Intensive care management of acute liver failure

Georg Auzinger and Julia Wendon

Liver Intensive Care Unit, King's College Hospital, London, UK

Correspondence to Dr Georg Auzinger, Consultant LITU, Institute of Liver Studies, King's College Hospital, Denmark Hill, London SE5 9RS, UK
Tel: +44 3 299 9000 ext 2624; fax: +44 3 2993899; e-mail: georg.auzinger@kch.nhs.uk

Current Opinion in Critical Care 2008, 14:179–188

Purpose of review
The mortality of acute liver failure remains unacceptably high and liver transplantation is the only effective treatment available to date. This review focuses on new research developments in the field and aims to provide a pragmatic organ-based treatment approach for liver failure patients requiring intensive care support.
Recent findings
The pathophysiological basis for cerebral edema formation in acute liver failure continued to be the focus of various investigations. In-vivo observations confirmed the link between ammonia, cerebral glutamine content and intracranial hypertension. The role of arterial ammonia as an important prognostic indicator formed the basis of prospective, observational studies. Reduced monocytic HLA-DR expression linked acute liver failure with poor prognosis, and the cerebral effects and side effects of vasoactive therapy with terlipressin were investigated with two studies showing contradictory results.
Summary
Despite increased knowledge of the pathophysiological events leading to organ dysfunction in acute liver failure, supportive treatment options remain limited in their efficacy and largely noncurative.

Keywords
acute liver failure, HLA-DR expression, intracranial hypertension, systemic inflammatory response syndrome

Curr Opin Crit Care 14:179–188

1070-5295

Introduction

Acute liver failure (ALF) is a life-threatening multisystem illness resulting from massive liver injury. The defining clinical symptoms are coagulopathy and encephalopathy occurring within days or weeks of the primary insult [1] in patients without preexisting liver injury.

The prognosis of patients with ALF varies depending on aetiology, patient age and the length of time over which the illness evolves. The heterogeneity of ALF in terms of underlying aetiology, its rarity (2000 cases per year in the US) [2] and the usually progressive, severe disease course with a high fatality rate result in limited controlled trial data being available to guide optimal therapy.

Despite significant improvement in survival over time (Fig. 1), in part due to better intensive care management, mortality remains high, exceeding 90% in the most severe cases, where emergency liver transplantation remains the only effective treatment option.

An unpredictable and often rapidly progressing disease course complicated by multiple organ failure (MOF) makes ALF one of the most challenging conditions to treat. The purpose of the review is to provide a synopsis of the intensive care management of patients presenting with ALF.

General management aims

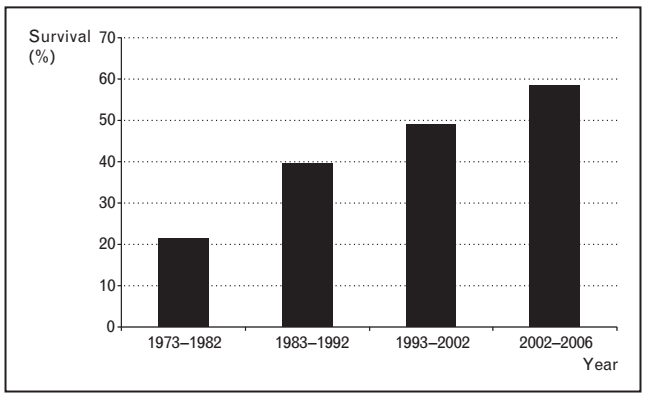
All patients presenting with ALF should be managed following a uniform investigative and treatment pathway.

First, the aetiology of the insult has to be determined, as disease-specific therapy may be available and ameliorate or reverse liver failure.

Patient outcome is often determined by the severity and number of organ failure. Even in the presence of hepatic regeneration patients often succumb to complications such as sepsis and MOF. Close monitoring and prevention of infectious complications and aggressive treatment of organ dysfunction may successfully bridge patients through this phase and allow time for the liver to recover.

