

Management of acute liver failure

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Abstract | Acute liver failure (ALF) is a syndrome of diverse etiology, in which patients without previously recognized liver disease sustain a liver injury that results in rapid loss of hepatic function. Depending on the etiology and severity of the insult, some patients undergo rapid hepatic regeneration and spontaneously recover. However, nearly 60% of patients with ALF in the US require and undergo orthotopic liver transplantation or die. Management decisions made by clinicians who initially assess individuals with ALF can drastically affect these patients' outcomes. Even with optimal early management, however, many patients with ALF develop a cascade of complications often presaged by the systemic inflammatory response syndrome, which involves failure of nearly every organ system. We highlight advances in the intensive care management of patients with ALF that have contributed to a marked improvement in their overall survival over the past 20 years. These advances include therapies that limit the extent of liver injury and maximize the likelihood of spontaneous recovery and approaches to enable prevention, recognition and early treatment of complications that lead to multi-organ-system failure, the most common cause of death. Finally, we summarize the role of orthotopic liver transplantation in salvage of the most severely affected patients.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the most common causes of acute liver failure (ALF) in the United States and in the world.
- 2 Describe the clinical features of hyperacute and subacute liver failure.
- 3 Identify 4 management decisions that critically influence the outcome of ALF.
- 4 Describe the King's College criteria for recognizing poor prognosis in patients with ALF.
- 5 Identify differences in outcomes of liver transplantation between patients with ALF and chronic liver disease.

Competing interests

The authors, the Journal Editor N. Wood and the CME questions author D. Lie declare no competing interests.

Introduction

The classic description of acute liver failure (ALF) involves the abrupt loss of hepatocellular function in a patient with previously normal liver function, the expression of which includes coagulopathy and hepatic encephalopathy. However, the pathogenic and clinical etiologies of ALF are diverse, and three such etiologies—acute Wilson disease, reactivation (flare) of hepatitis B and autoimmune hepatitis—are commonly recognized to be chronic liver diseases rather than ALF. The distinction between patients with ALF and those with acute-on-chronic liver disease may be difficult to make on clinical grounds, unless examination of a liver biopsy sample confirms the absence of cirrhosis. Even with histological studies, however, the architectural collapse of the liver that is characteristic of ALF may be difficult to distinguish from fibrosis associated with chronic liver disease. A working definition of ALF might include the absence of previously recognized liver disease, preferably with liver histology findings that confirm the absence of mature collagen or other evidence of chronic liver disease.

The relative prevalence of etiologies of ALF differs markedly according to geography.¹ In the US and many countries in western Europe, drug-induced liver injuries predominate, including those related to the intrinsic hepatotoxin, paracetamol (acetaminophen).¹ The US ALF Study Group Registry of over 1,400 cases observed in 23 major medical centers has documented that paracetamol overdose is the cause of ALF in ~45% of patients (Figure 1). Suicidal intent is the reason for roughly half of these overdoses and the remainder occur as a consequence of therapeutic misadventure.^{2,3} Idiosyncratic drug reactions comprise the etiology of about 15% of cases of ALF in the US (Figure 1), among which antibiotics,

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NSAIDs and anticonvulsants constitute some of the most commonly involved classes of prescription medications.^{4–6} Worldwide, viral hepatitis is the predominant cause of ALF; however, acute viral hepatitis A and B cause ALF infrequently in the US. Despite extensive investigations, the etiology of ALF remains elusive (indeterminate) in ~15% of patients in the US, but data from 2006 suggest that in 20% of such patients ALF may be attributable to an undiagnosed paracetamol overdose.⁷ The principles of managing ALF that are discussed in this Review are applicable widely despite geographic differences in etiology; however, the availability of resources will often govern individual practices.

The prognosis of patients with ALF was uniformly very poor in older series; spontaneous (transplant-free) recovery resulted in survival of less than 20%.⁸ However, in the era of transplantation and with improvements in the intensive care of patients with ALF, spontaneous recovery and overall survival in the US now exceed 40% and 65%, respectively.^{4,9} The likelihood of spontaneous recovery is not uniform and depends on the etiology of the liver injury. The rapidity of evolution of the clinical course of ALF (as estimated by the interval between onset of jaundice and that of encephalopathy) also predicts outcome, partially as a consequence of its relationship to etiology. Hyperacute liver failure, which has a jaundice-to-encephalopathy interval of ≤ 7 days and is usually caused by paracetamol overdose, has a relatively good likelihood of spontaneous recovery. Conversely, subacute liver failure, which has a jaundice-to-encephalopathy interval of >28 days and is usually caused by idiosyncratic drug reactions, has a very poor prognosis without orthotopic liver transplantation.¹⁰ An apparent paradox in this observation is that patients with hyperacute liver failure more often develop cerebral edema, a complication with few effective therapies that is often fatal.

In this Review we discuss current management strategies for patients with ALF. As a result of the rarity of the condition, its clinical heterogeneity and its high mortality, some of the opinions expressed below reflect the consensus view of experts or personal experience, as few randomized, controlled studies have been accomplished. We should also emphasize that the successful management of patients with ALF transcends the fields of gastroenterology and hepatology, and relies heavily on excellent intensive care medicine. This Review, therefore, includes practical decisions that must be made by emergency medicine physicians and gastroenterologists who initially assess patients with ALF and who must anticipate and treat specific complications of this disease, as well as manage practical aspects of the intensive care of affected patients. Finally, we briefly discuss the role of orthotopic liver transplantation in managing patients with ALF.

