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Acute liver failure

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Abstract

Acute liver failure is a rare and severe consequence of abrupt hepatocyte injury, and can evolve over days or weeks to a lethal outcome. A variety of insults to liver cells result in a consistent pattern of rapid-onset elevation of aminotransferases, altered mentation, and disturbed coagulation. The absence of existing liver disease distinguishes acute liver failure from decompensated cirrhosis or acute-on-chronic liver failure. Causes of acute liver failure include paracetamol toxicity, hepatic ischaemia, viral and autoimmune hepatitis, and drug-induced liver injury from prescription drugs, and herbal and dietary supplements. Diagnosis requires careful review of medications taken, and serological testing for possible viral exposure. Because of its rarity, acute liver failure has not been studied in large, randomised trials, and most treatment recommendations represent expert opinion. Improvements in management have resulted in lower mortality, although liver transplantation, used in nearly 30% of patients with acute liver failure, still provides a life-saving alternative to medical management.

Introduction

The term acute liver failure applies to a unique and infrequently observed syndrome of severe injury to liver cells, which leads to altered coagulation and mentation in the absence of chronic liver disease. Acute liver failure is unexpected and has a rapid onset, affecting previously healthy individuals, with a frequently fatal outcome. Despite having diverse causes (figure 1), acute liver failure is characterised by remarkably similar clinical features. The principal manifestations of acute liver failure are prolonged international normalised ratio of prothrombin time and hepatic encephalopathy, which were first described in 1970²

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Declaration of interests

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as fulminant hepatic failure, a term which has now been largely abandoned. Acute liver failure should not be confused with acute-on-chronic liver failure,³ which is the acute decompensation of cirrhosis resulting in the failure of extrahepatic organ systems. Three causes of acute liver failure can present as a fulminating acute decompensation of chronic liver disease, and might still be considered cases of acute liver failure: Wilson disease, reactivation of chronic hepatitis B infection, and autoimmunity. Other common features of acute liver failure include cardiovascular instability, susceptibility to infection, acute kidney injury, and, most unique among liver diseases, the presence of cerebral oedema.⁴ Despite its rarity, acute liver failure generates interest and study by multiple disciplines because it affects all organ systems, requires substantial resource use, and has a 30% mortality. Interest in studying acute liver failure is also driven by the insight the syndrome provides into the pathogenesis of liver injury and liver failure itself. Estimates of the incidence of acute liver failure are difficult to obtain, but range from 1 case per million people per year to about 2–3000 cases per year in the USA.⁴ The overall incidence of acute liver failure might be declining, but as a result of its rarity and heterogeneity, few population-based studies have been published. Most data originate from large registries in the USA and Europe and are descriptive in nature. All-encompassing guidelines and position papers have been written about acute liver failure, reflecting expert opinion rather than evidence-based medicine.^{6–8}

Substances that lead to hepatocyte injury cause either direct toxic necrosis, or apoptosis and immune injury, which is a slower process. The time from the onset of symptoms to the onset of hepatic encephalopathy distinguishes the different forms of acute liver failure: a direct, very rapid injury (within hours), referred to as hyperacute liver failure; and a slower, immune-based injury (days to weeks), considered acute or subacute. Although previous reviews have categorised these different forms into three timeframes (hyperacute, acute, and subacute),^{9,10} it seems more logical to group acute and subacute into a single syndrome, because their speed of evolution overlaps, whereas patients with hyperacute liver failure have a distinct disease pattern. Hyperacute causes, principally paracetamol toxicity (referred to as acetaminophen in North America) and ischaemia, become clinically detectable within 6–36 h of insult, resolving within 3–5 days. By contrast, slower evolving injuries usually take 7 days to 24 weeks to become clinically evident. In this category of slowly progressing liver failure (caused by hepatitis B virus, autoimmunity, or drug-induced liver injury), evolution might vary, but more than 7 days are reliably required before there are signs of liver failure. Hyperacute causes feature very high aminotransferase concentrations, and low bilirubin concentrations, whereas acute and subacute causes have lower aminotransferase concentrations and higher bilirubin concentrations. In general, patients with hyperacute liver injuries have better short-term survival than do patients with slowly progressing liver injuries, who do less well (table 1). Prognosis for acute liver failure has been linked to duration of illness, but the cause of the injury is a better predictor of outcome than the time of evolution. This Seminar highlights recent progress and future directions for a better understanding and management of this unusual and intriguing condition.

Causes of acute liver failure

Establishing the cause of acute liver failure is essential to guide treatment, as well as to predict outcome and the need for liver transplantation. Thus, recognition of clinical

signatures on presentation is paramount, as they provide important clues to the cause of liver injury (table 1). The five most prevalent causes in developed countries are paracetamol toxicity, ischaemia, drug-induced liver injury, hepatitis B virus, and autoimmunity, which account for nearly 80% of cases. By contrast, viral hepatitis A, B, and E are the main causes of acute liver failure in developing countries (appendix p 4).

Paracetamol

The most commonly observed cause of acute liver failure in developed countries is paracetamol toxicity, which causes 45·7% of cases recorded in North America,¹¹ and 65·4% of cases in the UK;¹² the incidence of paracetamol overdose is considerably lower or absent in most of Asia and Africa (appendix p 4). A uniform pattern of liver injury is unique to paracetamol and similar to ischaemia: extremely rapid-onset injury beginning within 8–12 h of ingestion of a quantity of paracetamol exceeding a threshold dictated by glutathione availability and nutritional state, leading to very high plasma aminotransferase concentrations and international normalised ratio of prothrombin time, but normal or only slightly elevated bilirubin, peaking at approximately 72 h.¹³ The evolution of injury and subsequent cytokine cascade is predictable, is observed in animal models as well as in humans, and appears to be enhanced in the presence of alcohol use or misuse and non-alcoholic fatty liver disease.¹⁴