Finally, early identification of patients who are unlikely to survive with supportive treatment should be made, to enable successful liver transplantation.

Figure 1 Acute liver failure survival over time



Survival percentages for all aetiologies of acute liver failure (grades 3–4 encephalopathy only) since the Liver ICU at Kings College Hospital opened in 1973. Total of 2017 patients shown. Data supplied by Dr W Bernal (unpublished).

Specific therapy depending on aetiology

If implemented early, disease-specific therapy may reverse liver failure in a limited number of conditions.

N-acetylcysteine (NAC) is recommended for the treatment of acetaminophen overdose [3]. Treatment is usually well tolerated and continued until reversal of synthetic liver dysfunction or transplantation.

Previous investigations from this institution [4] and results from a recent multicentre randomized controlled trial of the Adult US Acute Liver Failure Study Group (ALFSG) suggest benefit of NAC also for the treatment of nonacetaminophen etiologies [5]. NAC therapy is safe; however, some at least theoretical concerns remain with regard to anticoagulant and platelet inhibiting action [6], as well as radical oxygen scavenging properties with reduction in radical burst of neutrophils and increased infection risk [7].

ALF due to fatty liver of pregnancy and the HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome is usually reversible following rapid delivery of the fetus [8].

Some limited data show benefit and reversal of ALF in patients with acute hepatitis B virus infection treated with lamivudine [9] and penicillin G therapy in *Amanita phalloides* intoxication has proven successful in selected patients [10]. Steroid therapy for autoimmune hepatitis [11] and treatment with chelating agents in Wilson's disease are usually not of any benefit once patients have progressed to ALF.

Patient referral and prognosis

Patients presenting with hyperacute or ALF can progress rapidly to MOF. Encephalopathy, haemodynamic instability and significant metabolic acidosis commonly in association with renal failure are the main indications for ICU referral and admission. Specific indications for referral to specialist transplant units have been drafted which differ for acetaminophen and nonacetaminophen etiologies (Tables 1 and 2). Once admitted to a liver transplant centre further patient assessment focused on determination of underlying disease aetiology and prognosis should accompany ongoing resuscitative efforts. Several poor prognostic criteria for acetaminophen and other etiologies of ALF are in use with varying diagnostic accuracy. In the UK the King's College Hospital (KCH) criteria are widely used (Table 3) [12]. The addition of a simple bedside arterial blood lactate measurement in patients with acetaminophen induced ALF improves sensitivity of the KCH criteria and identifies patients in need for orthotopic liver transplantation earlier [13].

Early ICU treatment

Patients with progressive encephalopathy, grade III or IV, should be intubated and sedated. High-grade encephalopathy is usually a consequence of increasing cerebral edema and often complicated by intracranial hypertension (ICH). Similar to secondary insult prevention in traumatic brain injury (TBI), transferring medical staff should be alerted to the significant risk of intracranial pressure (ICP) elevation in the context of hypoxemia, hypotension and hypercarbia.

ALF is invariably complicated by intravascular volume depletion, due to 'insensible' fluid losses, vomiting and poor oral intake. Early and adequate fluid resuscitation is therefore mandatory, but some points regarding the choice of fluid used should be highlighted. Due to the lack of hepatic metabolic function any exogenous lactate load is poorly tolerated and may lead to worsening lactic acidosis,

Table 1 Criteria for referral to specialist unit following acetaminophen ingestion

Day 2	Day 3	Day 4
Arterial pH < 7.3	Arterial pH < 7.3	INR > 6 or PT > 100 s
INR > 3.0 or PT > 50 s	INR > 4.4 or PT > 75 s	Progressive rise in PT
Oliguria	Oliguria	Oliguria
Creatinine > 200 μmol/l	Creatinine > 200 μmol/l	Creatinine > 300 μmol/l
Hypoglycaemia	Encephalopathy	Encephalopathy
	Severe thrombocytopenia	Severe thrombocytopenia

INR, international normalized ratio; PT, prothrombin time.

