Update on acute liver failure

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Purpose of review
Although advances in critical care management and liver transplantation have improved survival in acute liver failure (ALF), mortality remains significant. An evidence base to support management has been lacking, due to the condition's rarity, severity and heterogeneity. The purpose of this review is to critically appraise the latest evidence, updating clinicians on the current understanding of the best management.

Recent findings
Transplant-free survival in acetaminophen-related ALF has improved considerably, such that reconsidering thresholds for transplant is required, perhaps utilizing biomarkers of liver regeneration. Autoimmune hepatitis-related ALF may be too advanced to permit rescue with corticosteroids, which could be deleterious in the sickest patients. Acute kidney injury is commoner in ALF than previously suspected. Intracranial pressure monitoring does not appear to alter mortality. Despite altered traditional indices of coagulation, new thrombin generation assays suggest a rebalanced coagulation in liver failure. Antimicrobial prophylaxis may not be required in all patients. Liver support systems remain controversial and require further evaluation.

Summary
Traditional dogma in ALF management is questioned: transplant thresholds for acetaminophen overdose, steroid use in autoimmune ALF, routine antimicrobial prophylaxis, the coagulopathy of liver disease, the value of intracranial pressure monitoring and extracorporeal liver support.

Keywords
acetaminophen, acute liver failure, artificial liver support, autoimmune, coagulopathy

INTRODUCTION

Acute liver failure (ALF) is a rare and life-threatening condition characterized by rapid-onset severe liver injury with hepatocellular necrosis and diminished hepatic function, often defined as coagulopathy [international normalized ratio (INR) at least 1.5], and any grade of encephalopathy in a patient without preexisting liver disease [1].

Presentation may be categorized in a number of ways, with one commonly utilized definition subcategorizing into hyperacute, acute and subacute, dependent upon the interval between jaundice to onset of encephalopathy (Fig. 1) [2]. The highest rates of spontaneous survival are seen in hyperacute patients, in whom coagulopathy and encephalopathy are most pronounced; poorest survival is paradoxically seen in patients with subacute liver failure, in whom coagulopathy may be modest and brain oedema rare.

Survival over the decades has improved (Fig. 2), partly due to advances in intensive care management and the effective utilization of emergency liver transplantation (ELT) [3]. However, mortality remains high even when ELT is available [4–6].

GENERAL MANAGEMENT OF ACUTE LIVER FAILURE

Once recognized, clinical care should occur in a critical care setting, making early contact with a liver specialist centre. Determining cause (Table 1) is a priority because disease-specific therapies may reverse or ameliorate liver injury. Management aims to rapidly identify cause and provide multisystem support to facilitate hepatic regeneration, preventing infection and other complications, continually assessing prognosis so that if required, ELT wait-listing can be performed expediently (Table 2) [7,8].

CAUSES AND SPECIFIC THERAPIES

Drug-induced liver injury is the primary cause of ALF in the developed world. In northern Europe and

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KEY POINTS

- Improved spontaneous survival in ALF, especially acetaminophen-related, has provoked debate on prognostic tools and use of transplantation.
- Corticosteroid use in drug-induced autoimmune and indeterminate ALF shows no apparent benefit and may even harm those with severe disease.
- Routine prophylactic transfusion of blood products for assumed coagulopathy should be avoided in light of evidence of rebalanced coagulation in liver failure.
- Antimicrobial prophylaxis does not necessarily alter mortality and might be best restricted to those with evolving or established encephalopathy, organ failure or in whom transplantation is likely.
- Further research is required on artificial liver support systems.