A suicide attempt usually consists of ingestion of multiples of a fatal dose at a single timepoint; in other instances, ongoing use of paracetamol at excessive daily doses, often with hydrocodone or other opioids, has a very similar result.^{15,16} Paracetamol is present and measurable in plasma shortly after ingestion, but has a short half-life; thus, only about half of patients with acute liver injury or acute liver failure will show any of the parent compound.¹⁷ Detection of paracetamol adducts in plasma, which are toxic byproducts of cell injury (paracetamol bound to cell proteins), have a longer plasma half-life than the parent compound, and might provide a valuable confirmatory test for paracetamol as the cause of acute liver failure, particularly for ingestions at multiple timepoints or more than 3 days before medical care.^{18,19} Acetylcysteine prevents liver injury if taken within 12 h of paracetamol ingestion and might be beneficial at later timepoints, although this is less certain.^{17,20} Despite efforts to reduce fatalities after paracetamol overdose, whether intentional or unintentional, little progress has been made.^{11,21}

Hepatic ischaemia

Inadequate perfusion of oxygenated blood to the liver has various causes, and leads to a hyperacute but self-limited hepatic injury, characterised by very high aminotransferase concentrations and low bilirubin concentrations. With few exceptions (eg, heat stroke and cocaine toxicity), the differential diagnosis of aminotransferase concentrations of more than around 3000 IU/L and bilirubin less than 5·0 mg/dL includes mainly ischaemia and paracetamol (table 1). Ischaemia that is due to severe heart failure can be readily characterised by an echocardiogram showing depressed left-ventricular ejection fraction. Other causes of poor perfusion include hypotension due to depletion of blood volume (ie, shock), septic shock, hypoxia (such as respiratory depression due to opioids), pulmonary failure, and cocaine use. Acute kidney injury occurs in nearly equal numbers of patients

as does acute liver injury in these settings. Although the short-term prognosis for acute liver failure caused by ischaemia is good because intravascular volume can be restored and cardiac haemodynamics improved quickly, the long-term outcome is uncertain if the underlying cause of haemodynamic failure is not reversible.²² Ischaemic liver injury rarely leads to a requirement for liver transplantation, unless the cause is a direct compromise of the hepatic circulation (eg, inadvertent surgical occlusion of the hepatic artery).²³

Drug-induced liver injury

Idiosyncratic, drug-induced liver injury is the second most common cause of acute liver failure after paracetamol,¹¹ and has a different pathogenesis with a worse prognosis.²⁴ Only 10% of all patients with drug-induced liver injury develop acute liver failure, with the potential for liver transplantation or death.²⁵ The pathogenesis of drug-induced liver injury is thought to be immune based, with some individuals having a genetic predisposition, caused by unique HLA haplotypes;²⁶ few unique polymorphisms responsible for liver injury have been identified.²⁷ Antibiotics account for nearly 50% of all cases of drug-induced liver injury, partly because they are frequently prescribed, but also because they typically require high daily doses (ie, at least 500–1000 mg per day), which increases the risk of liver injury.²⁸ By contrast with viral-induced acute liver failure, there are no specific diagnostic tests for drug-induced liver injury. Identification of a specific drug requires a careful history and exclusion of other causes.²⁹ By contrast with ischaemia and paracetamol injuries, drug-induced liver injuries reaching the threshold of acute liver failure present with lower aminotransferase concentrations, higher bilirubin concentrations, and worse overall outcomes (table 1), with fewer than 25% of patients recovering after any degree of encephalopathy has occurred.^{24,30}

Autoimmune hepatitis

Acute liver failure caused by autoimmune hepatitis presents as an acute-to-subacute liver injury that might defy initial diagnosis. This type of acute liver failure frequently begins insidiously and is suggested, but not definitively diagnosed, by the presence of hyperglobulinaemia, antinuclear antibodies, or anti-smooth-muscle antibodies, or any combination of these. 80% of patients with acute liver failure caused by autoimmune hepatitis are women. A liver biopsy could be helpful in diagnosing acute liver failure caused by autoimmune hepatitis.³¹ Encephalopathy might mean that it is challenging to take biopsy samples safely, although the transjugular approach is now widely used in tertiary centres.³² Many instances of indeterminate acute liver failure might actually be caused by autoimmune hepatitis, but specific diagnostic tests are absent. Similar to drug-induced liver injury, acute liver failure caused by autoimmune hepatitis has particularly poor outcomes and frequently requires liver transplantation (table 1).

Hepatitis B and hepatitis A

In the USA and Europe, hepatitis B virus causes around 8% of all cases of acute liver failure, considerably fewer than paracetamol, drug-induced liver injury, or autoimmune hepatitis, but this virus is still an important and readily diagnosed cause. Two-thirds of cases of hepatitis B are caused by new infections, and the remainder are caused by reactivation of often unrecognised chronic hepatitis B infection in the setting of chemotherapy or other immune

modulation.³³ Acute liver failure caused by reactivation of hepatitis B infection occurs when immunosuppression allows increased viral replication that had been at least partially contained by host immune surveillance and carries a worse prognosis than that caused by de-novo hepatitis B infection.³⁴ Reactivation of hepatitis B infection might occur even in patients who appeared to have cleared the infection—ie, those who are HBsAg negative when subjected to intense immune suppression.³⁵ Early treatment after diagnosis once liver failure is present is of uncertain value.^{36,37}

Hepatitis A virus infection generally has a mild course and seldom causes acute liver failure, causing fewer than 3% of cases of acute liver failure in developed countries. Outbreaks of hepatitis A infection among homeless people in the USA in the last 3 years have led to a spike in hospitalisations, highlighting the infrequent use of hepatitis A vaccines in the general population.³⁸ Acute liver failure caused by hepatitis A has nearly 70% spontaneous or transplant-free survival (table 1), a better overall outcome than that caused by other viruses.³⁹

Other causes of acute liver failure

The remaining causes of acute liver failure comprise fewer than 15% of the total and include heat stroke, pregnancy-associated injury (eg, acute fatty liver of pregnancy and HELLP [haemolysis, elevated liver enzyme, and low platelet] syndrome), Budd-Chiari syndrome, nonhepatotropic viral infections such as herpes simplex, and diffusely infiltrating malignancies.^{40–44} Heat stroke resembles ischaemia in its features of vascular collapse and hyperacute evolution, and occasionally requires liver transplantation.⁴⁵ Fulminant Wilson disease presents with fibrosis or well established cirrhosis and a unique clinical signature, including intense intravascular haemolysis and acute kidney injury, that allows early diagnosis.⁴⁶ Only rarely can a patient with this condition recover without liver transplantation, despite the best intensive care. Acute hepatitis C virus infection rarely progresses to acute liver failure; well documented cases that do not involve underlying non-alcoholic fatty liver disease or preexisting cirrhosis are difficult to find in the literature. Hepatitis E virus is a major cause of acute liver failure in Asia, parts of Africa, and the Indian subcontinent; the virus occasionally causes infection and acute liver failure in Europe, but is rarely encountered in the USA.^{47,48}