Table 2 Referral criteria for nonacetaminophen etiologies

Hyperacute	Acute	Subacute
Encephalopathy	Encephalopathy	Encephalopathy
Hypoglycaemia	Hypoglycaemia	Hypoglycaemia (rare)
PT > 30 s	PT > 30 s	PT > 20 s
INR > 2.0	INR > 2.0	INR > 1.5
Renal failure	Renal failure	Renal failure
Hyperpyrexia		Hyponatremia
		Shrinking liver volume computed tomography

INR, international normalized ratio; PT, prothrombin time.

hence the use of Hartmann's or lactated Ringer's solution has to be discouraged. The sole use of normal saline and colloid solutions with nonphysiological chloride content will frequently result in unwanted hyperchloremic metabolic acidosis [14].

Five percentage dextrose water solutions often utilized as first-line maintenance fluid in liver disease not only lack volume-expanding effects, but will lead to hyponatremia and increase the risk of cerebral edema. As opposed to chronic liver disease, most patients presenting with ALF are not sodium overloaded, hence sodium restriction is not indicated.

Haemodynamic monitoring requires the use of invasive procedures. These are usually safely performed by experienced physicians, even in the presence of profound coagulopathy [15]. Spontaneous haemorrhagic complications are rarely seen and as the prothrombin time serves as an important prognostic marker, prophylactic treatment with fresh frozen plasma is usually not recommended; however, platelet administration may seem prudent in case of significant thrombocytopenia or for procedure cover.

Acute liver failure and systemic inflammatory response syndrome/sepsis

Patients with ALF are susceptible to both bacterial and fungal infections, and the majority of deaths are attributable to sepsis and MOF. The increased infection risk is due to a number of factors including reduced innate immunity with impaired phagocyte function, decreased complement production, and reduced clearance of cytokines and gut-derived toxins by Kupffer cells.

Table 3 Kings College criteria

Paracetamol-induced acute liver failure	Nonparacetamol aetiology
pH < 7.3 (irrespective of grade of encephalopathy) following volume resuscitation	PT > 100 s (INR > 6.5)
or	or
concurrent findings of	any three of the following
Grade III–IV encephalopathy	Aetiology: seronegative hepatitis or drug induced liver failure
Creatinine > 300 μmol/l	Age < 10 or > 40 years
PT > 100 s (INR > 6.5)	Jaundice to encephalopathy > 7 days
[a]Serum lactate > 3.5 mmol/l at 4 h or > 3 mmol/l at 12 h	Bilirubin > 300 μmol/l
	PT > 50 s (INR > 3.5)

PT, prothrombin time.
[a] Blood lactate criteria [13].

Two observational studies from the UK and the US ALFSG [16,17] showed a high incidence of systemic inflammatory response syndrome (SIRS) and sepsis in ALF patients. The magnitude of SIRS correlated strongly with progression of encephalopathy and mortality. A recent study investigated monocyte function in liver failure patients [18••]. HLA-DR expression on monocytes was significantly reduced in ALF patients compared to healthy controls or patients with chronic liver disease. In addition, HLA-DR expression appeared to be a powerful prognostic marker of outcome since levels were higher in survivors compared to nonsurvivors and those requiring transplantation (cutoff level for poor prognosis $\leq$15%). A strong negative correlation of HLA-DR percentage on one side and cytokine levels and markers of disease severity on the other was observed. Interestingly the elevated level of both pro- as well as anti-inflammatory cytokines supports the concept of a compensatory counterregulatory immune mechanism in response to severe inflammation leading to 'immune paralysis'.

Prophylactic treatment with intravenous antibiotics and antifungal agents is commonly performed. This approach has been shown to significantly reduce the risk of sepsis, decrease the risk of progression to high-grade encephalopathy and increase the potential for successful transplantation; however, survival was not affected [19].