Management decisions on presentation

Making a timely diagnosis of ALF in a patient who presents with liver dysfunction and an altered mental state

Key points

- Administration of *N*-acetylcysteine to all patients with ALF regardless of its etiology may become standard-of-care
- Four management decisions critically influence the clinical course and outcome of patients with ALF: early and accurate diagnosis; *N*-acetylcysteine administration; transfer to a liver transplant center; listing for liver transplantation
- Evolution of the clinical syndrome of ALF includes multi-organ-system failure (MOSF), often triggered by infection; the earliest signs of deterioration are elements of the systemic inflammatory response syndrome
- Clinical trials in ALF are lacking; consequently, intensive care management of affected patients is largely based on experience in other disease entities characterized by cerebral edema, systemic inflammation and MOSF
- Patients with ALF rarely experience clinically significant bleeding complications and the optimal management of abnormal clotting in these patients requires further study
- The incidence of cerebral edema and intracranial hypertension in ALF seems to be decreasing, but these conditions portend poor outcome as treatment merely delays brain herniation rather than reverses pathogenesis

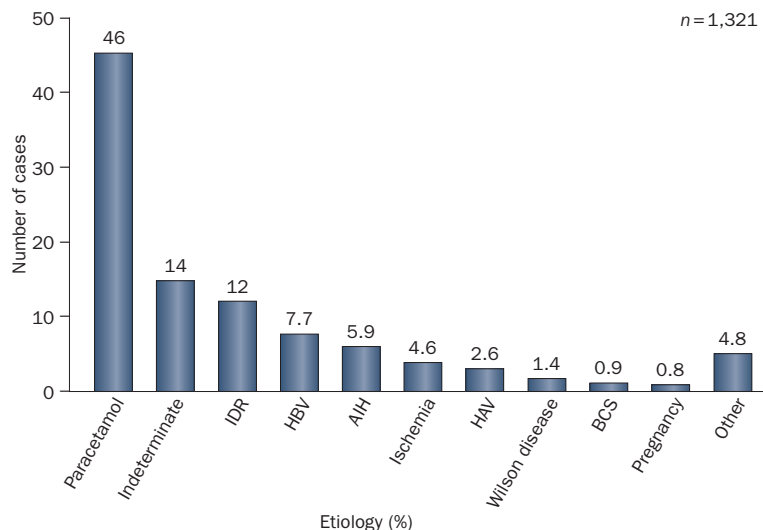


Figure 1 | Etiologies of acute liver failure in the US. Data from the Acute Liver Failure Study Group Registry, 1998–2008. (W. M. Lee, personal communication). Abbreviations: AIH, autoimmune hepatitis; BCS, Budd–Chiari syndrome; HAV, hepatitis A virus; HBV, hepatitis B virus; IDR, idiosyncratic drug reaction.

constitutes the single most important decision for the clinician in the community as a delay can be disastrous. The differential diagnosis includes acutely decompensated chronic liver disease and sepsis, although these alternatives can usually be excluded by taking a medical history and performing a physical examination, basic laboratory tests and abdominal ultrasonography.

After recognition of ALF, the second critical management decision is whether to administer *N*-acetylcysteine. The role of *N*-acetylcysteine in limiting liver injury and improving prognosis in patients with ALF following paracetamol overdose has been well-documented in large case series^{11–13} and a small, controlled trial.¹⁴ In addition to its role in limiting liver injury via repletion of hepatic glutathione,¹⁵ *N*-acetylcysteine also has beneficial effects on

Table 1 | NAC treatment for acute liver failure not due to paracetamol overdose¹⁸

Outcome	Grade 1 or 2 hepatic encephalopathy		All grades of hepatic encephalopathy		Overall P value
	Placebo (n = 56)	NAC (n = 58)	Placebo (n = 92)	NAC (n = 81)	
Survival at 21 days (%)	75	79	66	70	0.283
Survival at 1 year (%)	61	72	57	63	0.195
Transplant-free survival at 1 year (%)	18	45	18	35	0.008
Proportion of patients transplanted at 1 year (%)	52	28	48	32	0.035

Abbreviation: NAC, N-acetylcysteine.

systemic hemodynamic parameters and oxygen delivery to peripheral tissues.^{16,17} Consequently, N-acetylcysteine has also been tested as a treatment for forms of ALF unrelated to paracetamol overdose. The US ALF Study Group recently completed a study of 173 patients with ALF that was not due to paracetamol overdose who were randomly allocated to receive either intravenous N-acetylcysteine (in standard doses as for paracetamol overdose) or placebo (Table 1).¹⁸ The primary outcome of the study was overall survival at 21 days from randomization, which was not significantly different between the two groups. However, secondary outcomes of transplant-free survival and the proportion of patients who underwent orthotopic liver transplantation at 1 year were improved in patients who received N-acetylcysteine compared with those who received placebo. Furthermore, in the subgroup of patients with grade 1 or 2 hepatic encephalopathy, survival at 1 year was significantly better in those who received N-acetylcysteine than in all other individuals, after adjustment for age. As these data were gleaned from subgroup analyses, they will probably be interpreted to mean that all patients with ALF should receive N-acetylcysteine regardless of the etiology of this disease, as another, more-definitive study of N-acetylcysteine in this population of patients is unlikely ever to be performed.

The third critical management decision is whether a patient with ALF should be transferred to a liver transplant center. Management of patients with ALF in liver transplant centers after resuscitation in the community offers several potential advantages. First, in the US, 25% of patients with ALF undergo orthotopic liver transplantation, and the proportion is even higher (40–50%) for etiologies of ALF that have a poor prognosis.¹ Second, the determination of transplant candidacy can only be made by experts in the field. Apparent psychosocial barriers to orthotopic liver transplantation that are common in patients with paracetamol-induced ALF (for example, a psychiatric and/or substance-abuse history and a lack of medical insurance) must be balanced against the potential death of a young (average age 36–42 years) and often otherwise healthy individual.^{2,9} Finally, the management of multi-organ-system failure (MOSF), which frequently complicates ALF, requires considerable expertise in intensive care medicine. Transfer to a specialized

intensive care unit (ICU) that has experience in the care of individuals with liver failure should be arranged when the patient's international normalized ratio exceeds 2.0 or grade 2 hepatic encephalopathy develops. High-risk patients, including those at the extreme ends of the age range (>45 years or <10 years) or with etiologies of ALF that carry a poor prognosis,^{10,19} should be considered for transfer to a liver transplant center whenever any degree of encephalopathy develops. During transportation of the patient, dextrose in saline should be given as a continuous, intravenous infusion to maintain euglycemia. Rapidly progressive encephalopathy confers an increased risk of airway compromise (loss of the gag reflex and effective cough) during transfer; consequently, orotracheal intubation should be undertaken before the patient is released from the referring institution.

