Chapter 2
Acute Liver Failure

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Key Learning Points

- Recognition of the acute liver failure syndrome.
- Understanding of the role and limitations of prognostic criteria.
- Knowledge of initial resuscitative measures.
- Recognition of the common life-threatening complications specific to acute liver failure.
- Understanding of the specialist interventions available in a tertiary referral centre.

Chapter Review Questions

A 20-year-old female presents to her local Emergency Department having been found drowsy in her bedroom by a family member. Her mother states she is usually well and was last seen 2 days ago.

She looks very unwell. She has a Glasgow Coma Score of 8. Her saturations are 95% on air, she is tachypnoeic at 35 breaths per minute. She is tachycardic (140/min) and hypo-

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tensive (90/30 mmHg). Her lactate is 12 mmol/L. Her blood glucose is 2 mmol/L.

She has an alanine aminotransferase (ALT) of 10,360 iU/L, a Bilirubin of 54 umol/L and an alkaline phosphatase (ALP) of 138 iU/L. Her white cell count is moderately elevated and her platelets slightly low at 90 × 10^9/L. Her international normalised ratio (INR) is 4.9.

The Emergency Department clinicians have called you, asking for medical input.

1. What is the most likely diagnosis?
2. What initial measures should be taken in the Emergency Department?
3. The ammonia level is reported as 230 umol/L, what is the resulting key concern and what measures can you take to mitigate this?

Introduction

Acute liver failure (ALF) is a clinical syndrome in which an acute insult provokes massive hepatocellular necrosis in the absence of pre-existing chronic liver disease.

ALF is characterised initially by jaundice, coagulopathy (INR > 1.5) and encephalopathy and can rapidly progress to a life-threatening multi-organ failure [1, 2].

Patients with a significant acute liver injury (a combination of jaundice and coagulopathy) should undergo regular assessment for deterioration or for the onset of hepatic encephalopathy.

Modern classifications are based upon time interval between development of jaundice and encephalopathy (Fig. 2.1) and give clues to likely causes and therefore prognosis (Table 2.1):

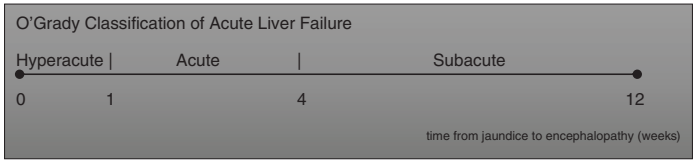

Figure 2.1 O'Grady classification as described by O'Grady et al. in 1993 [3]

Table 2.1 Summary of the more common causes of Acute Liver Failure

Cause		Presentation	Specific test(s)	Specific treatment(s)
Infectious/ Viral	Hepatotropic (A, B, D, E) Nonhepatotropic (CMV, EBV, HSV1/2, VZV, dengue)	Hyperacute or Acute Viral prodrome	Viral serology	Antivirals
Drugs	Paracetamol (acetaminophen) Non-paracetamol (carbamazepine, cocaine, ecstasy, flucloxacillin, isoniazid, nitrofurantoin, sodium valproate, statins, Phenytoin, many others) Mushrooms (*Amanita phalloides*)	Hyperacute Hyperacute or acute Diarrhoea	History, paracetamol levels History, drug screen History, eosinophil count	N-acetylcysteine Possible role for trial of corticosteroids Penicillin G
Cardiovascular	Ischaemic/hypoxic hepatitis Budd-Chiari syndrome Portal venous thrombosis	Hyperacute or acute Acute or subacute Acute or subacute	Clinical findings of shock, echocardiogram Imaging Imaging	Cardiovascular support TIPPS, revascularisation TIPPS, revascularisation

(continued)

TABLE 2.1 (continued)