Indeterminate acute liver failure

A small percentage of cases of acute liver failure might have an indeterminate cause—ie, assignment of a cause is impossible with the available data. Historically, it was suggested that the disease in these patients was brought about by unrecognised or occult viruses.⁴⁹ However, it is more likely that patients with indeterminate acute liver failure have been incompletely evaluated—eg, by insufficient history-taking (in patients with encephalopathy), or absence of full serological testing. Intensive screening using new methods, such as the paracetamol adduct test, deep sequencing for viruses, and adjudication by independent experts, reaches a diagnosis in at least 50% of patients with acute liver failure with an initially indeterminate cause;¹ only around 5% of all diagnoses of acute liver failure therefore have indeterminate causes.

Pathogenesis and establishing a diagnosis

The pathology of acute liver failure on explant or autopsy most often shows widespread hepatic necrosis and apoptosis, with few remaining viable hepatocytes; regenerative nodules are often seen (figure 2). Liver weight can decrease from 1600 g to around 500 g, leaving only the hepatic stromal framework. Failure of regeneration is also an important feature of acute liver failure, at least for some causes. Human genetic factors probably have a role in confining liver injury to a small fraction of patients exposed to a drug or virus,^{26,50,51} and some HLA alleles have been associated with this effect.^{52,53}

Although the striking presentation of most patients with acute liver failure seldom leaves the diagnosis in question, some patients present a conundrum, with a differential diagnosis that includes biliary sepsis, alcoholic hepatitis, and acute-on-chronic liver failure. Beyond a thorough history and physical examination, a standard battery of tests and considerations should be applied to all patients with acute liver failure to establish the correct cause (appendix p 1). There are some exceptions: if the diagnosis is obvious, such as an admitted paracetamol overdose with detectable paracetamol in the blood, then searching for other causes is pointless.¹ However, when no clear diagnosis is apparent after basic viral and autoimmune serologies, more intensive, second-tier testing is indicated (appendix p 1). Because the cause of acute liver failure influences the prognosis, and the time to correct diagnosis might be crucial, the most rapid and available methods of testing are required. For example, Wilson disease that is causing acute liver failure can be reliably discerned by measurements of haemo globin, alkaline phosphatase, and bilirubin, rendering copper measurements in plasma or urine confirmatory.⁴⁶ Likewise, herpes simplex virus IgM is reported more rapidly than nucleic acid assays, and is therefore preferred if infection is suspected.⁴¹ A smartphone application for clinicians who treat acute liver failure is now available and includes a diagnostic and daily checklist to remind clinicians to review routine diagnostic and therapeutic measures.⁵⁴

Management

General considerations

The management of patients with acute liver failure varies between individual centres and physicians because of a dearth of randomised clinical trials. A liver transplantation centre should be consulted regarding possible transfer shortly after stabilising the patient, because the complexity of care is beyond the scope of all but tertiary-care hospitals with the capability to do liver transplantations.

Cause-specific management

Few data support the efficacy of any cause-specific therapy for the primary liver injury (appendix p 2). Women with acute liver failure who present with pre-eclampsia and liver injury in their third trimester of pregnancy should be promptly delivered, and thereafter generally have a favourable prognosis,⁴³ although some women continue to deteriorate postpartum.^{55,56} Patients with acute liver failure associated with hepatitis B virus should receive nucleos(t)ide hepatitis B virus DNA polymerase inhibitors to reduce the risk of

recurrence after liver transplantation.³⁷ Unfortunately, a randomised controlled trial did not show improvement in transplant-free survival in patients with severe, acute hepatitis B virus disease who received lamivudine compared with placebo.⁵⁷ Any patient with acute liver failure that is suspected to be secondary to infection with herpes simplex virus on the basis of clinical features (ie, fever, skin or mucous membrane vesicles, or a patient who is immunosuppressed)⁵⁸ should receive aciclovir while awaiting nucleic acid confirmation; however, favourable responses are uncommon.⁵⁹ *Amanita phalloides* (and related species) mushroom poisoning, which causes acute liver failure, is rare in the USA, but occurs more frequently worldwide;⁶⁰ anecdotal case reports suggest a potential benefit of silibinin, as well as acetylcysteine, penicillins, and nasobiliary drainage.^{61,62} Even in acute liver failure caused by autoimmune hepatitis, corticosteroids have not been convincingly shown to improve outcome.⁶³ A trial of corticosteroids should be administered to patients with low-grade (grade 1 or 2) hepatic encephalopathy due to autoimmune hepatitis, and only for a finite period of time (around 1 week) to avoid increasing the risk of peritransplantation infection.⁶⁴

Acetylcysteine has been used as a treatment for paracetamol overdose for decades on the basis of a study using historical controls,⁶⁵ and of small, randomised trials showing improved survival,⁶⁶ with little toxicity and a thoroughly defined mechanism of action.⁶⁷ However, the quality of the data on the optimal route of administration (ie, oral or intravenous), dose, and even the efficacy of acetylcysteine for paracetamol overdose is poor.⁶⁸ Despite this poor data quality, authorities advise acetylcysteine administration when paracetamol overdose is first suspected, intravenously to ensure delivery, even for patients without an ingestion history or when paracetamol is undetected in the blood.¹⁷ Acetylcysteine might also be effective in treating patients with acute liver failure with causes other than paracetamol overdose; several uncontrolled studies suggest improved outcome in these patients when they receive acetylcysteine,^{69–71} but only one study in adults was randomised and placebo-controlled.⁷² Although this study did not meet its primary endpoint of improved overall survival, acetylcysteine was associated with improved transplant-free survival in patients with grade 1 or 2 hepatic encephalopathy, a secondary endpoint.

