Acute liver failure: updates in pathogenesis and management

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Abstract

Acute liver failure is a life-threatening illness precipitated by an acute liver injury in patients with no pre-existing liver disease. Acute viral hepatitis and drug-induced liver injury account for most cases, the clinical course characterized by the development of coagulopathy and hepatic encephalopathy, often progressing to multi-organ disease, which is associated with high fatality rates. The outcomes have improved significantly over time with improving standards of organ system support and access to liver transplantation for very sick individuals. The King's College criteria are the most commonly used tool for determination of prognosis and consideration for transplantation. Prompt diagnosis, immediate initiation of supportive care and aetiology-specific treatment, where applicable, as well as early discussions and transfer to a transplant centre, are the keys to successful outcome.

Keywords Acute liver failure; critical care; fulminant hepatitis; hepatic encephalopathy; intensive care; liver transplantation; MRCP; multiorgan failure

Key points

- Acute liver failure is associated with high risk of death
- King's College criteria defines prognosis
- Liver transplantation saves lives of patients with poor prognosis
- Long-term survival is observed in those who recover spontaneously
- Multi-organ support is the basis of supportive care
- Plasma exchange improves transplant-free survival

Definition and classification

Acute liver failure (ALF) is a rare, life-threatening illness triggered by a *de novo* liver injury to a previously healthy liver, and frequently progressing within hours and weeks to multisystem involvement and failure. Coagulation abnormalities of liver origin (elevated prothrombin time (PT), international normalized ratio (INR) > 1.5) and mental alterations caused by hepatic encephalopathy (HE) are the key defining clinical criteria required to make a diagnosis.

ALF is a specific clinical entity in terms of the clinical phenotype, disease course, prognosis and eligibility for emergency liver transplantation. This must be distinguished from secondary liver injury in sepsis or congestive cardiac disease or failure after major liver resection, none of which qualify as ALF or are an indication for emergency liver transplantation. Conversely, acute presentations of Wilson's disease, acute Budd–Chiari syndrome and some cases of autoimmune hepatitis can have undiagnosed chronic liver involvement but are treated as ALF because of the poor prognosis without transplantation in these conditions, and the clinical features consisting predominantly of coagulopathy and HE.

ALF is a rare condition with an estimated annual worldwide incidence of 1–6 per million population. The incidence is declining because of better vaccination programmes against viral hepatitis and fewer drug-induced cases, particularly those related to paracetamol toxicity; these are the two main aetiologies of ALF, making up most cases worldwide, viral hepatitis in developing countries, and paracetamol toxicity predominantly in developed countries. The outcomes, both transplant-free and after transplantation, have continued to improve in recent decades owing to better understanding of the disease, a more refined organ system support platform, better aetiology-specific interventions and access to liver transplantation in severe cases.

Accurate prognostication to identify patients who are unlikely to survive without transplantation remains a challenge. The most commonly used tool, the King's College criteria, have identified the major prognostic determinants: aetiology of ALF, patient age and rapidity of disease progression, defined as the time from development of jaundice to onset of HE – 7 days (hyperacute), 7–28 days (acute) and 28 days to 12 weeks (subacute). Subacute presentation is associated with the worst prognosis without liver

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transplantation. Disease duration >28 weeks is considered to be chronic liver failure.[1]

Aetiology

Viral hepatitis (A, B, E) is the most common cause of ALF in developing countries and worldwide. Hepatitis B virus (HBV) is the most commonly encountered virus in most of Asia, Africa and the Amazon region, while hepatitis E virus is common in the Indian subcontinent. Drug-induced liver injury (DILI), in particular paracetamol toxicity, which accounts for 50–70% of DILI, is the most common offender in developed world.

Other rarer causes include other viral infections (herpes simplex virus 1 and 2, herpes virus 6, varicella, Epstein–Barr virus, cytomegalovirus, parvovirus (erythrovirus) B19), specifically in immunocompromized patients, autoimmune hepatitis, metabolic disorders and pregnancy-related liver diseases. No underlying cause is found in up to 20% of patients, which is referred to as 'indeterminate' or 'seronegative' ALF.