Cause		Presentation	Specific test(s)	Specific treatment(s)
Autoimmune	Autoimmune hepatitis		Auto-antibodies and serum IgG levels	Possible role for trial of corticosteroids
Metabolic	Wilson's disease		Copper, caeruloplasmin, Kaiser-Fleischer rings, genetic testing	Chelation
Pregnancy-related	Acute fatty liver of pregnancy (AFLP) HELLP syndrome	Hyperacute or acute	Pregnancy test Imaging	Delivery
Others	Heat stroke Malignancy HLH Seronegative/indeterminate		Temperature Imaging/biopsy Ferritin, triglycerides, clinical scores	Cooling/rehydration Etoposide, dexamethasone, cyclosporine A

- Hyperacute liver failure is frequently caused by paracetamol or other drug toxicity and is the subtype with the highest rates of transplant free survival.
- Subacute liver failure is commonly associated with drug-induced liver injury or indeterminate (seronegative) hepatitis and generally has a worse prognosis.

Epidemiology

Acute liver failure is a rare syndrome, and the incidence and aetiologies vary globally, particularly between more and less economically developed countries:

- In more developed countries annual incidence is approximately 1–6 per million [4], the most common aetiology is paracetamol overdose and viral hepatitis is less common [5–7].
- In less developed countries annual incidence is higher (e.g. 63 per million in Thailand), viral hepatitis (particularly Hepatitis B) is the most common aetiology and paracetamol overdose is rarer [8].

There are a multitude of other potential rarer causes including inborn errors of metabolism.

Aetiology of ALF can be divided into:

- primary—due to direct liver-specific injury, e.g. viral hepatitis or paracetamol-overdose,
- secondary—due to systemic illness, e.g. hypoxic hepatitis or malignant infiltration.

Liver transplantation is only likely to be considered in primary aetiologies [1].

Prognosis

Prognosis in ALF has improved dramatically over the last 5 decades: approximately 75% of patients now surviving, and up to 60–72% without transplantation [5–7].

Likely reasons for this improvement are [1]:

- Improved living conditions in developing countries (reducing incidence of viral hepatitis).
- Public health interventions (e.g. some countries, including the UK, restrict the quantity of paracetamol that can be easily bought).
- Better recognition and initial management of ALF.
- More rapid referral and transfer to specialist centres.

Better survival outcomes without transplantation can paradoxically make decision-making about liver transplantation more difficult. Transplantation incurs major perioperative risks and the complications inherent in life-long immunosuppression. This is clearly better avoided if the patient will survive without transplantation [1]. There is also a societal cost to unnecessary transplantation, in that the donor liver will then be unavailable for another listed patient.

Prognostic criteria help identify those most at risk of death from ALF, and therefore those most likely to benefit from transplantation. The most widely used in UK clinical practice have historically been the Modified King's College Criteria (KCC) [9] (Table 2.2).

The specificity of the KCC is high, especially for paracetamol-induced ALF, at between 92 and 95%, however, the sensitivity is lower at 58–69% [10]. Put simply this means that if a patient meets the criteria they are highly likely to die without transplantation. However, rigidly applying the criteria alone risks transplanting a substantial group of patients who would survive without transplantation.

Some argue that better outcomes in ALF since the criteria were formulated mean they now lead to unnecessary trans-

Table 2.2 UK revised Criteria/Modified King's College Criteria for identifying a poor prognosis in ALF (currently used by the UK Organ Donor and Transplant Service, NHSBT) https://www.odt.nhs.uk/transplantation/liver/

Paracetamol-induced	Any of: • Arterial pH < 7.25 (despite 24 h of fluid resuscitation) • All three of: – An international normalised ratio (INR) of greater than 6.5 – Serum creatinine of greater than 300 micromoles per litre – Encephalopathy (of grade III or IV) • Serum lactate >4.0 mmol/L (despite 24 h of fluid resuscitation)
Non-paracetamol-induced	Favourable aetiologies (ecstasy/acute viral hepatitis) with encephalopathy: • INR > 6.5 (PT > 100S) or • Three of: INR > 3.5 (PT > 50S), age > 40 or < 10 years, bilirubin>300 μmol/L and J-E > 7 days Unfavourable aetiologies (idiosyncratic drug-induced, indeterminate) • INR >6.5, or • If hepatic encephalopathy is absent, then INR >2 and any two from the following: Age > 40 or < 10 years; INR >3.5 • If hepatic encephalopathy is present, then jaundice to encephalopathy time > 7 days; serum bilirubin >300 umol/L

plantation [11, 12]. In paracetamol-overdose in particular centres have recently reported 69% survival in those meeting the KCC [12].