Management of liver failure

Despite little change in the severity of illness during the past two decades, outcomes for patients with acute liver failure have improved because of more widespread options for liver transplantation and improved intensive care. Improved outcomes have occurred despite lower use of resources in intensive care units (eg, vasopressors, blood products, ventilation, and intracranial pressure monitors) over the same time period.¹¹ Innovative technologies, such as albumin dialysis and bioartificial devices using hepatocyte cell lines or porcine hepatocyte bioreactors, have yielded poor results. Although liver-support devices might transiently improve biochemical indices of liver function, none has been shown to reliably bridge patients with acute liver failure to recovery with their native or a transplanted liver.⁷³

In many regards, high-volume plasma exchange recapitulates liver support, because it removes metabolic end-products, toxins, and pro-inflammatory mediators, and replaces many beneficial, liver-derived proteins. In a multicentre, randomised study of standard

medical treatment versus standard treatment plus high-volume plasma exchange,⁷⁴ survival to hospital discharge stratified for liver transplantation was higher in patients who received high-volume plasma exchange. Thus, this treatment might be more readily available and better substantiated than other liver-support devices, but further study is required.

Management of systemic complications of acute liver failure

The most common cause of death in patients with acute liver failure is systemic complications, which follow the release of pro-inflammatory cytokines and damage-associated molecular patterns from necrotic hepatocytes, endothelial cells, and leucocytes.^{75,76} No clinical trial of specific inhibitors of any of these mediators has been done in humans. Consequently, the following discussion will outline the management of failure of individual organ systems.

In patients with acute liver failure, multisystem organ failure often appears as a battery of affected systems,⁷⁷ including the cardiovascular system, heralded by systemic inflammatory response syndrome and haemodynamic instability. On presentation, patients with acute liver failure are often hypotensive because of volume depletion; therefore, the first intervention should include intravenous normal saline. Persistent hypotension (mean arterial pressure <60 mm Hg) despite volume repletion should prompt vasopressor support; norepinephrine has been suggested by consensus as the preferred initial vasopressor.⁷⁸ Cultures of blood and urine should be considered on admission for all patients with hypotension. Hypotension despite volume repletion and norepinephrine should prompt the addition of vasopressin. Persistent hypotension despite norepinephrine and vasopressin or terlipressin warrants consideration of treatment with hydrocortisone (300 mg intravenously), because relative adrenal insufficiency has been documented in a substantial proportion of patients with acute liver failure.⁷⁹ Unfortunately, patients with acute liver failure who receive vasopressors might not reliably increase peripheral oxygen delivery because of persistent vasoconstriction of the microcirculation, and might thereby continue to have end-organ dysfunction, tissue hypoxia, and lactic acidosis; vasodilators such as epoprostenol might be helpful.⁸⁰

As well as cardiovascular collapse, patients with acute liver failure might have intracranial hypertension due to cerebral oedema. The pathogenesis of cerebral oedema in patients with acute liver failure is multifactorial and incompletely understood.⁸¹ Hyperammonaemia is a key driver of astrocyte swelling. Severe hyperammonaemia appears to be associated with the presence of cerebral oedema.^{82,83} Because astrocytes comprise a large proportion of brain volume, even small increases of brain water within the rigid confines of the skull increase intracranial pressure, which can result in brain-stem herniation.^{82,83} Imaging by CT is not very sensitive,⁸⁴ but might show poor differentiation of grey and white matter, swollen gyri, and flattening of sulci (figure 3). Although the incidence of cerebral oedema has decreased in the past 20 years, intracranial hypertension remains a substantial cause of mortality.^{11,12}

Prophylaxis against cerebral oedema is of paramount importance, because established intracranial hypertension can lead to permanent brain damage, and treatments delay the problem, but do not reverse the underlying pathogenesis of astrocyte swelling (appendix p 3). A patient with acute liver failure should be positioned to include elevation of the head of the bed to 30° and maintenance of the neck in neutral rotation to promote venous drainage of

the brain. Hepatic encephalopathy drives central hyperventilation and respiratory alkalosis, which improves autoregulation of the cerebrovascular circulation; therefore, patients should be allowed to hyperventilate.⁸⁵ Although standard drugs for hyperammonaemia in cirrhosis, such as lactulose and non-absorbable antibiotics (eg, rifaximin), have never been tested in patients with acute liver failure, they are intuitively appealing and reasonable; however, gaseous distension of the bowel caused by lactulose might hinder surgical access to the liver at transplantation.

Hyponatraemia promotes water entry into astrocytes and should be corrected. In a randomised, placebo-controlled study,⁸⁶ patients who were managed at a serum sodium of 145–155 mEq/L after hypertonic saline boluses maintained lower intracranial pressure compared with patients managed at near-normal concentrations (137–142 mEq/L). Early initiation of renal replacement therapy by continuous veno-venous haemofiltration should also be considered in patients with oliguria, evidence of volume overload, or clinically significant hyperammonaemia (>150 µmol/L), because each of these have been associated with the development of cerebral oedema, and continuous renal replacement therapy can help to lower serum ammonia.⁸⁷ Patients should not be warmed, as spontaneous hypothermia to 33–35°C might decrease the incidence of intracranial hypertension. Induction of moderate hypothermia has been shown to lower intracranial pressure as a bridge to liver transplantation in patients with acute liver failure with intracranial hypertension.⁸⁸ However, as prophylaxis against intracranial hypertension, management of patients with high grade hepatic encephalopathy under moderately hypothermic core temperature (34°C) was not more effective than management under normothermic conditions (36°C).⁸⁹ Once cerebral oedema has developed, therapeutic methods should be considered as a bridge to transplantation, because no treatment is curative. The decision to insert a monitor for intracranial pressure is centre-dependent and controversial. Although retrospective studies^{90–92} have repeatedly shown that patients with intracranial pressure monitors receive more interventions to lower intracranial pressure than do patients without these monitors, none have suggested improvement in outcome and the use of these monitors appears to be declining. An intracranial pressure monitor might have value in identifying patients who should not have a transplantation because of prolonged intracranial hypertension or low cerebral perfusion pressure, by predicting poor or no neurological recovery.⁹³