The fourth critical management decision is whether a patient with ALF should be listed for orthotopic liver transplantation. Such listing is, in many cases, tantamount to the patient undergoing transplantation, as transplant surgeons are reluctant to turn down organ offers for patients with an unpredictable clinical course. The King's College criteria (Box 1)¹⁹ remain the most widely applied parameters for predicting the prognosis of patients with ALF, although they lack the sensitivity to replace an experienced transplant physician's 'gut feeling'.²⁰ Many other prognostic schemes have been proposed, but none has been accepted to be more accurate than the King's College criteria.^{21,22}

Management of specific complications

Many patients with ALF experience MOSF, which is the most common cause of death in this population (Figure 2). Nearly all organ systems may succumb to failure in a cascade of events that is frequently triggered by infection.^{23–25} Systemic inflammatory response syndrome (SIRS) is characterized by a body temperature >38 °C or <36 °C, a white blood cell count >12 × 10⁹/l or <4 × 10⁹/l and a heart rate of >90 bpm, which presumably result from a massive release of inflammatory cytokines from the necrotic liver. SIRS can develop in patients with ALF who may not manifest infection, and often presages the development of MOSF.^{24,26,27} Moreover, the clinical syndrome of ALF, even in the absence of infection, closely resembles that of septic shock.^{28,29} Effective

Box 1 | King's College criteria for poor prognosis in ALF**Paracetamol-induced ALF**

Arterial pH <7.30 after fluid resuscitation

OR all of the following features:

Prothrombin time >100 s (international normalized ratio >6.5)

Serum creatinine >259 $\mu\text{mol/l}$ (3.4 mg/dl)

Grade 3 or 4 hepatic encephalopathy

Non-paracetamol-induced ALF

Prothrombin time >100 s (international normalized ratio >6.5)

OR any three of the following features:

Non-A, non-B viral hepatitis, drug-induced or indeterminate etiology of ALF

Time from jaundice to hepatic encephalopathy >7 days

Age <10 years, or >40 years

Prothrombin time >50 s (international normalized ratio >3.5)

Serum bilirubin >297.6 $\mu\text{mol/l}$ (17.4 mg/dl)

Abbreviation: ALF, acute liver failure.

management of a patient with ALF, therefore, begins with prevention or early identification of triggers of MOSE, the first evidence of which is elements of SIRS.

Infection

Immune dysfunction occurs on many levels in patients with ALF,³⁰ most of whom require invasive monitoring. This monitoring provides a portal for infection. In centers that perform surveillance cultures of blood and urine as well as daily chest radiography, up to 90% of patients develop some evidence of infection.²³ Both bacterial and fungal pathogens have been identified in patients with ALF, among which respiratory, urinary tract and catheter-related infections predominate.^{23,31} Infections with Gram-positive organisms including *Staphylococcus* and *Streptococcus* species outnumber those with Gram-negative enteric organisms and *Candida* species.^{23,30,32} Infections include pneumonia in 50%, urosepsis in 22%, intravenous-catheter-induced bacteremia in 12% and spontaneous bacteremia in 16% of patients.³⁰ Unfortunately, the usual signs of infection may be absent in nearly one-third of individuals with ALF.^{23,33}

Several studies have examined the role of antibiotic prophylaxis in patients with ALF. Three studies in which patients with ALF were treated with parenteral and enteral antibiotics show that antibiotic prophylaxis seems to decrease the incidence of infection with some organisms, but the results are inconclusive.^{33–35} Although these studies do not provide definitive evidence to

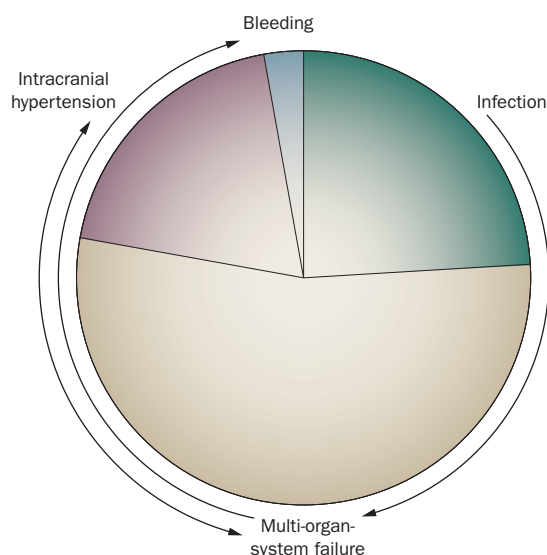


Figure 2 | Proximate causes of death in patients with ALF and how these causes are inter-related. Complications of ALF involve almost every organ system. Improvements in intensive care management and the widespread use of orthotopic liver transplantation to rescue patients with ALF have decreased overall mortality from >80% to 33% in the US over the past ~25 years.⁸ Proximate causes of death have also changed over the same period; the incidence of death from hemorrhage has decreased from ~25% to <5%,¹⁰⁷ and the incidence of death from intracranial hypertension and/or brainstem herniation has decreased to ~20–25%.⁸ The most common cause of death in patients with ALF is multi-organ-system failure, which is often triggered by sepsis, may exacerbate the bleeding diathesis, and increase the risk of developing intracranial hypertension. Abbreviation: ALF, acute liver failure.

support the administration of prophylactic antibiotics to all patients with ALF, several practical guidelines should be considered.³⁴ As with all critically ill patients, intravenous lines should be minimized and their placement and maintenance performed with the strictest aseptic technique. In severely ill patients who require numerous indwelling life-support and monitoring devices, chest radiography and surveillance cultures of blood, urine and sputum should be performed daily. Finally, broad-spectrum antibiotics should be empirically administered to patients with ALF in situations in which infection has been reported frequently; that is, for those patients with progression to grade 3 or 4 hepatic encephalopathy, renal failure and/or any of the components of SIRS. Clinicians at most centers also administer prophylactic antibacterial and antifungal agents to patients with ALF who are awaiting orthotopic liver transplantation, as infection might preclude transplantation.