the United States, acetaminophen-induced hepatotoxicity is most common, resulting from intentional or inadvertent overdose. In the United Kingdom, national legislation in 1998 to reduce pack sizes and limit availability has resulted in a sustained reduction in mortality [9]. A hyperacute course is typical with acetaminophen-induced disease, often with the development of acute kidney injury (AKI) but favourable survival with medical management alone [10]. A recent prospective study evaluating 2-year clinical outcomes of ALF highlighted the higher transplant-free survival of acetaminophen (89.5%) compared with nonacetaminophen causes (75%) [11▪]. Moreover, higher mortality on the ELT waitlist was seen in patients with acetaminophen-induced disease compared with other causes, and increased posttransplant mortality due to suicide or nonadherence to immunosuppression. Such findings have challenged thresholds for transplantation in acetaminophen-induced ALF [12]. Alternative strategies, such as liver support systems, may become important for hyperacute causes such as acetaminophen. The improvements in outcome with medical management alone have generated the need for novel prediction systems for ELT candidate selection and research into early indicators of prognosis. Measurement of serum biomarkers such as those reflecting mitochondrial damage or bile acids might assist in transplantation decision-making [13,14].

N-acetylcysteine therapy restores hepatic glutathione stores, supports mitochondrial function and is the recommended treatment for acetaminophen overdose. It may be effective even when started late after drug consumption [15]. Treatment is generally

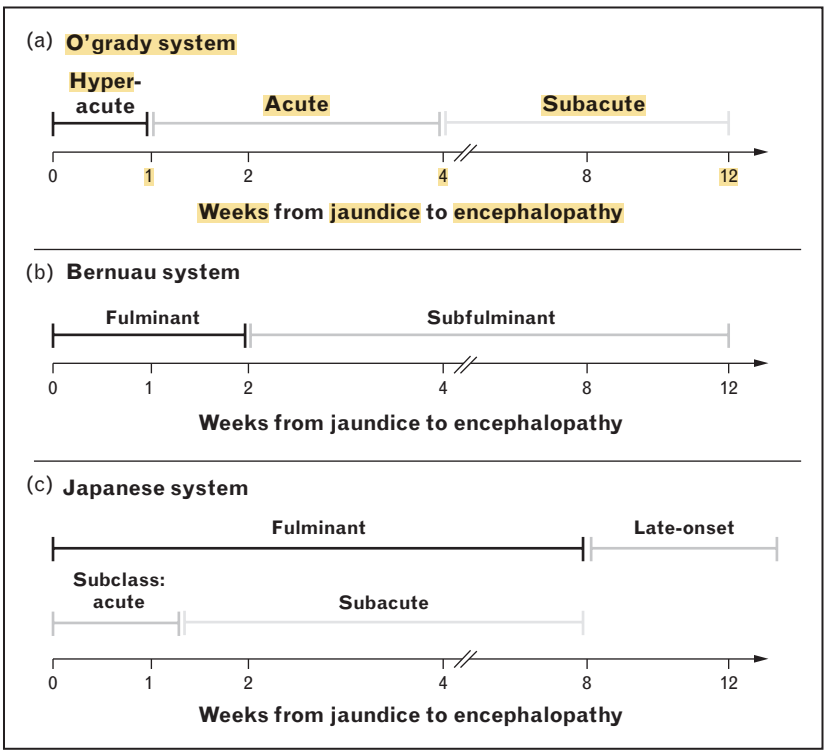

FIGURE 1. Classification systems for ALF. The late onset period runs from 8 to 24 weeks in the Japanese system. ALF, acute liver failure. Reproduced from [2].

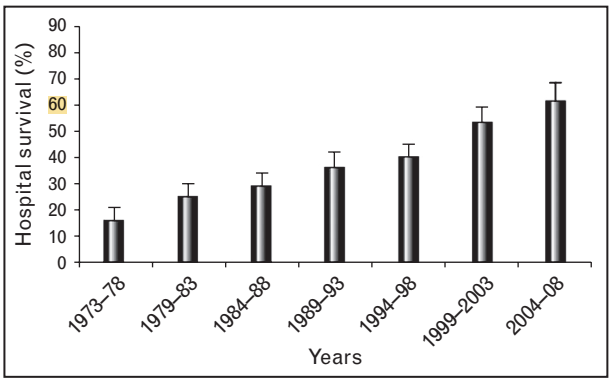

FIGURE 2. Hospital survival in admissions with ALF by era. Error bars are 95% confidence intervals ($P < 0.00001$). ALF, acute liver failure. Reproduced from [3].

well tolerated, and is often continued until synthetic dysfunction reverses or transplantation is performed. A prospective randomized controlled trial suggested that *N*-acetylcysteine also improved transplant-free survival in nonacetaminophen ALF patients but only those treated early in the disease course with mild or moderate encephalopathy [16].