Standard ammonia-lowering drugs have not been systematically tested as treatment of established cerebral oedema in patients with acute liver failure. Although ammonia-scavenging agents such as ornithine might lower serum ammonia in patients with acute liver failure,⁹⁴ these drugs have never been compared with placebo, and are not widely available. However, continuous veno-venous haemofiltration should be administered in all patients with established cerebral oedema for the reasons already cited.⁸⁷ At the first signs of intracranial hypertension (intracranial pressure >20 mm Hg) or when the patient shows deterioration in neurological condition (often pupillary changes), a bolus of mannitol (0.5–1.0 g/kg bodyweight) should be administered intravenously.^{95,96} Alternatively, authorities in the field have used hypertonic saline boluses with an equivalent reduction in intracranial pressure.^{97,98} Relapse after initial therapy should prompt consideration of repeating mannitol or hypertonic saline boluses, and deeper sedation with propofol or

barbiturates.^{99,100} If other supportive measures are absent, clinicians could consider bridging a patient to liver transplantation with therapeutic hypothermia (32–33°C).¹⁰¹

Acute kidney injury complicates acute liver failure in 70% of patients and requires renal replacement therapy in 30%.⁷⁷ The risk of acute kidney injury depends on the cause of acute liver failure. In addition to pre-renal azotaemia on presentation of acute liver failure, acute kidney failure frequently follows, either because of acute tubular necrosis or functional renal failure. Renal tubular injury can follow exposure to a hepatotoxin with nephrotoxic potential; paracetamol is the most common. Other hepatotoxins that also cause tubular injury include sulfonamides, halothane, and amatoxin. Renal tubular injury usually develops shortly after the liver injury, and can be persistent, but usually resolves; treatment is supportive. By contrast, functional renal failure similar to the hepatorenal syndrome of cirrhosis can occur in patients with acute liver failure from any cause. Here, vasoactive cytokines are thought to lower systemic vascular resistance, resulting in hypoperfusion of the kidneys.¹⁰² Treatment should include the restoration of mean arterial pressure as well as renal replacement therapy.

A crucial rule for managing patients with acute liver failure is to begin renal replacement therapy early. This therapy should be initiated if oliguria persists despite volume repletion and restoration of mean arterial pressure with vasopressors. Renal replacement therapy should be considered in any patient with a serum ammonia of more than 150–200 µmol/L, an increasing serum ammonia, or with established cerebral oedema, regardless of the serum creatinine. Continuous renal replacement therapy is preferred over intermittent haemodialysis because intermittent haemodialysis has been associated with wider swings in mean arterial pressure, with adverse effects on cerebral oedema and perfusion.¹⁰³

Infection in patients with acute liver failure often triggers cerebral oedema and multisystem organ failure, and often renders the patient unfit for transplantation. Although systemic inflammatory response syndrome often heralds sepsis, this syndrome can occur in the absence of infection, and is associated with worsening hepatic encephalopathy and a poor outcome.¹⁰⁴ Prophylactic antibiotics have not been shown to decrease the incidence of infection in patients with acute liver failure.^{105–107} However, a few practical guidelines can be extrapolated from these studies. First, the usual sites of infection associated with treatment in an intensive care unit apply to patients with acute liver failure, including pneumonia, urinary tract infections, catheter-associated blood stream infections, and spontaneous bacteraemia. These infections are caused by Gram-positive as well as Gram-negative organisms, with fungal (predominantly *Candida*) and anaerobic infections accounting for a small proportion.¹⁰⁸ Therefore, antibiotics should be chosen to cover a wide spectrum of organisms. Second, surveillance cultures of blood, urine, and sputum should be sent for testing on presentation and regularly after admission to the intensive care unit. Third, prophylactic antibiotics should be strongly considered in patients awaiting liver transplantation because peritransplant infection has severe implications; patients with the highest risk of infection include individuals with renal failure or those fulfilling King's College Criteria¹⁰⁹ for poor outcome. Finally, empiric broad-spectrum antibiotics should be administered in the setting of systemic inflammatory response syndrome,¹⁰⁴ worsening hepatic encephalopathy,¹¹⁰ or hypotension.

Patients with acute liver failure have elevated international normalised ratio of prothrombin time and variable degrees of thrombocytopenia, the severity of which is proportional to that of systemic inflammatory response syndrome.¹¹¹ Despite these clinical hallmarks of abnormal haemostasis, bleeding complications in patients with acute liver failure are uncommon (occurring in around 10% of patients) and are usually not clinically significant.¹¹² Several groups have shown that apparent deficiencies in haemostasis in patients with acute liver failure are rebalanced by compensatory mechanisms fuelled by systemic inflammation and endothelial activation or injury; such mechanisms include hypersecretion by the endothelium of clotting factor VIII, which might compensate for deficient liver-derived coagulation factors, and von Willebrand factor, which might compensate for thrombocytopenia.^{113,114} Procoagulant microparticles, another result of systemic inflammation, also might compensate for deficiencies in haemostasis.¹¹⁵ Fibrinolysis can also be markedly impaired in patients with acute liver failure.¹¹⁶ Management of coagulation abnormalities should focus on whether there is evidence of clinically significant bleeding. The use of blood products has steadily decreased during the past 17 years in the USA, whereas bleeding complications have remained stable at around 10% of patients with acute liver failure, suggesting that prophylactic transfusions might not be required.¹¹¹

The failure of peripheral oxygenation in patients with acute liver failure culminates in progressive lactic acidosis, which is associated with poor prognosis.¹¹⁷ Respiratory failure is multifactorial, and can include ventilatory failure as well as defective delivery of oxygen to peripheral tissues. Respiratory failure from hypoventilation must be anticipated when patients develop high-grade hepatic encephalopathy; endotracheal intubation and mechanical ventilation should be a planned, highly controlled procedure when patients develop grade 3 hepatic encephalopathy. Failure of peripheral oxygen delivery is also multifactorial, and involves macrocirculatory and microcirculatory dysfunction. Restoration of mean arterial pressure with vasopressors might restore systemic circulation haemodynamics, but microcirculatory arteriovenous shunting and defective oxygen dissociation from haemoglobin might continue to hamper peripheral tissue oxygenation.^{20,80}

Liver transplantation

Before the widespread availability of liver transplantation for acute liver failure, overall mortality approached 80%. In studies from the USA and the UK in the past decade, around 25% of patients with acute liver failure received a liver transplant, contributing to the decrease in overall mortality to around 33%.^{11,12} Early post-transplantation mortality in patients with acute liver failure exceeds that of patients who receive a transplant for cirrhosis, reflecting the acuity and severity of acute liver failure. Thereafter, long-term survival stabilises. Patients with acute liver failure who have received a liver transplant have a lower mortality at 2 years than patients who survived the initial 21 days after liver injury but who were not transplanted (appendix p 5). In the USA and Europe, patients with acute liver failure receive status 1, or super-urgent status, on the transplant waiting list, ahead of patients who are awaiting liver transplantation for cirrhosis, because of the high risk of death within 7 days.