Pulmonary considerations

Meticulous attention to airway, breathing and circulation is of paramount importance in patients with ALF who are managed in the ICU. Airway compromise, followed

Box 2 | Intubation and ventilation of patients with ALF

Therapeutic maneuvers during intubation of a patient with ALF and high-grade encephalopathy include preoxygenation, prevention of hypercapnia and the avoidance of hypotension. In terms of intubation, neuromuscular blockade with the non-depolarizing agent *cis*-atracurium might be preferable to the depolarizing agent succinylcholine, as the latter causes muscle contraction, which in turn increases intracranial pressure. In addition, metabolism of *cis*-atracurium is also independent of renal and hepatic function, and permits neurologic assessment 40–60 min after the bolus. Initial ventilator settings should be selected to achieve constant, minute ventilation while minimizing lung trauma by use of low-tidal-volume ventilation (6 ml/kg of ideal body weight). Arterial PaCO₂ is an important determinant of intracranial pressure in patients with ALF.^{37,38} An initial PaCO₂ goal of 35 mmHg after intubation enables subsequent hyperventilation to address transient spikes in intracranial pressure without compromising cerebral blood flow.¹⁰⁸ PaCO₂ can be later titrated to intracranial pressure by adjusting minute ventilation after placement of an intracranial pressure monitor.

Abbreviations: ALF, acute liver failure; PaCO₂, carbon dioxide tension.

by impaired gas exchange that leads to respiratory and metabolic acidosis, may cause a sudden progression from neurologic dysfunction to grade 3 hepatic encephalopathy.^{35,36} Consequently, if a patient develops grade 3 hepatic encephalopathy their airway should be secured by endotracheal intubation. A rapid intubation technique that takes care to avoid exacerbation of intracranial hypertension or cerebral hypoperfusion is appropriate. Intubation and ventilation techniques and procedures for patients with ALF and high-grade encephalopathy are discussed in Box 2.

Acute lung injury and acute respiratory distress syndrome occur in approximately one-third of patients with ALF and can cause intractable hypoxemia that may contribute to death.³⁷ The development of acute lung injury and acute respiratory distress syndrome may also result in increased lung dead space and a rising carbon dioxide tension (PaCO₂), which leads to cerebral vasodilation and increased intracranial pressure.^{38,39} The temptation to lower PaCO₂ by increasing tidal volume should be resisted as the consequences of worsening lung injury outweigh the potential consequences of hypercapnia to increase intracranial pressure. The hypoxemia that results from acute lung injury and acute respiratory distress syndrome should be managed with recruitment (a transient increase in mean airway pressure to expand the lungs) and positive end expiratory pressure titrated to optimize compliance and minimize decrease in venous return and cardiac output.

Cerebral edema and intracranial hypertension

Although the incidence of cerebral edema in patients with ALF seems to be decreasing,⁸ intracranial hypertension accounts for ~20–25% of deaths and may contribute to residual neurologic impairment after recovery.⁴⁰ The pathogenesis of cerebral edema in ALF remains incompletely understood, but involves both osmotic and hemodynamic abnormalities within the confines of the rigid skull. The most important source of osmotic

stress is glutamine, the product of the amidation of glutamate by ammonia, which accumulates within astrocytes. Hyperperfusion of the brain also contributes to cerebral edema as a consequence of loss of cerebrovascular autoregulation and an increase in circulating inflammatory cytokines that cause vasodilation.⁴¹

Several risk factors for the development of cerebral edema have been identified in patients with ALF. Cerebral edema more frequently develops in individuals with hyperacute rather than subacute liver failure as the accumulation of glutamine occurs quickly in such patients and overwhelms the compensatory expulsion of organic osmolytes from astrocytes.⁴¹ Moreover, high serum ammonia concentrations (>150–200 μmol/l) and their clinical correlate (grade 3 or 4 hepatic encephalopathy) also increase the risk of cerebral edema, although the relationship between ammonia and intracranial pressure is not linear.^{42–44} The need for vasopressors or renal replacement therapy as well as the presence of infection and/or SIRS also predict the progression of hepatic encephalopathy and cerebral edema.^{24,26,44}

The decision to insert an intracranial pressure monitor, the technical details of its insertion (for example, location and type of device) and the goals of intracranial pressure monitoring remain contentious issues in ALF that have not been systematically studied. Some centers routinely insert intracranial pressure monitors in patients with ALF who are at high risk of cerebral edema; others reserve such monitoring for patients awaiting orthotopic liver transplantation.⁴⁵ Advocates of the practice cite evidence that prolonged high intracranial pressure (>25 mmHg) and low cerebral perfusion pressure (<40 mmHg) for >2 h portends poor neurologic recovery and should contraindicate orthotopic liver transplantation.⁴⁶ However, these pressure thresholds have been challenged by reports of complete neurologic recovery after prolonged intracranial hypertension (intracranial pressure >35 mmHg for >24 h) associated with low cerebral perfusion pressure (<50 mmHg).⁴⁷ Advocates of monitoring also note that medical treatment of intracranial hypertension can transiently decrease intracranial pressure and that this parameter provides a much more accurate measure of the need for, and response to, treatment than a physical examination or head CT scan.⁴⁸ Detractors of such monitoring counter that placement of the device carries significant risk of intracranial bleeding,⁴⁹ did not improve outcome in nonrandomized trials⁴⁵ and that pressure goals in patients with ALF have never been defined. We should note, however, that the risk of clinically significant intracranial bleeding after monitor placement is low (<5%)^{45,50} and that intracranial pressure and cerebral perfusion pressure goals have also not been rigorously defined for other clinical situations where monitoring is widely advocated.^{51,52} Preparation of the patient for intracranial pressure monitor placement also remains controversial with regard to correction of the perceived bleeding diathesis.⁵³