For liver transplant listing in the UK Revised Criteria are now used. These more complex criteria better predict mortality than the KCC with a sensitivity of 92% and specificity of 80% [1, 12, 13].

Initial Resuscitation and Referral

Management of ALF is based upon rapid recognition of the syndrome, early resuscitation and commencement of appropriate organ support. Once the patient is initially stabilised, systematic investigations should be undertaken to diagnose or exclude likely causes.

N-acetylcysteine is highly effective in paracetamol-induced acute liver injury. Benefit may be seen in other aetiologies and its use is recommended in all aetiologies [1].

The potential severity of the organ failures seen in ALF mandates early and close collaboration between the initially admitting clinicians and local critical care services, and tertiary centre specialist hepatology, transplant surgery and specialist liver critical care teams.

Measures to avoid cerebral oedema with severely raised intracranial pressure and fatal brainstem herniation into the foramen magnum ("coning") must be considered early.

Patients with ALF can be expected to deteriorate rapidly so early liaison with specialist centres and critical care support with transfers (usually intubated) is highly recommended (Table 2.3).

Table 2.3 Initial Resuscitation in ALF

Initial assessments	**Potential concerns**	**Initial actions**
Airway	Inability to protect own airway (typically Glasgow coma score < 8)	Intubation
Breathing	Oxygen saturation < 94%	Supplemental oxygen
Circulation	Hypotension, clinical signs of shock, hyperlactataemia	Fluid resuscitation and advanced cardiovascular support

Table 2.3 (continued)

Initial assessments	Potential concerns	Initial actions
Disability	Hypoglycaemia Young patient Encephalopathy > grade 2 Hypercapnia	Supplemental parenteral glucose Early implementation of a neuroprotective strategy (see section below)
Exposure	Evidence of organ failure or encephalopathy Coagulopathy	Early broad-spectrum antibiotics and anti-fungal Consider an individualised strategy with point of care viscoelastic testing N-acetylcysteine infusion

Respiratory Support

Endotracheal intubation and invasive ventilation is required in high grade encephalopathy both to prevent aspiration and to maintain normocapnia as part of neuroprotection (alleviating the risk of hypercapnia-mediated cerebral vasodilation contributing to raised intracranial pressure).

As with other critically ill patients, those with ALF are at risk of developing pulmonary oedema, pneumonia and acute respiratory distress syndrome secondary to their multi-organ dysfunction and iatrogenic interventions [14].

Lung protective ventilation (with lower tidal volumes, higher positive end expiratory pressure [PEEP] and tolerance of hypercapnia) reduces the risk of ventilator-acquired lung injury but in ALF this must not be at the expense of neuroprotection (via hypercapnia or very high PEEP reducing cerebral venous drainage) [1, 15].

Cardiovascular Support

Fluid resuscitation is crucial in early management to restore circulating volume and adequate systemic perfusion. Resuscitation should be guided initially by close clinical assessment and the use of advanced haemodynamic monitoring is advisable.

Lactate as a prognostic marker in ALF is best considered once adequate fluid resuscitation has been completed [1]. Crystalloids (ideally buffered solutions) should be used [16]. Albumin containing solutions are commonly used but lack a convincing evidence base [17].

ALF typically progresses to a severe vasodilatory shock and, once hypovolaemia has been corrected, vasopressors are likely to be required. Noradrenaline is the mainstay vasopressor with vasopressin and steroids as potential adjuncts in refractory shock [18].