Strict adherence to universal precautions for prevention of nosocomial infections is mandatory. First-line antibiotic choice is somewhat dependent on unit-specific antimicrobial surveillance data and results from admission cultures. Patients who show rapid improvement in liver function may be sufficiently treated with a 5-day course of broad spectrum antibiotics; however, those showing progression in disease severity or patients listed for transplantation are usually treated for extended time periods with adjustment of therapy according to culture results.

The role of selective decontamination of the digestive tract (SDD) in ALF is unclear. SDD combined with a 4-day course of a third-generation cephalosporin decreased mortality and colonization with resistant Gram-negative bacteria in a large cohort of general ICU patients ($n = 934$) in The Netherlands [20]. One must exert caution in extrapolating these results to a wider ICU population of different geographical location as the prevalence of colonization with resistant Gram-positive organisms is low in The Netherlands. Trials of SDD in ALF performed in the 1990s did not show any outcome benefit [21].

Recent interest has focused on topical bacterial decontamination, with oral chlorhexidine and chlorhexidine bathing (soaked wipes), in ICU patients. Two studies showed reduction in the rates of ventilator-associated pneumonia and catheter-related bloodstream infection [22,23]. The advantage of this universally applicable approach lies in a decreased risk of antibiotic resistance induction.

Acute liver failure and cerebral edema

Despite a decline in the incidence of cerebral death over the last 20 years, 25–35% of patients are still succumbing to the sequelae of intracerebral hypertension. The pathogenesis of cerebral edema in patients with ALF appears to be multifactorial.

The prominent pathogenetic role of ammonia has been the focus of extensive animal and human research. Net hepatosplanchnic ammonia release and lack of hepatic ammonia metabolism leads to an increase in arterial ammonia concentration and increased cerebral ammonia uptake, which results in astrocytic glutamine accumulation. The speed of onset overwhelms any adaptive process to control intracellular osmolarity. In human ALF an arterial ammonia level above 200 μmol/l was associated with cerebral herniation [24]. The ammonia hypothesis has recently been given weight by an elegant brain microdialysis study performed by Tofteng *et al.* [25••]. In 17 patients with ALF who were instrumented with cerebral microdialysis catheters, arterial ammonia concentrations correlated with brain glutamine content. Persisting elevation or increase in arterial ammonia level and brain glutamine concentration identified patients who developed ICH. Brain glutamine and arterial ammonia level correlated with ICP.

Ammonia appears to be also of significant prognostic importance.

In an analysis of 165 patients with ALF admitted to our institution a high arterial ammonia concentration was an independent risk factor for severe encephalopathy and ICH [26•]. Patients who developed ICH had persistently high ammonia levels. The model for end-stage liver disease score, younger age, and requirement for vasopressor and renal replacement therapy were additional independent risk factors for hepatic encephalopathy. These findings support the hypothesis of a multifactorial cause for cerebral edema development.

High admission ammonia levels may also predict mortality as shown by Bhatia *et al.* [27•]. In a prospective study of 80 patients with ALF an admission ammonia level above 124 μmol/l had a 77.5% diagnostic accuracy of predicting mortality with an odds ratio of 10.9.

The detrimental effect of glutamine-induced astrocyte swelling appears to be dependent on cerebral blood flow (CBF). An increase in flow can accelerate brain edema independent of brain glutamine concentration [28]. CBF is variable in patients with ALF [29,30] and may show regional differences [31], but hyperemia appears to be more prevalent in those who develop ICH. An increased release of proinflammatory cytokines from the necrotic liver and the brain has also been shown to contribute to alterations in CBF and ICH [32,33].

In a recent elegant observation evidence of cytotoxic edema formation in ALF has been postulated based on diffusion-weighted MRI scanning in seven patients. Compared to controls, significantly lower diffusion coefficients were found in ALF patients with resolution of abnormal findings in one of two survivors on repeat imaging [34].