Outcomes

The cause of the liver injury is the most important determinant of transplant-free survival in patients with acute liver failure.¹¹ Approximately 75% of patients with paracetamol-induced acute liver failure recover with their native liver compared with around 40% of patients with acute liver failure with other causes. Causes other than paracetamol with relatively favourable transplant-free survival include hepatitis A virus (transplant-free survival of 56%), ischaemic liver injury (74%), and pregnancy (83%). By contrast, causes that are associated with low transplant-free survival include hepatitis B virus (26%), drug-induced liver injury (41%), autoimmunity (25%), and indeterminate causes (33%). The development of high-grade hepatic encephalopathy is the second most important determinant of prognosis after the cause of the acute liver failure.

Establishing prognosis

Predicting which individuals will recover with their native liver and which individuals will die without liver transplantation is imprecise. Death without transplantation, and transplantation in a patient who would have recovered without it, are both highly undesirable outcomes. Accurate prognostic indices have, therefore, been a focus of many investigations. Any prognostic score must take into account the diverse causes encountered as well as measures of disease severity, such as the grade of hepatic encephalopathy and various laboratory parameters. The two most important predictors of prognosis are the cause of the liver injury and the grade of hepatic encephalopathy on presentation (appendix p 6).¹¹⁸

Clinical characteristics that are associated with low transplant-free survival include single laboratory values (high ammonia, lactate, phosphate, international normalised ratio of prothrombin time, and clotting factor VIII; low platelet count, clotting factor V, and clotting factor VII), and several indices derived from retrospective analysis of large databases (table 2). The first prognostic indices for acute liver failure, one for paracetamol toxicity and one for the other causes, have become known as the King's College Criteria.¹⁰⁹ These indices sought to identify patients who were destined to die from acute liver failure, and were produced before liver transplantation became widely used for this condition. Validation of the King's College Criteria using modern databases has shown them to be inaccurate, particularly for acute liver failure that is not induced by paracetamol.¹¹⁸ The model for end-stage liver disease (MELD), designed to predict death in patients with cirrhosis, might have better accuracy than the King's College Criteria, but is inherently flawed because creatinine, a component of MELD, does not seem to be highly predictive of outcome in recent studies.¹¹⁸ A meta-analysis¹²⁷ has suggested that the King's College Criteria perform better than MELD at identifying in-hospital mortality in acute liver failure associated with paracetamol toxicity, but MELD might out-perform the King's College Criteria in acute liver failure with other causes. Liver stiffness by transient elastography increases in patients with acute liver failure and is associated with hepatocyte death, but has not yet been linked to prognosis.¹²⁸ Liver volume, determined by CT, of less than 1000 cm³, is a measure of parenchymal collapse, and predicts death in patients with acute liver failure that is not caused by paracetamol.¹²⁶

In contrast to the King's College Criteria and MELD, which predict mortality, the Acute Liver Failure Study Group Prognostic Index was proposed in 2016, to identify 21-day transplant-free survival in patients with acute liver failure of all causes.¹¹⁸ The index, based on data from 1974 patients with test and validation cohorts, uses the five factors that were most associated with transplant-free survival to predict recovery without transplantation. These five factors are cause (favourable or unfavourable), grade of hepatic encephalopathy (mild or severe), requirement for vasopressors (yes or no), plus admission international normalised ratio of prothrombin time, and bilirubin concentrations, which are both continuous measurements (appendix p 6). The Acute Liver Failure Study Group Prognostic Index was found to be more accurate than the King's College Criteria or MELD in predicting transplant-free survival (the area under the receiver operating characteristic curve=0.84) and is available as an application for smartphones (appendix pp 7–8). Another prognostic index, published in 2017, identified patients with acute liver failure induced by paracetamol at high risk of transplant futility (ie, death despite transplantation) with very high accuracy.¹²⁹

Long-term outcomes

Most patients who recover from acute liver failure bear no overtly detectable renal, neurological, or hepatic dysfunction, although some studies have questioned this.^{130,131} Some of the poor long-term functioning of patients after paracetamol overdose can be ascribed to poor function before acute liver failure, due to underlying psychiatric illness and substance abuse.¹³¹ Self-reported quality of life is lower in survivors of acute liver failure than in the general population. Transplant-free survival in patients with acute liver failure that was not caused by paracetamol 2 years after recovery is 76%, which is significantly lower than in transplant-free survivors of paracetamol overdose (90%), or in patients who are recovering from acute liver failure of any cause after receiving a liver transplant (92%), probably because of comorbid medical disorders (appendix p 5). At times, neuro psychological dysfunction after acute liver failure might persist despite recovery from the primary liver injury.¹³²

Future research questions and needs

Randomised, placebo-controlled studies using cause-specific treatments as well as targeting key pathogenic mediators of acute liver failure are urgently needed but are very difficult to complete. One requirement for such studies is an adequate number of patients with acute liver failure, a rare and very heterogeneous syndrome. Consequently, research consortia that are willing to adhere to uniform management protocols, rather than single-centre studies, are required. Overall, the suspected decline in the incidence of acute liver failure might be due to widespread vaccination for hepatitis A virus and hepatitis B virus, increased scrutiny of prescription drug approvals, and better patient education and product labelling about the risk of unintentional paracetamol overdoses.¹³³ A decreasing incidence of acute liver failure is a desirable outcome. By contrast, a reduced number of new cases adds complexity to efforts to study this highly morbid and lethal condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Search strategy and selection criteria

We searched PubMed and MEDLINE using the terms “acute liver failure” or “fulminant hepatic failure” to identify studies and publications not already familiar to the authors, with no restrictions on date or location of publication. The final search occurred on March 2, 2019. We reviewed our findings to identify work relevant to acute liver failure and chose references that provided the most insight and that were, where possible, evidence-based rather than expert opinion, so that readers could understand current knowledge of various aspects of both diagnosis and critical care of patients with acute liver failure.

