despite elevations in the international normalised ratio. To reduce the risk of bleeding, fibrinogen should be replaced using cryoprecipitate (10–20 units) to maintain a fibrinogen concentration of at least 1.5 g/litre, and thrombocytopenia should be corrected with platelet transfusion if the platelet count is less than $75x10^9$/litre (Warrillow et al, 2019).

Infectious diseases

Infections often develop early in the course of acute liver failure, with a median onset of 2–5 days following hospital admission (Lee, 1994). Sepsis must be actively sought out, with regular blood, sputum and urine cultures, assessment of indwelling lines and appropriate radiological imaging. If infection is suspected, antibiotics and antifungals should be commenced early and source control, including removal of central lines, obtained.

Therapeutic plasma exchange

Therapeutic plasma exchange, in which plasma is removed and replaced with fresh frozen plasma, has been shown to improve transplant-free survival in acute liver failure (Larsen et al, 2016; Maiwall et al, 2022). Further research is needed to ascertain ideal volume, type, duration, frequency and timing of plasma exchange in acute liver failure, as well as whether this approach is superior to the early initiation of continuous renal replacement therapy for patients at high risk of cerebral oedema.

Indications for referral to a liver transplantation centre

Given the high mortality in acute liver failure, any patient who is deteriorating rapidly, or who requires intensive or high dependency level care, should be urgently referred to a centre capable of liver transplantation. Early referral should be made for patients with:

Key points

- Acute liver failure is the rapid onset of severe liver dysfunction in the absence of pre-existing liver disease. Establishing the cause of acute liver failure is important to guide treatment and predict transplant-free survival.
- The key clinical challenges of acute liver failure include cerebral oedema, sepsis, hypoglycaemia, coagulopathy, renal impairment and haemodynamic instability.
- The overall aim in managing patients with acute liver failure is to treat and prevent complications, while allowing sufficient time for hepatic regeneration or liver transplantation.
- Severe cerebral oedema in acute liver failure may be reduced by quadruple H therapy (haemofiltration, hypernatraemia, hypothermia and hyperventilation).

Curriculum checklist

This article addresses the following requirements from the general internal medicine curriculum:

- Managing an acute unselected take
- Providing continuity of care to medical inpatients, including management of comorbidities and cognitive impairment
- Delivering effective resuscitation and managing the acutely deteriorating patient

- International normalised ratio >3
- pH <7.2
- Lactate >4.0 mmol/litre
- Alanine aminotransferase >1000 units/litre
- Glasgow Coma Scale <14 (Farley and Warrillow, 2015).

The decision to list a patient for urgent liver transplantation is complex. A transplant that is performed too early, when the patient's own endogenous liver may yet still regenerate, subjects the patient to an unnecessary operation with lifelong immunosuppression, and a scarce organ is given to a patient who would have survived without it. Listing for transplant too late runs the risk that a suitable liver may not be available in time, and the patient may be too unwell to survive the operation. Current scoring systems to predict transplant-free survival may not be sufficiently reliable to guide transplantation decisions, so expert review by experienced clinicians is the recommended approach.

Conclusions

Acute liver failure has a high rate of mortality. Identifying the aetiology of acute liver failure by taking a thorough history and organising appropriate investigations allows specific therapies to be initiated. The clinical challenges of acute liver failure include hepatic encephalopathy and cerebral oedema, sepsis, hypoglycaemia, coagulopathy, renal impairment and haemodynamic instability. The aim in managing patients with acute liver failure is to prevent and treat such complications, allowing time for hepatic regeneration or liver transplantation.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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