Management of encephalopathy and cerebral edema

Adequate levels of sedation and analgesia will minimize ICP rises associated with agitation and painful stimulation. Sedation can reduce the cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral oxygen consumption. It will alleviate ICH caused by an increase in cerebral blood volume since metabolic demand and CBF are coupled. Propofol is a widely used neurosedative agent preferred by many practitioners due to its rapid onset and short duration of action. Concerns relate to the risk of propofol infusion syndrome during long-term administration, hence the hourly dose should not exceed 5 mg/kg body weight [35]. Propofol can also effectively decrease the risk of seizure activity – this is of major practical significance as the incidence of clinically covert nonconvulsive seizure activity is high in ALF [36].

Narcotic agents such as fentanyl are commonly added to provide for adequate analgesia. Caution must be exerted with bolus administration as this has been associated with a significant fall in mean arterial pressure (MAP) and rise in ICP in patients with TBI [37].

As in traumatic head injury, low arterial blood pressure and drop in cerebral perfusion pressure (CPP) can lead to critical neuronal ischemia and cytotoxic cerebral edema formation. A CPP threshold of above 55 mmHg is usually sufficient to maintain adequate cerebral oxygen supply in ALF.

Treatment of arterial hypotension that persists despite adequate intravenous volume replacement requires addition of vasopressor medication to maintain CPP. Norepinephrine is the preferred substance; however, more recently the vasopressin analog terlipressin has been used in ALF with conflicting results. In a case

series of six patients bolus administration of 0.25 mg of terlipressin increased CBF and ICP; a significant increase in jugular venous saturations suggested worsening of cerebral hyperemia [38]. In a more recent study by Eefsen *et al.* [39••] 10 patients received a 1-mg bolus of terlipressin. CPP and CBF increased; however, ICP remained unchanged. Interestingly the slope between CPP and CBF (a marker for autoregulation) which was initially abnormal in all patients was normalized in three following terlipressin administrations. Cerebral lactate measured via microdialysis decreased and lactate:pyruvate ratio remained unchanged, excluding untoward side effects on a cellular level.

Monitoring of intracranial pressure and cerebral blood flow

The individual variability in CBF coupled with a lack of defining clinical signs and laboratory (ammonia) cutoff levels for the diagnosis of ICH are strong arguments in favour of ICP monitor insertion. Opponents of ICP monitoring argue that the procedure carries a high bleeding risk and does not improve outcome. In a recent observational study of the ALFSG, use and complication rate of ICP monitoring was prospectively studied in 92 patients. Compared to a previous study published some 10 years earlier the bleeding complication rate was reduced at 10 vs. 20%. Half of the haemorrhagic complications were incidental radiological findings. Not surprisingly patients who had their ICP monitored received more vasopressor and ICP targeted therapy [40].

The risk of intracranial haemorrhage is influenced by the type of device used. Extradural monitors carry the lowest bleeding risk; however, they suffer from measurement inaccuracies and even intracerebral microdialysis catheters have been successfully inserted without any obvious untoward effects [25••]. Unpublished data from our institution show a low risk of ICP bolt-related complications. Over an 8-year observation period 126 of 426 patients with ALF and grade III or IV hepatic encephalopathy had an extra- or subdural ICP bolt inserted. Only one patient suffered from intracranial haemorrhage; however, this was multifocal in nature and possibly not monitor related. We routinely correct the international normalized ratio with fresh frozen plasma, and administer platelet concentrate and cryoprecipitate as indicated prior to the procedure. Prophylactic recombinant factor VII administration has been advised by some investigators; however, is in our opinion not necessary [41].

Noninvasive monitoring of ICP with computed tomography, MRI, PET scanning or transcranial Doppler is inaccurate, noncontinuous and often impractical in advanced stages of ALF.

Intermittent blood sampling or continuous oximetry via an indwelling catheter sited in the jugular bulb can provide information about cerebral oxygen utilization. Jugular venous saturation is proportional to CBF for a given metabolic rate. Low saturations (below 55%) are indicative of cerebral hypoperfusion, whereas high levels (above 85%) may be a sign of cerebral hyperemia or inadequate neuronal metabolism.