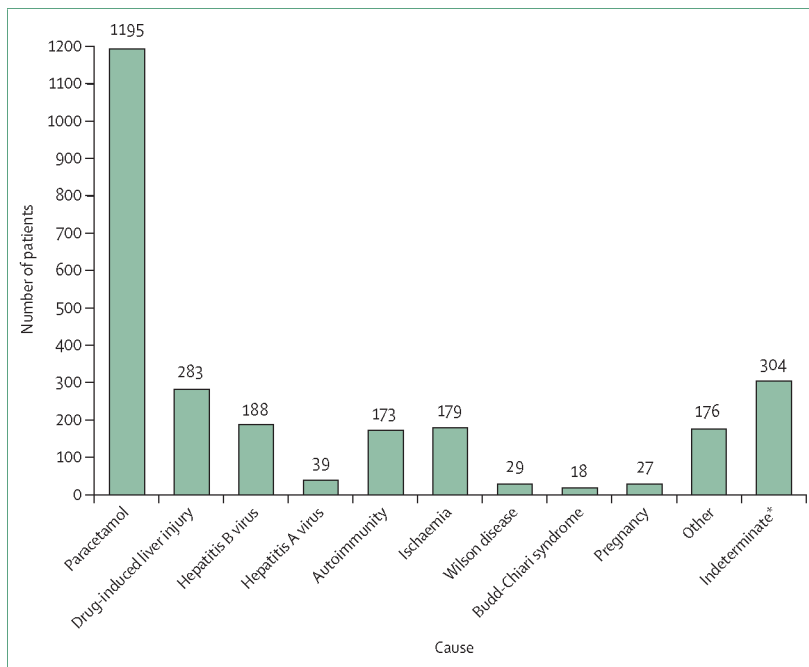


Figure 1: Causes of acute liver failure, as recorded by the site principal investigator in the US Adult Acute Liver Failure Study Group Registry
 Data were collected between Jan 1, 1998 and March 31, 2019. The total number of patients enrolled is 2614; paracetamol accounts for 46% of cases, 12% of cases have indeterminate causes, and drug-induced liver injury accounts for 11% of cases. *The number of patients with acute liver failure with an indeterminate cause decreased to 161, or 5.5% of the total, after review.¹

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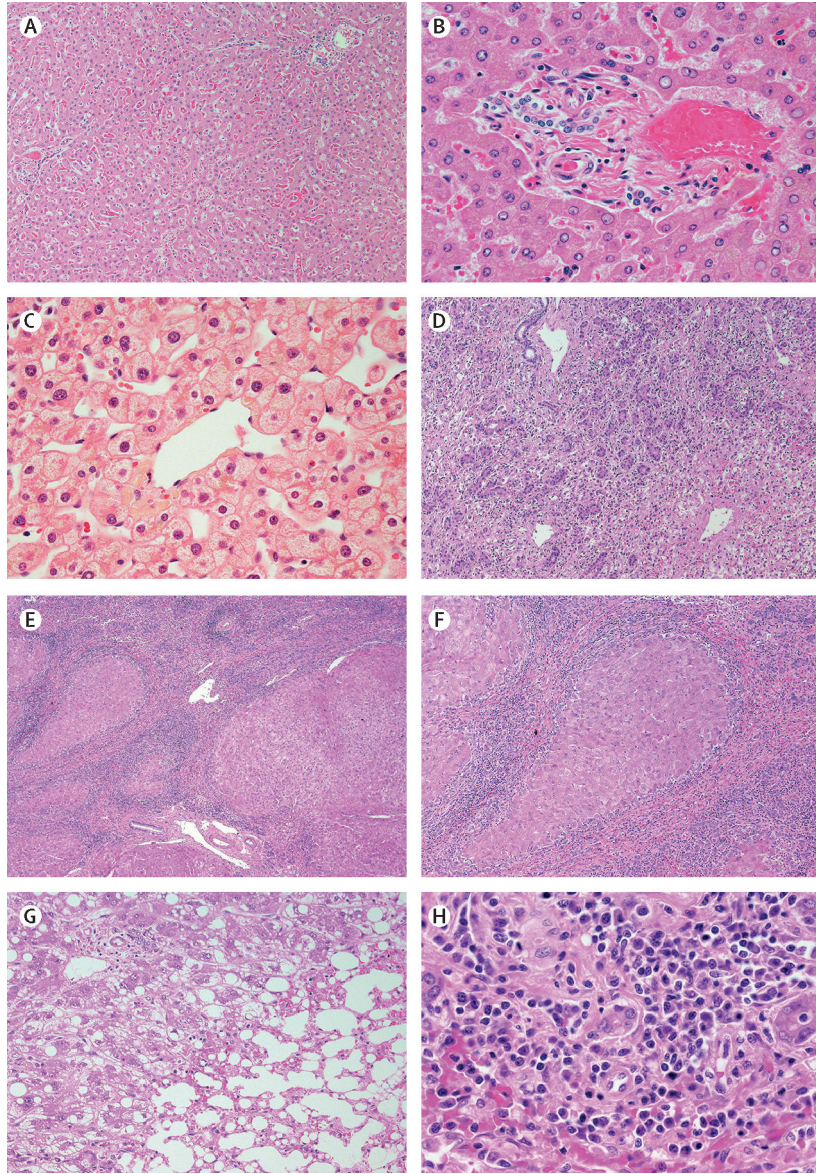


Figure 2: Examples of histopathology of acute liver failure

(A) Normal liver at low power (100×). (B) Higher power (400×) view of a normal hepatic lobule showing a portal tract. (C) Higher power (400×) view of a normal hepatic lobule showing central hepatic vein. (D) Isoniazid toxicity with complete parenchymal loss, no hepatocytes remain and the normal parenchyma has been replaced by ductular reaction (400×). (E) Heterogeneous areas of necrosis and parenchymal regeneration observed with nitrofurantoin toxicity (40×). (F) Regenerative nodules are rimmed by chronic inflammation at higher power (100×) in the same case as in (E); the patient had taken nitrofurantoin intermittently for nearly 6 months before developing liver failure. Regenerative nodules are often seen in this setting and might be confused on imaging with cirrhosis. (G) Paracetamol toxicity with zone 3 (centrilobular) necrosis. Many hepatocytes show steatosis and in the necrotic zone, lipid drops have coalesced (200×). (H) Acute liver failure related to hepatitis B, with prominent plasma-cell infiltrate within a portal tract, a unique but common finding

in fulminant hepatitis B (600×).⁵⁰ Representative explants were drawn from the Acute Liver Failure Study Group pathology registry, courtesy of David E Kleiner, Laboratory of Pathology, National Cancer Institute, Bethesda, MD, USA.