Other causes of drug-induced liver injury may follow a more subacute course, often with a poor prognosis in the absence of transplantation. Prescription, over-the-counter and herbal drugs may be implicated, although elucidation of the culprit drug can be challenging. Reactions tend to be idiosyncratic, occurring within 6 months of initiation. Typical medications include amoxicillin/clavulanic acid, nonsteroidal anti-inflammatory drugs and azathioprine [17].

Autoimmune hepatitis may present as ALF, and i.v. corticosteroids are often administered, but might increase the risk of sepsis and compromise transplantation. In a retrospective cohort study, evaluating ALF due to presumed immune-mediated pathogeneses (autoimmune, idiosyncratic drug-induced ALF and indeterminate ALF), corticosteroids did not improve overall survival in any group, suggesting autoimmune hepatitis ALF might be too advanced to permit steroid rescue. Indeed, steroid use in ALF patients with high Model of End Stage Liver Disease (MELD) scores was associated with decreased survival [18▪▪].

Viral causes predominate in the developing world, especially hepatitis A, B and E. Hepatitis A and E are spread by the faeco-oral route. Both are usually self-limiting, rarely resulting in ALF [2].

Hepatitis B can cause de-novo ALF but is more severe with 'reactivation' in patients with chronic carrier states, particularly after initiation of immunosuppressive or antineoplastic agents [19]. In ALF, nucleoside analogue therapy is controversial. Although consensus guidelines and meta-analyses recommend its use, some studies suggest no survival benefit [20].

Hepatitis C rarely causes ALF. Herpes simplex virus must be considered in immunosuppressed or pregnant patients, often following a severe course. Other potential causes include cytomegalovirus, Epstein–Barr virus, varicella zoster virus, parvovirus B19 and adenoviruses. Therapeutic agents comprise intravenous ganciclovir for CMV and aciclovir for herpes simplex and varicella zoster viruses.

Acute fatty liver of pregnancy and haemolysis, elevated liver enzymes and low platelets syndrome are generally associated with a good prognosis with medical management alone, and both usually improve rapidly after delivery. Incomplete recovery should prompt consideration of transplantation [21,22].

Wilson's disease, a disorder of copper metabolism associated with Kayser–Fleischer corneal

Table 1. Routine laboratory investigations for acute liver failure

Haematology	Full blood count, and coagulation studies including prothrombin time/INR
Biochemistry	Liver function tests (aspartate transaminase/alanine transaminase, alkaline phosphatase, γ-glutamyltransferase, bilirubin and albumin), electrolytes (sodium, potassium, urea, creatinine, magnesium and phosphate), thyroid function tests, glucose, amylase, creatine kinase and lipids
Autoantibodies	Antinuclear antibody, antismooth muscle antibody, liver/kidney microsomal antibody and immunoglobulins
Hepatitis serology	Anti-HAV IgM, HBsAg, anti-HBcIgM and anti-HEV IgM
Extended viral screen	Epstein–Barr virus, cytomegalovirus, herpes simplex virus, parvovirus B19, adenovirus and HIV
Arterial blood gases including lactate	
Blood group	
Toxicology screen including acetaminophen levels	
Serum copper (in addition to bilirubin : alkaline phosphatase ratio >2 for diagnosis of Wilson's disease)	
Arterial ammonia	

HAV, hepatitis A virus; HBcIgM, hepatitis B core IgM; HBsAg, hepatitis B surface antigen; HEV, hepatitis E virus; IgM, immunoglobulin M; INR, international normalized ratio.