Pathogenesis

Irrespective of the aetiology of ALF, the common pathway causing damage involves an intense inflammatory surge mediated by cytokines and other inflammatory mediators produced by damaged hepatocytes. This leads to severe impairment of the synthetic, metabolic and immune functions of the failing liver, followed by progression to extrahepatic organ manifestations and multiorgan failure.

Encephalopathy: HE is generally multifactorial, and its mechanism is not well understood (see pages 833–837 in this issue for more on the pathogenesis of HE).

Cerebral oedema and intracranial hypertension (ICH) are the most dreaded complications of ALF and are considered the leading cause of death in advanced stages. However, mortality from ICH is declining because of targeted monitoring and a proactive approach to managing the causes. High blood ammonia concentrations, particularly associated with rapid increases, are associated with higher mortality. It has been found that an arterial ammonia concentration ≥124 micromol/litre can predict mortality and is associated with higher rates of complications. More recently, a concentration of ammonia >200 microg/dl has been shown to be a strong predictor of severe cerebral oedema and brain herniation in patients with grades 3 and 4 HE, while values <75 microg/dl or a falling ammonia concentration are rarely related to intracranial complications.

Hyponatraemia further contributes to the development of cerebral oedema and ICH. A sodium target of 145–155 mmol/litre is desirable in the management of these patients.

Coagulopathy: the severely injured liver is unable to synthesize coagulation factors, which leads to a prolonged INR. However, there is a simultaneous and proportional reduction in the production of natural anticoagulant proteins such as protein C, protein S and antithrombin, as well as increased production of endothelium-derived procoagulants, factor VIII and von-Willebrand factor. Together, this leads to an overall balanced haemostasis with little risk of bleeding that is spontaneous or related to invasive procedures. Platelet and fibrinogen derangements are more likely to predict bleeding risk in the setting of ALF.

Metabolic derangements: the most common metabolic complications are hypoglycaemia, metabolic acidosis, renal failure and adrenal insufficiency. Hypoglycaemia is usually the result of depletion of glycogen stores and impaired gluconeogenesis in the liver. Metabolic acidosis is usually associated with paracetamol toxicity or results from circulatory impairment, sepsis and renal failure. Renal failure is usually the sequela of circulatory failure, sepsis and disseminated intravascular coagulation or a toxic effect in DILI. It occurs in about 50% of patients with ALF. Acute adrenal insufficiency is recorded in up to 65% of individuals with

Initial assessment of patients presenting with ALF

Laboratory tests

Coagulation: PT/INR

Chemistries: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose

AST, ALT, alkaline phosphatase, GGT, total bilirubin, albumin, creatinine, blood urea nitrogen, creatine kinase, arterial blood gas, arterial lactate, amylase and lipase

Ammonia (arterial if possible)

Haematology: complete blood count, blood group and Rhesus factor

Toxicology: acetaminophen concentration, toxicology screen

Viral aetiology: viral hepatitis serologies including hepatitis A, B, C and E

Serology for Epstein–Barr virus, herpes simplex and varicella zoster viruses

Serology for human immunodeficiency virus HIV-1 and HIV-2

Autoimmune: ANA, ASMA, immunoglobulin concentrations

Others: ceruloplasmin concentration (if Wilson's disease is suspected)

Pregnancy test (in women of child-bearing age)

Imaging

Abdominal ultrasound scan with Doppler

ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 1

ALF. Corticosteroid treatment reduces vasopressor requirements, is not associated with survival benefits but increases infection risk. Other metabolic abnormalities are hyponatraemia, respiratory alkalosis and hypokalaemia.

Cardiorespiratory changes: patients with ALF tend to have a hyperdynamic high-cardiac-output state characterized by systemic vasodilatation and a low mean arterial pressure, which predisposes to tissue hypoperfusion. Respiratory alkalosis and hypoxaemia are present in most cases of fulminant ALF, and arise secondary to HE, sepsis, aspiration and acute lung injury.