The effective medical management of cerebral edema in a patient with ALF usually begins with the management of hepatic encephalopathy (Figure 3). Patients who progress to grade 3 or 4 hepatic encephalopathy should be endotracheally intubated under adequate sedation and analgesia; propofol and fentanyl, respectively, are reasonable choices for these purposes.³⁴ Although orally administered lactulose and/or nonabsorbable antibiotics (for example, rifaximin) may lower serum ammonia levels in patients with cirrhosis and theoretically may lower the risk of developing cerebral edema in patients with ALF, this hypothesis has never been tested; oral lactulose may also have adverse effects.³⁴ A bowel cleanse with lactulose or a saline enema has been advocated.³⁴ Several simple maneuvers should be applied to all patients with ALF and grade 3 or 4 encephalopathy to prevent the development of cerebral edema (Figure 3). Fever increases intracranial pressure and should be vigorously treated with cooling blankets;⁵⁴ conversely, the spontaneous hypothermia (for example, body temperature 35–36 °C) that frequently accompanies ALF may prevent intracranial hypertension (see below) and should not be reversed. Hypo-osmolality, specifically hyponatremia, should be avoided and corrected immediately.

The development of intracranial hypertension despite these prophylactic measures should prompt urgent treatment (Figure 3). First-line therapy includes increasing blood osmolality, either with mannitol and/or hypertonic saline boluses, which draws water from swollen astrocytes back into the intravascular space. The earliest reports of the efficacy of mannitol included a small number ($n = 27$) of patients with intracranial hypertension.^{55,56} Mannitol (1 g/kg body weight) decreased intracranial pressure in many patients, but was ineffective in returning intracranial pressure to an acceptably low level (<25 mmHg) in patients with severe intracranial hypertension (>40–60 mmHg).⁵⁶ Unfortunately, improvements in intracranial pressure achieved by the administration of mannitol usually wane, which necessitates use of multiple doses that can result in hyperosmolality (>320 mOsm/l). Ultimately, mannitol administration may stabilize a patient with ALF until orthotopic liver transplantation can be performed, but this agent does not provide definitive therapy. Similar to other conditions characterized by cerebral edema, hypertonic saline boluses have been advocated for the treatment of established cerebral edema in patients with ALF,⁵⁷ although no studies have yet examined the efficacy of this practice. However, in ALF patients with normal intracranial pressure, the induction of prophylactic hypernatremia (serum sodium levels 145–155 mmol/l) with hypertonic saline boluses effectively prevented the development of intracranial hypertension compared with normonatremia (serum sodium levels 135–145 mmol/l).⁵⁸

Patients with ALF for whom osmotic therapy does not successfully treat intracranial hypertension usually succumb to brainstem herniation if orthotopic liver transplantation does not immediately follow. Desperate

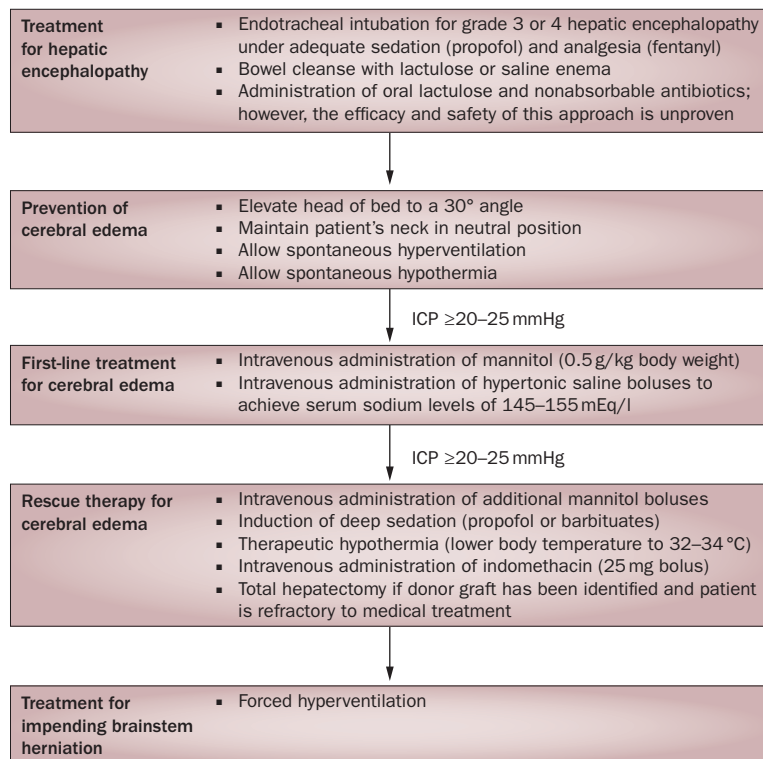


Figure 3 | Management of hepatic encephalopathy and cerebral edema in patients with ALF. Oral lactulose should be given cautiously to avoid aspiration, diarrhea, and gaseous distention of the bowel, which may interfere with orthotopic liver transplantation. Physical stimulation, including endotracheal suction, should be minimized. Patients should be positioned with their head elevated to 30° and in a neutral neck position. Spontaneous hyperventilation, which occurs regularly in patients with ALF, should not be inhibited; it results in mild hypocapnia and promotes cerebrovascular constriction.^{37,38} Additional boluses of mannitol can be given if serum osmolality is <320 mOsm/l, or the osmolar gap remains normal.¹⁰⁹ In patients with intracranial hypertension refractory to medical therapy, hypothermia effectively lowers intracranial pressure, restores autoregulation of cerebrovascular blood flow, may limit liver injury, and can be used as a bridge to transplantation.^{111–114} Hypothermia during orthotopic liver transplantation also prevents spikes in intracranial pressure during surgery.⁹⁸ Concern has been raised about adverse effects of hypothermia on hepatic regeneration.¹¹⁵ Whether hypothermia can assist patients with ALF to recover spontaneously without orthotopic liver transplantation has never been documented, and the safety of hypothermia in this critically ill population remains inadequately assessed.¹¹⁰ Abbreviation: ALF, acute liver failure.