Table 2. King's College criteria for the selection of recipients for emergency liver transplantation

Acetaminophen-induced ALF	Nonacetaminophen-induced ALF
List for transplantation if	List for transplantation if
Arterial pH less than 7.30 (regardless of grade of encephalopathy) or arterial lactate more than 3.0 mmol/l after adequate fluid resuscitation	INR more than 6.5 and encephalopathy present (irrespective of the grade)
Strongly recommend listing if	
Arterial lactate more than 3.5 mmol/l after early fluid resuscitation	
List for transplant if all three of the following occur within 24 h	Or, any three of the following (irrespective of the grade of encephalopathy) are present
Grade 3 or 4 hepatic encephalopathy	Age less than 10 or more than 40 years old
INR more than 6.5	Interval from jaundice to encephalopathy of more than 7 days
Creatinine more than 300 μmol/l	INR at least 3.5
	Serum bilirubin at least 300 μmol/l
	Unfavourable cause (seronegative hepatitis, idiosyncratic drug reaction or Wilson's disease)

ALF, acute liver failure; INR, international normalized ratio.

rings, high bilirubin, low ALP and Coombs' negative haemolysis can cause ALF, and is associated with an exceptionally high mortality with medical care alone, only effectively treated by liver transplantation [23].

Budd–Chiari syndrome (acute hepatic venous thrombosis) is a rare cause of ALF, presenting classically with tender hepatomegaly and fluid retention. Liver transplant may be a key management option, with care taken to exclude malignancy prior to transplantation when a prothrombotic state is present [24].

Hypoxic hepatitis may involve arterial hypoxaemia, ischaemia and passive hepatic venous congestion that combine to cause ALF. Cardiac failure, respiratory failure or sepsis is frequently the underlying trigger. A brisk substantial transaminasemia (ALT > 1000) improves on treating the underlying cause and restoring systemic haemodynamics. Transplantation is seldom required. However, prognosis is governed by the underlying condition rather than the resulting liver injury, with in-hospital mortality exceeding 60% [25,26].

ALF may be found with malignant infiltration (e.g. lymphoma), heat shock and seizures. In 15% of cases, the cause of ALF is indeterminate [27,28].

ORGAN SUPPORT

Resuscitative measures and organ support provide the optimal environment for liver regeneration. High cardiac output, low mean arterial pressure and low systemic vascular resistance is frequently seen in ALF. Invasive monitoring devices are often used to optimize circulating volume and cardiac output [29,30].

Volume depletion is common and addressed by fluid replacement. Fluid-refractory hypotension may warrant the use of vasopressor agents. In the United Kingdom and United States, noradrenaline is the first-line agent, although data to support its use are lacking [1]. In patients unresponsive to fluid challenges and noradrenaline, the adjunctive use of vasopressin, or its analogue terlipressin, may be considered. However, their use is controversial with conflicting data on its effect on intracranial pressure (ICP) [31,32]. Fluid and vasopressor unresponsiveness may also indicate functional adrenocortical insufficiency, which appears common in ALF [33]. Confirmed by dynamic adrenal function testing, correction may be achieved by intravenous hydrocortisone. Cardiac troponin I, a sensitive and specific marker of myocardial injury, is elevated in 60–80% of ALF cases and likely to represent an epiphenomenon of multiorgan failure rather than myocardial injury [34,35].

Acute respiratory distress syndrome, identified by impaired oxygenation and bilateral infiltrates on chest radiography, has a 30% prevalence in ALF patients and represents a contraindication to transplantation [36,37]. However, presence or severity of hypoxia does not seem to affect overall survival or outcome after transplantation [38]. Management involves low tidal volume ventilation to reduce pulmonary injury, limiting positive end-expiratory pressure to achieve adequate oxygenation but minimizing risk of cerebral oedema and avoiding marked hypercapnia [39].

AKI is common in ALF and associated with increased mortality. Causes may be multifactorial, including direct drug toxicity, acute tubular necrosis or associated with the presence of the systemic

inflammatory response syndrome [40]. A retrospective observational study, in which AKI was categorized using contemporary RIFLE criteria, identified that 70% of ALF patients had AKI to some degree, commoner with increasing severity of critical illness, especially in patients with high-grade encephalopathy who required vasopressors [41▪].