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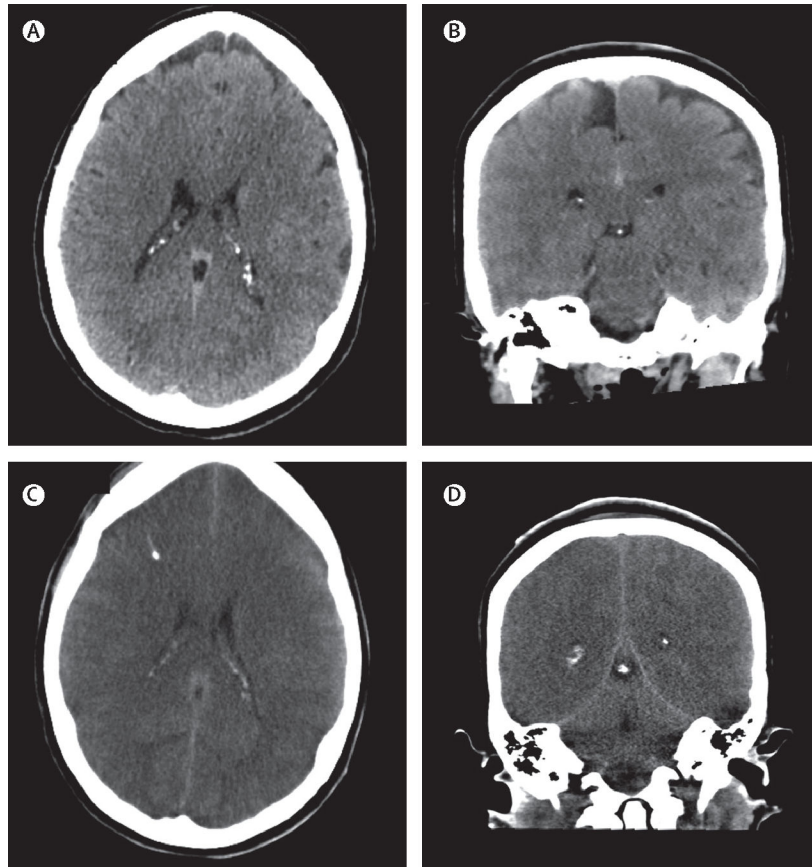


Figure 3: CT of the head in a patient with acute liver failure who developed cerebral oedema (A) Axial scan before the development of cerebral oedema. (B) Coronal scan before the development of cerebral oedema. (C) Axial scan after the development of cerebral oedema. (D) Coronal scan after development of cerebral oedema. All in a dying patient with brainstem herniation due to paracetamol-induced acute liver failure. (C) and (D) show the loss of grey–white demarcation and effacement of sulci.

Table 1: Comparison of demographics, admission laboratory results, and outcome between different causes of acute liver failure in the Acute Liver Failure Study Group Registry

	Paracetamol (n=1195)	Ischaemia (n=181)	Drug-induced liver injury (n=283)	Autoimmunity (n=173)	Hepatitis B virus (n=188)	Hepatitis A virus (n=39)	Pregnancy (n=27)	All other causes (n=528)
Age (median, years)	37	53	47	46	45	50	31	40
Women (%)	75%	58%	67%	81%	45%	44%	100%	64%
Jaundice coma (median, days)	1	2	12	16	8	4	7	7
Hepatic encephalopathy grade 3 or higher (%)	54%	56%	36%	27%	51%	54%	54%	44%
Alanine aminotransferase (median, IU/L)	3780	2311	654	404	1410	2229	43	758
Bilirubin (median, mg/dL)	4.3	3.8	19.6	22.8	19.2	12.0	9.0	16.2
Transplanted* (%)	9%	2%	39%	57%	40%	33%	4%	36%
Transplant-free survival* (%)	65%	57%	24%	14%	19%	51%	78%	22%
Overall survival* (%)	72%	58%	58%	63%	53%	77%	82%	55%

Data were collected between Jan 1, 1998, and March 31, 2019. Total number of patients=2614.

* Represents outcomes 21 days after admission to the Acute Liver Failure Study Group Registry.

Tests and indices for predicting mortality and need for liver transplantation in patients with acute liver failure

Table 2:

	Cause of acute liver failure	Threshold for poor prognosis or need for liver transplantation
King's College Criteria ¹⁰⁹	Paracetamol	Arterial pH <7.30 or all of the following: prothrombin time >100 s (international normalised ratio >6.5), creatinine >3.4 mg/dL, and grade 3 or 4 encephalopathy
King's College Criteria ¹⁰⁹	Non-paracetamol	Prothrombin time >100 s (international normalised ratio >6.5) or any three of the following: non-A, non-B viral hepatitis, or drug or halothane cause; jaundice to encephalopathy >7 days; age between 10 and 40 years; prothrombin time >50 s; bilirubin >17.4 mg/dL
Factor V (Clichy criteria) ^{119,120}	Viral	Age <30 years with clotting factor V <20% or any age with clotting factor V <30% and grade 3 or 4 encephalopathy
Liver biopsy ¹²¹	Mixed causes	Hepatocyte necrosis >70%
Arterial phosphate ¹²²	Paracetamol	>1.2 mmol/L
Serum lactate ¹¹⁷	Paracetamol	>3.5 mmol/L
APACHE II score ¹²³	Paracetamol	Score >15
MELD score ¹²⁴	Paracetamol	Score >33
BiLE score ¹²⁵	Mixed causes	Score >6.9
Volumetric CT ¹²⁶	Non-paracetamol	Liver volume <1000 cm ³
ALFSG Prognostic Index ^{8,18}	Mixed causes	Continuous

MELD=model for end-stage liver disease. BiLE=bilirubin, lactate, and etiology score. ALFSG=Acute Liver Failure Study Group.

* The ALFSG Prognostic Index, in contrast to the other indices listed, is designed to predict transplant-free survival rather than death or need for liver transplantation.