measures considered under these conditions include the induction of deep sedation with propofol⁵⁹ or barbiturates,^{46,60} intravenous boluses of indomethacin⁶¹ and therapeutic hypothermia (Figure 3). Finally, in patients with intracranial hypertension that is refractory to all medical measures but for whom a liver graft donor has been identified, total hepatectomy has been advocated.⁶² This procedure is presumably recommended because it removes the major source of proinflammatory cytokines that contribute to cerebral vasodilation.⁶³

Seizures in patients with ALF increase cerebral blood flow and intracranial pressure, and result in cerebral edema. Seizures that are unremitting can exacerbate neuronal damage. In patients with ALF, seizures are

often nonconvulsive and can be detected only by electroencephalography. Prophylaxis with phenytoin has been studied in two randomized, controlled cohorts of patients with ALF and high-grade hepatic encephalopathy.^{64,65} Unfortunately, the studies came to different conclusions with regard to the efficacy of phenytoin in preventing seizures and cerebral edema, and in influencing survival.

Cardiovascular considerations

ALF dramatically alters systemic hemodynamic parameters. Early hemodynamic changes include increased portal pressure, splanchnic sequestration of blood and decreased central venous return.⁶⁶ The primary hemodynamic abnormality in ALF is systemic arterial vasodilation due to reduced precapillary sphincter tone, an abnormality that also occurs in sepsis.⁶⁷ Volume status in a hypotensive patient with ALF can be difficult to assess, but a normal saline challenge guided by changes in central venous pressure should be administered before considering the use of vasopressors. In hypotensive patients with ALF who do not respond to volume resuscitation, vasopressors should be administered and titrated to achieve a mean arterial pressure >75 mmHg and a cerebral perfusion pressure 60–80 mmHg. Patients with liver disease manifest reduced vasoconstriction in response to α -adrenergic agents.⁶⁸ However, β -adrenergic sensitivity does not seem to be downregulated in these individuals. Dopamine and norepinephrine both increase hepatic blood flow in parallel with cardiac output,⁶⁹ but the latter may be associated with fewer β -adrenergic side effects (such as tachycardia) for the same vasopressor response and is, therefore, preferred over dopamine. Dobutamine may be considered if left ventricular dysfunction is severe, but may increase arterial vasodilation and worsen hypotension. Vasopressin and its analogs potentiate the vasoconstricting effect of norepinephrine, which enables the infusion rate of norepinephrine to be reduced, but controversy about the potential of vasopressin to increase intracranial pressure in patients with ALF relegates it to a secondary role in this setting.^{70–72} Patients with ALF who remain persistently hypotensive despite the administration of vasopressors should be evaluated for adrenal insufficiency, which occurs frequently in this setting and correlates with the severity of illness.⁷³

An algorithm for resuscitating a hypotensive patient with ALF includes intravenous administration of normal saline, which is then changed to 0.45% normal saline with 75 mmol/l sodium bicarbonate to maintain the infused sodium concentration at 152 mmol/l. The latter infusion will minimize the potential for hyperchloremic acidosis. At our center, once cardiac filling pressures are optimized, norepinephrine is titrated according to the mean arterial pressure, to keep cerebral perfusion pressure >60 mmHg. In patients without an intracranial pressure monitor, we assume that the intracranial pressure is 20 mmHg and use a target mean arterial pressure of >80 mmHg. In the face of escalating norepinephrine requirements, or if

side effects such as arrhythmias develop, vasopressin at a fixed dose of 0.04 U/min can be added to permit the downward titration of norepinephrine. Adrenal insufficiency is corrected with a stress dose of hydrocortisone (200–300 mg daily, given in divided doses).

Bleeding

Increased prothrombin time or international normalized ratio, and the frequent coexistence of thrombocytopenia in patients with ALF, underlies the perception that all such patients have a bleeding diathesis. While an increase in either prothrombin time or international normalized ratio is requisite for the diagnosis of ALF, thrombocytopenia (platelet count $<150 \times 10^9/l$) also occurs frequently—in 50–70% of patients with ALF.⁷⁴ Defective synthesis and increased consumption of procoagulant factors accounts for the increased prothrombin time in patients with ALF,⁷⁵ and this parameter is a determinant of prognosis (Figure 3).^{19,76} However, serum concentrations of thrombopoietin, the liver-derived stimulator of platelet production, do not correlate with platelet counts.⁷⁴ The pathogenesis of thrombocytopenia in patients with ALF, therefore, remains unclear.