Sepsis: immune dysregulation and immune paresis predisposes to secondary microbial infections. Sepsis has emerged as the most common cause of death in ALF, surpassing cerebral complications, which a decade ago accounted for most fatalities. Bacteraemia is reported in up to 80%, and fungaemia in up to 32%, of ALF patients. The most frequently associated organisms are *Staphylococcus aureus*, enterococci, *Escherichia coli*, *Klebsiella* and *Candida*. Antibacterial and antifungal prophylaxis (in high grades of HE) have been shown to improve cerebral complications and overall outcomes, and should be used as routine.

Diagnosis

Diagnosis is usually made from the clinical and laboratory features, essentially showing evidence of acute liver injury associated with coagulopathy and encephalopathy. Diagnostic laboratory and imaging baseline investigations are shown in Table 1 and should be undertaken in every patient with presenting with ALF.

Management

Initial management: early multidisciplinary team management involving hepatology, critical care and liver transplant teams is crucial. Management of severe cases should ideally be carried out in a tertiary centre with experience of and facility for performing emergency liver transplantation.[2] A summary of intensive care management strategies is shown in Table 2.

Aetiology-specific management: every measure should be made to diagnose the underlying aetiology, and specific management should start immediately.[2] This includes giving *N*-acetylcysteine (NAC) to treat paracetamol overdose, antiviral treatment for viral hepatitis-related ALF (lamivudine for HBV, aciclovir for herpes simplex virus) and immunosuppression for autoimmune hepatitis. NAC, when used early in the illness before progression to higher HE grades, has been shown to improve outcomes even for non-paracetamol aetiologies.

Cardiovascular support: aggressive fluid replacement with invasive cardiac monitoring and intravenous vasopressors are usually required. General data from large randomized trials favour the use of balanced crystalloids as the best option. If fluids are not effective in treating shocked patients, or if there is a risk of overinfusion, vasopressors can be used. Corticosteroids are sometimes used when treating refractory shock with other vasopressors.

Summary of initial intensive care management of patients with ALF

Brain/CNS	• CT of the head to exclude other intracranial reasons (e.g. intracerebral haemorrhage) for decreased mental state. Grade 3 and 4 HE: refer to the algorithm in Figure 1
Coagulation	• FFP or prothrombin complex to correct INR but only if there is clinical bleeding or before major interventions such as ICP bolt insertion or transplantation • Aim for a PLT >30 and fibrinogen >1
Haemodynamic/renal	• Aggressive fluid resuscitation in the early stages of illness. Avoid fluid overload. Maintain serum sodium at 145–155 mmol/litre • Pressors if needed to maintain haemodynamic stability (MAP >70 mmHg) • Renal support for renal reasons, metabolic reasons (ammonia >150 micromol/litre) or temperature control
Sepsis	• Active surveillance and screening for infections and prompt treatment • Prophylactic antibiotics and antifungals, especially in high grades of HE
Metabolic	• Monitor glucose levels, avoid hypoglycaemia • Serum sodium 145–155 mmol/litre • Close monitoring of electrolytes • Nutrition, best as enteral, or parenteral if needed

CNS, central nervous system; CT, computed tomography; FFP, fresh frozen plasma; MAP, mean arterial pressure; PLT, platelets.

Table 2

Respiratory support: endotracheal intubation and ventilation support are essential in higher grades of encephalopathy (≥grade 3) and is performed electively for airway protection, modulation of carbon dioxide tension and control of agitation.

Neurological support: the basic tenets of cerebral management are early elective intubation in patients with an encephalopathy grade >2 and measures to control cerebral complications. This is achieved by maintaining adequate sedation, normocapnia, normoglycaemia and moderate hypothermia.[3] Figure 1 outlines an algorithm for the management of grade 3 and 4 HE.

Renal support: this is often required for renal and extra-renal indications such as hyperammonaemia, temperature control and fluid balance. Overhydration is often associated with worsening cerebral oedema. Continuous modes of dialysis confer better haemodynamic and cerebral control.