Neurological Support

Raised intracranial pressure (ICP) is now only seen in approximately 20% of patients with ALF. However once present mortality remains greater than 50% [1].

The likely pathological mechanism is a "dual hit":

- high blood ammonia leading to glutamine accumulation, astrocyte swelling and mitochondrial dysfunction,
- high levels of circulation inflammatory cytokines, as part of the severe systemic inflammatory response.

both leading to development of cerebral oedema.

The risk of severe intracranial hypertension is highest in:

- young patients (with little or no cerebral atrophy and so less space within the skull to accommodate cerebral oedema before intracranial hypertension occurs);
- hyperacute presentations;
- high grade encephalopathy;
- persistently elevated ammonia.

High arterial ammonia levels (>100 μmol/L) are associated with cerebral oedema and very high levels (>200 μmol/L) with spontaneous intracranial haemorrhage [19].

Invasive ICP monitoring is now rarely used in ALF in the UK as severe intracranial hypertension has become less common. Invasive ICP monitors are associated with a risk of iatrogenic intracranial haemorrhage (up to 4.2%) [1]. Reverse jugular venous catheters and transcranial doppler offer potential less invasive alternatives.

Neuroprotective measures should be instituted as standard in critically ill patients with ALF, especially in high risk subgroups:

- *Hypertonic sodium infusion (30% NaCl) to maintain serum sodium 145–150 mmol/L* (to limit osmotic shifts into the brain worsening cerebral oedema).
- *Early continuous renal replacement therapy to reduce ammonia < 100micromol/L* (with ultrafiltration rate uptitrated to achieve effective clearance [20]).
- Deep sedation.
- Minimise non-essential nursing interventions.
- Maintenance of normothermia/avoidance of hyperthermia.
- Head of bed elevation to 30°.
- Maintenance of normoxia.
- Maintenance of normocapnia.
- Maintenance of mean arterial pressure to achieve cerebral perfusion pressure 55–60 mmHg.
- Maintenance of normoglycaemia.

Coagulopathy Management

The apparent coagulopathy seen in ALF—prolonged prothrombin time—is often not reflected by impaired functional testing or in a greater likelihood of clinically significant bleeding [21]. ALF patients have a complex coagulation picture: most have a “balanced coagulopathy” with reduced pro- and anti-coagulant factors; some are even pro-thrombotic.

Thrombocytopaenia and low fibrinogen levels are generally a better marker of bleeding risk than prothrombin time [1].

Key points in managing apparent coagulopathy are:

- Do not administer FFP for perceived bleeding risk alone or for minor procedures (e.g. central line insertions).
  - This is clinically unnecessary and may confound prognostic criteria.
- Should major bleeding occur use functional testing if available (e.g. thromboelastography) to guide coagulopathy correction.
- Vitamin K should be administered, especially if poor nutrition is suspected—this will not confound prothrombin time abnormality due to acute liver failure.

Metabolic Support

Hypoglycaemia is a marker of severe ALF and requires close monitoring and intravenous correction. Low volume high concentration dextrose solutions are advisable to avoid cerebral oedema.

ALF is a highly catabolic state requiring careful attention to nutrition. Early nutrition specialist input and enteral feeding is therefore recommended [22]. In patients with high grade encephalopathy and high ammonia levels, protein administration may be restricted for 24–48 h to avoid elevating ammonia further.

Renal Support

Acute kidney injury requiring haemofiltration is common (>50%) in ALF and appears to reflect the degree of systemic illness. Early and continuous renal replacement therapy improves survival in hyperammonaemia and severe lactic acidosis [20].

Microbiological Considerations

Patients with ALF are relatively immunosuppressed and have very high risk of infection (historical rates of bacteraemia up to 80% and fungaemia 32%) [23]. Empirical treatment with broad-spectrum antibiotics and antifungals is recommended [24].