Similar to cirrhosis,⁷⁷ an increased prothrombin time or international normalized ratio in patients with ALF may not denote an increased risk of bleeding, as concentrations of anticoagulant proteins decrease in concert with those of procoagulant proteins.⁷⁸ So, unless defective coagulation factor synthesis is accompanied by an inadequate platelet scaffold, a true bleeding diathesis may not exist.⁷⁹ These observations may explain the fact that clinically significant bleeding is uncommon (~5%) in patients with ALF.⁷⁶ Insignificant bleeding may occur from mucosal erosions, usually of the stomach, but also of the genitourinary system, lungs and nasopharynx.⁸⁰ Gastric acid suppression with histamine receptor 2 antagonists (and by inference, PPIs) decreases the risk of gastric mucosal bleeding in patients with ALF.⁸¹ Although portal hypertension can occur in patients with ALF because of the collapse of liver architecture, bleeding from varices almost never occurs.⁸² Furthermore, despite the development of intracranial hypertension, spontaneous intracranial bleeding is exceedingly rare in the absence of an intracranial pressure monitor.⁸³

A more relevant clinical situation involves the risk of bleeding in a patient with ALF who requires an invasive procedure, such as the placement of a central venous catheter or an intracranial pressure monitor. The commonly used goal for correction of the international normalized ratio to a value of ≤ 1.5 to minimize bleeding risk³⁴ remains untested and lacks a scientific basis. Furthermore, correction of a perceived coagulopathy obscures the all-important trends in prothrombin time and/or international normalized ratio that are required to assess prognosis and spontaneous recovery. Strategies for correction of abnormal coagulation parameters and thrombocytopenia include transfusion of blood products, plasmapheresis and the administration of recombinant

factor VIIa.^{53,84} However, such strategies also risk volume overload, transfusion-related acute lung injury and thromboembolism (in those who receive recombinant factor VIIa).⁸⁵ Clearly, further research is needed to clarify which patients with ALF have an increased risk of bleeding with invasive procedures and how such patients should receive prophylactic therapy.

Acute renal failure

Acute renal failure occurs in ~50% of patients with ALF, depending on its etiology, and is most common in patients whose ALF is due to paracetamol overdose.^{27,86} Two causes of acute renal failure are peculiar to this setting. Firstly, some etiologies of ALF have intrinsically nephrotoxic effects, including paracetamol, sulfonamides, halothane and toxins from the *Amanita* (mushroom) genus.^{25,87,88} Renal failure occurs early in the course of ALF in affected individuals and is characterized by acute tubular necrosis. Secondly, patients may develop functional renal failure that resembles the hepatorenal syndrome of cirrhosis; this type of failure generally develops late in the course of ALF.²⁵

The incidence of renal dysfunction in patients with paracetamol-induced ALF depends on its definition. In one study, ~50% of patients with paracetamol-induced ALF developed azotemia with serum creatinine levels $\geq 176.8 \mu\text{mol/l}$ ($\geq 2.0 \text{ mg/dl}$).² Acute kidney injury, defined as an increase in the level of serum creatinine to at least double that of baseline, was observed in 76% of a different cohort of patients with paracetamol-induced ALF.²⁷ The incidence of paracetamol-induced nephrotoxic effects in patients with ALF parallels the degree of liver injury in some series²⁷ but not in others,⁸⁷ which suggests that more than one mechanism of injury is involved. Studies in experimental models have supported the local production of reactive paracetamol metabolites by enzymes in the kidney as a mechanism of nephrotoxic effects.⁸⁷ However, studies in knockout mice deficient in cytochrome P450 reductase suggest that nephrotoxic effects also result from liver-derived reactive paracetamol metabolites.⁸⁹ Clinically and pathologically, the pattern of renal injury due to paracetamol is acute tubular necrosis (defined as urinary sodium levels $>20 \text{ mmol/l}$ with an active sediment).⁸⁷ Similar to paracetamol-induced hepatotoxic effects, the nephrotoxic effects of paracetamol usually reverse spontaneously, but whether administration of *N*-acetylcysteine contributes to this improvement remains unclear.

Similarly to patients with cirrhosis and hepatorenal syndrome, functional renal failure in patients with ALF is inferred after examination of urine reveals no evidence of tubular injury (normal sediment, urine sodium level $<10 \text{ mmol/l}$) and a 1.5l volume challenge rules out prerenal azotemia.⁹⁰ The pathogenesis of functional renal failure in ALF resembles that of hepatorenal syndrome in cirrhosis and includes intense renal arteriolar vasoconstriction due to loss of systemic vascular resistance and activation of compensatory vasoconstrictor

systems.²⁵ In contrast to cirrhosis, however, splanchnic pooling of blood occurs to a more modest degree in ALF, owing to lower portal pressures in patients affected by the latter.²⁷ The presence of SIRS on admission to the ICU predicts the development of functional renal failure in patients with non-paracetamol-induced ALF.²⁷ The prevention and treatment of functional renal failure in patients with ALF has not been studied, although the effects of aggressive maintenance of renal perfusion with volume repletion and vasopressors, treatment of infection and possibly removal of high circulating levels of inflammatory cytokines by plasmapheresis or albumin dialysis, deserve study.

In patients with ALF, renal replacement therapy is more often initiated to correct intravascular volume overload, acidosis or electrolyte imbalance than to address azotemia. Indeed, formation of urea is severely impaired in ALF. Renal replacement therapy should be applied early in the course of ALF, before the indications for this treatment exacerbate intracranial hypertension or precipitate cardiovascular instability. Although untested, potential triggers for instituting renal replacement therapy might include low urine production despite a normal body fluid volume, a rise in serum creatinine levels of $>26.52 \mu\text{mol/l}$ ($>0.3 \text{ mg/dl}$) over baseline (a new working definition of acute renal failure in patients with cirrhosis), or serum ammonia levels $>150 \mu\text{mol/l}$. Shifts in solute concentration and resultant intracranial hypertension may occur with intermittent hemodialysis in patients with ALF;⁹¹ consequently, the preferred dialysis technique is continuous renal replacement therapy. However, theoretical differences among continuous modes of renal replacement therapy have not been specifically investigated in patients with ALF.