Cessation of nephrotoxic drugs, intravascular volume replacement, inotropes or vasopressors may be required to optimize renal perfusion. Continuous modes of renal replacement therapy are preferable over intermittent dialysis to achieve stable haemodynamics and ICP.

MANAGEMENT OF INTRACRANIAL HYPERTENSION

Onset of hepatic encephalopathy in ALF confers a poor prognosis, associated with increased risks of cerebral oedema, intracranial hypertension (ICH) and mortality due to brain herniation [42]. For reasons that are currently uncertain, ICH is becoming increasingly uncommon, and now affects fewer than a quarter of those with advanced encephalopathy [3,43]. Its development may be linked to both the systemic inflammatory state and effects of neurotoxins. Hyperammonaemia, with concentrations greater than 200 μmol/l, or sustained levels below this threshold, indicates a much higher risk of significant ICH. The requirement for vasopressors and renal replacement therapy are also markers of greater risk [44].

Cerebral ammonia accumulation, due to compromised detoxification in the failing liver, results in its enzymatic conversion to osmotically active glutamine, with subsequent astrocyte swelling and brain oedema. Ammonia may impair mitochondrial function and generate toxic free radicals, affecting neurotransmission and gene expression [45].

Development of grade 3 or 4 encephalopathy should prompt sedation with propofol, intubation and ventilation. Propofol permits mandatory mechanical ventilation, may reduce ICP and has anticonvulsant actions [46,47].

Once intubated, monitoring of arterial ammonia and ICP should be considered. Reduced middle cerebral artery blood flow on noninvasive transcranial Doppler ultrasonography can indicate ICH, although inaccurate for mild to moderate ICP elevations [48]. Generally, the goal of therapy should be to maintain ammonia less than 100 μmol/l, ICP less than 20 mmHg and cerebral perfusion pressure higher than 60 mmHg.

Invasive intracranial pressure monitoring is controversial. It allows measurement of cerebral perfusion pressure and detection of ICH that is otherwise clinically silent. This may facilitate timely and rational use of ICP-lowering therapies, and allow optimization of ICP before and during liver transplantation. However, insertion of ICP monitors risks intracranial haemorrhage, and no mortality benefit has been demonstrated. A recent retrospective cohort study found that ICH was common in patients with ICP monitors, and haemorrhagic complications were rare (7%), but there was no 21-day mortality benefit in acetaminophen-related ALF and a worse prognosis in the nonacetaminophen group [49▪].

Continuous high-volume haemofiltration can achieve clinically significant reductions in circulating ammonia [50]. However, there is little evidence for the use of currently available ammonia-lowering medications in ALF. Lactulose is not recommended, and in a randomized controlled trial, L-ornithine L-aspartate, which may increase skeletal muscle detoxification of ammonia, did not reduce ammonia concentrations or improve survival [1,51].

Other management strategies are extrapolated from use in traumatic brain injury. Using hypertonic saline (30%) as an infusion fluid, aiming to maintain serum sodium at 145–150 mmol/l ensures an adequate osmotic pressure gradient across the blood–brain barrier to lower ICP and delay the onset of ICH [52]. Mannitol is an osmotic diuretic used to treat surges in ICP, and its introduction was associated with marked improvements in survival [53].

Moderate hypothermia to 34–35°C may control refractory ICH in patients awaiting transplant, with reduction in brain oedema resulting from decreased cerebral ammonia uptake, alterations in cerebral blood flow and oxidative stress [54,55]. However, a randomized controlled trial suggested that temperatures of 34°C have no advantage over 36°C in delaying the onset of ICH [56].

Short-term hyperventilation can be used cautiously to induce arterial hypocapnic vasoconstriction, reducing cerebral blood flow, ICP and restoring cerebral vascular autoregulation, although prolonged use can cause ischaemia [57].