Coagulopathy: major bleeding is uncommon despite highly elevated PTs. Routine correction is therefore is not recommended unless there is evidence of major bleeding. It is important to note

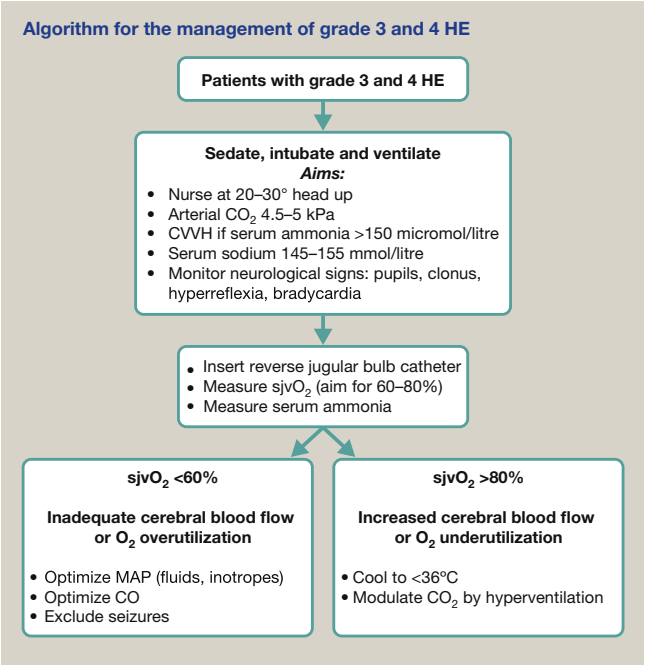

Figure 1

Criteria for liver transplantation in ALF

King's College Criteria (KCH)

Paracetamol overdose

1 *Irrespective of grade of encephalopathy:*
- Arterial pH <7.25 after volume resuscitation >24 hours after overdose

OR

2 *All of the following:*
- Grade 3 or 4 encephalopathy
- PT >100 seconds
- Serum creatinine >300 micromol/litre

OR

3 *The extended KCH criteria*
- Serum lactate >3.5 mmol/litre after early resuscitation
- Serum lactate >3.0 mmol/litre 24 hours after overdose, and adequate volume resuscitation

Non-paracetamol aetiologies

1 *Irrespective of grade of encephalopathy:*
- PT >100 seconds

OR

2 *Presence of encephalopathy + any three of the following:*
- Age <10 or >40 years
- Aetiology non-A, non-B hepatitis, drug reaction
- From jaundice to encephalopathy in >7 days
- PT >50 seconds
- Serum bilirubin >300 micromol/litre

Clichy criteria (non-paracetamol)

1. Confusion/coma + factor V concentration <20% + patient age <30 years

OR

2 Confusion/coma + factor V concentration <30% + patient age >30 years

Adapted from [5]

Table 3

that PT provides an important guide to monitoring the liver's synthetic function and is an important component of transplant criteria; it must not be corrected unless absolutely necessary.

Sepsis: active surveillance and screening for infections are necessary. Prophylactic broad-spectrum antibiotics and antifungals should be routinely used to prevent invasive bacterial and fungal infections. The antibiotics used should follow local policies and protocols depending on local sensitivity patterns.

Metabolic and nutritional support: frequent blood glucose monitoring and replacement with low-volume, high-concentration glucose preparations are essential to avoid cerebral oedema.

Artificial liver support and plasma exchange: unfortunately, none of the currently available artificial liver support systems has shown any survival benefit except high-volume plasma exchange; this was associated with improved transplant-free survival especially in patients in whom liver transplantation was contraindicated for medical or psychosocial reasons.[4]

Liver transplantation: super-urgent listing for liver transplantation is required for poor-prognosis patients. The King's College criteria highlighted in Table 3 are the most commonly used for patient selection. As per the European Liver Transplant Registry, 8% of organs are used for ALF, with 1-year survival rates close to 80%. The other criteria frequently used are the French Clichy criteria (Table 3), derived from a cohort of acute HBV-related ALF, for non-paracetamol aetiologies.