Transplantation as salvage therapy

Orthotopic liver transplantation has radically improved the overall survival of individuals with ALF, especially those whose condition is not due to paracetamol overdose.²¹ As paracetamol-induced ALF usually resolves spontaneously with the early administration of *N*-acetylcysteine and meticulous ICU management, only ~10% of individuals with paracetamol-induced ALF undergo orthotopic liver transplantation in the US, compared with 30–50% of patients with ALF of other etiologies.¹ In addition, patients with paracetamol-induced ALF often have psychosocial barriers to orthotopic liver transplantation.^{1,2} Overall, ~5% of orthotopic liver transplantation surgeries in the US are performed for patients with ALF⁹² and 25–30% of all patients with ALF undergo orthotopic liver transplantation.⁴ Schemes to predict mortality in ALF patients who do not undergo orthotopic liver transplantation have been compared.^{21,93}

Individuals with ALF who are listed for orthotopic liver transplantation in the US have 'Status 1A' priority, above that of patients with cirrhosis, according to the rules of the United Network for Organ Sharing.⁹⁴ In many ways, Status 1A criteria are surprisingly subjective;

they include a life expectancy without transplantation of <7 days, onset of hepatic encephalopathy within 8 weeks of the first symptom of liver injury, care within an ICU and the absence of pre-existing liver disease. Other criteria include age ≥ 18 years and at least one of the following characteristics: ventilator dependence, receiving renal replacement therapy, or an international normalized ratio >2.0 . Listing a patient with Status 1A priority broadens the geographic area from which a liver may originate, which means that waiting times for organs are typically short (~2–4 days).⁹⁵ Nevertheless, patients listed with Status 1A priority have extremely high mortality while on the liver transplant waiting list. In one 2006 study, 1,299 versus 117 deaths per 1,000 patient-years occurred in Status 1A patients versus all patients on the waiting list, respectively.⁹² In contrast to the US system, registration with 'Super-Urgent' transplant status in the UK is based on the relatively objective King's College criteria for poor prognosis (Box 1).⁹⁶

The challenges faced by surgeons who perform orthotopic liver transplantation in patients with ALF differ markedly from those faced in patients with cirrhosis. In the relative absence of portal hypertension, bleeding rarely poses a major problem in patients with ALF despite abnormal coagulation parameters, and the pre-operative degree of coagulopathy does not predict post-transplantation outcome.^{75,95} As expected, patients with ALF who die after orthotopic liver transplantation usually succumb to MOSF, but a significant fraction suffer brainstem herniation,⁹⁵ the result of spikes in intracranial pressure during dissection of the native liver or at reperfusion of the allograft.^{97,98} Not surprisingly, death is the primary cause of graft loss after orthotopic liver transplantation in patients with ALF, but primary graft nonfunction seems much more common in this population than in patients transplanted to treat cirrhosis.⁹⁵ Long-term survival of patients with ALF after orthotopic liver transplantation is generally worse than it is in patients transplanted for cirrhosis, but remains favorable (70–75% at 3 years).⁹⁹ In contrast to mortality in patients transplanted for cirrhosis, most of the deaths in patients transplanted for ALF occur very early after orthotopic liver transplantation (within 1 month).⁹⁹

Future perspectives

Future therapies for ALF would ideally maintain the patient's clinical stability long enough to allow liver regeneration to occur, which would obviate the need for orthotopic liver transplantation. Realistically, however, the goal of such therapies will be to serve as a bridge to orthotopic liver transplantation. Trials of plasmapheresis and hypothermia from European consortia are near completion. Drugs that facilitate the excretion of ammonia, such as L-ornithine phenylacetate,¹⁰⁰ may provide a neuroprotective bridge to orthotopic liver transplantation and deserve a randomized clinical trial. Liver support devices, used as a means to 'buy time', continue to entice but elude clinical practice.¹⁰¹ Unfortunately, no liver

support device conclusively improves transplant-free or overall survival, although parameters of liver failure (including hepatic encephalopathy, intracranial pressure, cerebral perfusion pressure, international normalized ratio and serum levels of neuroactive amino acids and bilirubin) improve with such devices.^{102–106} In the largest, randomized, controlled trial yet published, which used a porcine-hepatocyte-based bioartificial liver, 30-day and transplant-free survival were not statistically different in bioartificial-liver-treated and control patients.¹⁰⁶ However, post-hoc analysis of this trial has raised concerns about the device's lack of utility. Further studies of an expanded device are underway in the US.

Conclusions

The optimal management of individuals with ALF, who are among the most challenging of any patients managed by gastroenterologists and hepatologists, remains poorly defined. Generally, all patients with ALF (regardless of its etiology) should receive *N*-acetylcysteine, as evidence suggests that this agent improves spontaneous survival; therefore, the consequences of withholding the drug outweigh the rare incidence of adverse effects. In most cases, patients with ALF should be transferred to an ICU at a medical center with expertise in managing ALF and with liver transplant capabilities. Measures to reduce the risk of infection and cerebral edema, and the prompt treatment of these complications, will greatly improve a patient's probability of survival. Many issues in the management of patients with ALF warrant further study. Translational research to determine whether observations made in animal models can be extended to the bedside merit clinical trials. These questions include whether the deluge of inflammatory cytokines that are released into the circulation at the onset of liver injury and lead to SIRS and MOSF can be interrupted. Neuroprotective techniques should be applied to patients with ALF in multicenter, randomized, controlled studies. Such therapies seem to be particularly relevant, since the promise of artificial and bioartificial liver support devices has not been realized.¹⁰¹

Review criteria

PubMed was searched in December 2008 for publications containing the search terms "acute liver failure", and "fulminant liver failure", with modifying criteria including "cerebral edema", "intracranial hypertension", "hepatorenal syndrome", "coagulopathy", "bleeding", "acute lung injury", "adult respiratory distress syndrome", "liver transplantation", "infection", "systemic inflammatory response syndrome", "sepsis", "hypotension", "acute renal failure", "intracranial pressure", "hypothermia", "mannitol" and "hypertonic saline". Selection of papers for inclusion used the following criteria (in order of importance): randomized, controlled trials; nonrandomized case series; case reports; and consensus statements of experts in the field.

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