BLEEDING RISK

Blood clot formation is the result of a complex cumulative interplay of procoagulant and anticoagulant proteins, the endothelium, platelets and red cells. The liver generates most coagulation factors (procoagulants and inhibitors), and loss of hepatic synthetic function results in disordered conventional coagulation tests, including elevated INR. A higher bleeding risk has therefore traditionally been assumed and coagulation factors prophylactically transfused prior to invasive procedures. However,

there is poor correlation between routine coagulation tests and bleeding episodes in liver disease. INR is not an accurate marker of bleeding tendency due to the insensitivity of the assay to natural anticoagulants (protein C, S, Z and antithrombin) [58].

Thrombin generation assays, which incorporate the addition of thrombomodulin, may better reflect functional coagulation status *in vivo*. Several groups have demonstrated that although patients with liver cirrhosis have prolonged prothrombin times, they generate similar amounts of thrombin to normal controls [59]. Hence, the concept of 'rebalanced' haemostasis has been proposed, due to parallel declines in procoagulant and anticoagulant factors.

A recent study of patients with ALF showed similar results, with normal thrombin generation in the presence of thrombomodulin, suggesting rebalanced coagulation [60▪▪]. In some cases, ALF patients may be hypercoagulable, partly explained by increased levels of factor VIII and von Willebrand factor in response to endothelial injury [61].

Prophylactic reversal of assumed coagulopathy with blood products, such as fresh frozen plasma, might heighten portal venous pressures, promote bleeding, raise ICP and obscure true INR readings, limiting its value as a prognostic marker in ALF. Thrombotic complications may even be more common than bleeding, arguing against routine use of procoagulant factors. Fresh frozen plasma should only be given for active bleeding. Vitamin K deficiency should be corrected with parenteral administration. Because maximal clot strength is reduced in thrombocytopaenia, platelet transfusion is recommended if counts are less than 50×10^9/l, although a higher target might be more appropriate if bleeding continues.

SUSCEPTIBILITY TO INFECTION

Increased susceptibility to infection has been identified in ALF, with a high incidence of bacterial and fungal infection [62,63]. A functional immune paresis is present, which includes defects in monocyte, macrophage and neutrophil function, and complement deficiency [64].

Massive hepatocellular necrosis triggers an innate immune response, with proinflammatory cytokine production. Development of systemic inflammatory response syndrome is closely linked to subsequent multiorgan dysfunction and adverse outcomes. A compensatory anti-inflammatory response syndrome may follow to limit immune-mediated tissue injury, its persistence associated with recurrent secondary infections and mortality [65,66].

Antimicrobial prophylaxis is routinely instituted at the onset of ALF. However, a retrospective observational study found that antimicrobial prophylaxis did not reduce the blood stream infection rate or alter mortality [67▪,68]. A pragmatic approach is to restrict antimicrobial use to those patients at highest risk of encephalopathy and organ failure, or in whom transplantation is likely.

ARTIFICIAL SUPPORT DEVICES

Interest in liver support systems reflects the clinical need to stabilize wait-listed patients until a suitable organ becomes available or until hepatic function spontaneously regenerates.

The molecular adsorbent recirculating system (MARS) is the most commonly used nonbiological liver-assist device, utilizing albumin dialysis to extract both water-soluble and protein-bound toxins. Recently, published data from the FULMAR study, a prospective randomized controlled multicentre trial, which compared two groups (conventional treatment vs. conventional treatment and MARS) showed no significant difference in 6-month overall and transplant-free survival. A nonsignificant improvement in survival was seen in the acetaminophen-induced ALF subgroup. The brief period between randomization and transplantation (16.2 h) in this study precluded adequate evaluation of MARS [69▪].

CONCLUSION

ALF is a rapidly progressive condition associated with poor outcome. Early identification, and application of both cause-specific and generalized supportive therapy, is central to reducing mortality. Advances in intensive care management of extrahepatic organ dysfunction and the application of liver transplantation have resulted in dramatically improved survival. A greater understanding of the pathophysiology of ALF, better utilization of transplantation and effective means of optimizing liver regeneration may result in further survival gains.

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Conflicts of interest

Dr W.B. has received consulting fees from Ocera Pharmaceuticals and Vital Therapies. There are no conflicts of interest for A.S.

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