Liver transplantation is generally contraindicated in cases of irreversible brain damage, uncontrolled sepsis and presence of active malignancy. Because of limited organ availability and the life-long dependence on immunosuppression, it is important to identify patients who can potentially recover without transplantation. Early spontaneous survivors tend to have better long-term outcomes than those who undergo liver transplantation.

Future perspectives

Further research is required to establish prognostic scores to predict outcomes after liver transplantation and to prevent transplantation in patients for whom it will not work. Better listing criteria are still needed. Cellular and tissue-based extracorporeal liver support systems are an exciting area of research, although further trials are needed to establish survival and overall benefits. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 48-year-old man presented to the emergency department with acute onset of vomiting and confusion. Three days previously, he had taken an unknown quantity of paracetamol.
On clinical examination, he was confused, with a Glasgow Coma Scale score of 13/15. He was slightly jaundiced, with a 'flapping tremor'. His temperature was 38.0°C, heart rate 105 beats/minute, and blood pressure 134/88 mmHg. On abdominal examination, the liver was not palpable and there was no detectable free fluid.

Investigations

- Haemoglobin 145 g/litre (130–180)
- Mean cell volume 98 fl (80–96)
- White cell count 5.7 × 109/litre (4.0–11.0)
- Platelets 130 × 109/litre (150–400)
- Urea 15.7 mmol/litre (2.5–7.0)
- Creatinine 168 micromol/litre (60–110)
- Bilirubin 38 micromol/litre (1–22)
- Alanine aminotransferase (ALT) 2145 U/litre (5–35)
- Aspartate aminotransferase 1639 U/litre (1–31)
- Alkaline phosphatase 126 U/litre (45–105)
- Albumin 34 g/litre (37–49)
- International normalized ratio (INR) 1.9 (<1.4)
- Arterial blood gases (on breathing room air): pH 7.20 (7.35–7.45), PO_2 11.8 kPa (11.3–12.6), PCO_2 3.1 kPa (4.7–6.0), bicarbonate 18 mmol/litre (21–29), lactate 2.3 mmol/litre (0.5–1.6)

In addition to the evidence of hepatic encephalopathy, which feature confirms the diagnosis of acute liver failure?

A. Raised transaminases
B. Glasgow Coma Scale score
C. Prolonged INR
D. High bilirubin concentration
E. Blood gas results

Question 2

A 29-year-old woman was reviewed 24 hours after presenting with paracetamol-induced hepatotoxicity with acute liver failure. On admission she had been conscious with a Glasgow Coma Scale (GCS) score of 15/15; creatinine 80 micromol/litre (60–110), INR 2, ALT 4000 U/litre (5–35) and plasma lactate of 2.8 mmol/litre (0.6–1.8). She had been started on N-acetyl cysteine (NAC) and IV fluid hydration. On review she remained fully conscious.

Investigations

- Creatinine 70 micromol/litre (60–110)
- ALT 2000 IU/litre (5–35)
- INR 3
- Plasma lactate 4 mmol/litre (0.6–1.8)

What is the best management option at this stage?

A. Continue NAC and IV fluids in the local hospital
B. Stop NAC and continue IV fluids in the local hospital
C. Start continuous renal replacement therapy
D. Contact the nearest liver transplant centre for possibility of transfer
E. Discharge as there are no risk signs or need for organ support

Question 3

A 32-year-old man was being considered for liver transplantation. He had presented with acute liver failure but investigations had failed to identify the cause. Shortly after admission his conscious level deteriorated and he developed grade 3 hepatic encephalopathy. He was intubated, placed on high dose of vasopressor support and continuous renal replacement for a high blood ammonia. He was treated with antibiotics for a fever and positive blood cultures with resolution. However he still required high vasopressor support and hemofiltration, and his pupils have become dilated with a sluggish reaction to light.

Which of the following is a contraindication for liver transplantation in this patient?

A. High dose of vasopressor requirements
B. Presence of sepsis
C. Unknown aetiology of acute liver failure
D. Continuous renal replacement therapy
E. Neurological damage