Liver Transplantation

The supportive measures outlined above are crucial and effective organ support may allow time for native liver regeneration to occur, particularly in hyperacute ALF. However, in the UK liver transplantation remains the definitive treatment for those meeting poor prognostic criteria and hence expected to die without transplantation. Internationally, as discussed in the Prognosis section, there is increasing interest in managing ALF (particularly paracetamol-induced) without transplantation [7, 12].

In the UK, liver transplantation only occurs in a small number of specialist centres with donor organs allocated via a national system. Transplantation decision-making occurs in a collaborative manner with surgical, hepatology, anaesthetic and critical care input and, in difficult cases, discussion amongst specialist centres.

Decisions around transplantation are multifactorial: the UKRC help identify those unlikely to survive without transplantation but donor livers are a scarce resource and an assessment must also be made of the patient's medical comorbidities, physiological reserve and ability to comply with the demands of life-long immunosuppression and medical follow-up. It is possible for an individual with severe psychiatric comorbidities, active intravenous drug use or similar concerns to be considered inappropriate for transplantation, even in ALF [13].

5-year survival rates for patients transplanted in the UK for ALF are 84% Survival worsens with older age (particularly >65 years) and greater severity of multi-organ failure prior to transplantation.

Early recognition and listing of patients for transplantation is vital as they can be expected to become more physiologically unstable with time. In rare cases it may even be decided to perform a total hepatectomy (to remove the inflammatory drive of having a large amount of necrotic hepatic tissue) whilst awaiting organ availability as a temporary last ditch stabilising measure.

Plasma Exchange

Plasma exchange (or plasmapheresis) is the removal of the patient's plasma and replacement with donor fresh frozen plasma. It removes many low and medium molecular weight molecules—specifically including pro-inflammatory cytokines. High volume plasma exchange refers to replacement of 15% of body weight with fresh frozen plasma.

A single RCT has demonstrated improved transplant-free survival, as well as improved haemodynamic and biochemical markers, compared to standard medical therapy only [25].

Extra-Corporeal Liver Support

Multiple extra-corporeal liver support (ECLS) systems have been trialled without evidence of benefit. The most promising device may be the molecular adsorbent recirculating system (MARS), which has been trialled as a bridging therapy to transplantation in ALF but without a survival benefit [26]. Whilst further systems are being developed and trialled currently ECLS remains a potential hope rather than a clinical option.

Clinical Pearls

1. ALF requires early recognition, early invasive organ support and early referral to a specialist centre.
2. Have a high suspicion for cerebral oedema, especially in younger people.

3. Early renal replacement therapy improves mortality and reduces risk of cerebral oedema.
4. Empirical antimicrobials should be started before evidence of infection.
5. Coagulopathy in ALF is complex – in the absence of major bleeding attempting correction with blood products is unnecessary and will confound prognostication.

Chapter Review Answers

1. This is acute liver failure. In the UK the most common aetiology is paracetamol overdose although other causes must also be considered and excluded.
2. Key early interventions include:

   (a) Consideration of intubation given her low GCS.
   (b) Fluid resuscitation and likely vasopressors.
   (c) Correction of hypoglycaemia.
   (d) Empirical N-acetylcysteine.
   (e) Empirical broad-spectrum antibiotics.
   (f) Referral to Intensive Care to facilitate the above.

3. The key concern in a young person with a high ammonia level and decreased consciousness is cerebral oedema. This is likely to become life-threatening unless aggressively controlled.

   Key interventions will include:

   (a) Invasive ventilation to avoid hypercapnia and maintain normoxia.
   (b) Early and continuous renal replacement therapy to clear ammonia.
   (c) Hypertonic saline to minimise fluid shifts into the brain.
   (d) Deep sedation/minimal touch nursing/keeping the bed head up 30 degrees.
   (e) Maintaining adequate cerebral perfusion pressure with vasopressors.
   (f) Early referral for specialist opinion, transfer and consideration of liver transplantation.

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