We routinely consider the use of multimodule monitoring in patients with grade III–IV hepatic encephalopathy. Additional risk factors such as young age, hyperacute or acute disease onset, progression to MOF with significant vasopressor requirements, arterial ammonia level above 150 μmol/l, pupillary abnormalities and listing for liver transplantation further guide in the decision-making process.

Treatment of intracranial hypertension

Prolonged time periods of CPP below 50 mmHg or an ICP above 40 mmHg are associated with poor neurological outcome [42]. CPP below 40 mmHg for more than 2 h has been considered a contraindication for liver transplantation; however, a case series of four patients with refractory ICP elevation above 35 mmHg and CPP below 50 mmHg who made a full neurological recovery contradicted previous findings [43]. Very high levels of ICP up to 85 mmHg (personal experience) may be tolerated, if short lived and in the absence of any other poor prognostic neurological indicators.

Treatment of ICP should focus on strategies to minimize baseline ICP and those to prevent pressure surges.

Patients should be placed in a 20° head up position to reduce ICP without compromising MAP and CPP. Basic care principle as for patients with TBI and ICH apply such as avoidance of hypotension or hypoxemia, maintenance of normovolemia, normocapnia and adequate glycaemic control. Hyperthermia should be aggressively controlled and hyponatremia corrected.

Bolus mannitol (0.25–0.5 mg/kg) remains first-line treatment for ICH [44]. Reduction of ICP is mainly due to improvement in blood rheology and secondly related to an osmotic effect with reduction in brain water. Repeat administration is possible provided the serum osmolarity remains below 320 mOsm/l.

Hypertonic saline confers the benefits of mannitol treatment in terms of brain water reduction without associated haemodynamic side effects. In fact, blood pressure is usually improved following its administration. The osmotic reflection coefficient across an intact blood–brain barrier is higher for hypertonic saline compared to

mannitol (1.0 vs. 0.9) which makes it at least in theory a more effective osmotic agent. In a recent randomized controlled trial, induction of hypernatremia (serum sodium target 145–155 mmol/l) reduced the occurrence of ICP above 25 mmHg [45]. No comparative trials of mannitol vs. hypertonic saline for the treatment of ICH have been performed in ALF.

Hyperventilation is a controversial treatment tool for elevated ICP. It has been shown to restore CBF autoregulation in ALF [46] and reduce ICP in the short term; however, it can also lower both $CMRO_2$ and CBF to critical levels, and increase cerebral lactate production [29]. Hyperventilation should be guided by jugular bulb saturations and only used for the emergency treatment of refractory ICH.

Hypothermia with cooling to a core temperature of 32–33°C effectively reduced refractory ICP elevation in patients with ALF [47]. Arterial ammonia levels and cerebral uptake of ammonia were reduced; this was accompanied by reduction in cerebral hyperemia and an improvement in CPP. Concerns remain regarding the systemic side effects induced by body temperatures as low as 32°C. In patients not progressing to liver transplantation long-term hypothermia will require more intense sedation/paralysis. This will invariably prolong the duration of mechanical ventilation and increases the risk of nosocomial infections. Other known common side effects are coagulopathy, immune suppression and insulin resistance.

Less intense reduction in body temperature may not reduce ICP as effectively and does not appear to influence ammonia production [48]; however, mild hypothermia targeting 35–36°C may represent the best compromise in terms of risk benefit ratio.

Barbiturates control ICP by reducing $CMRO_2$ and cerebral blood volume. Unwanted side effects such as arterial hypotension, negative inotropic effects and immunosuppressant action make barbiturates a poor first choice treatment for ICH. Another controversial treatment option is bolus indomethacin [49] which induces ICP reduction via cerebral vasoconstriction. It should only be used in the context of proven hyperemia and guided by some form of CBF monitoring.

As an extreme measure for the treatment of refractory ICH and ALF, total hepatectomy and portocaval shunt formation has been reported with successful bridge to transplant in selected cases [50].

Cardiovascular system and acute liver failure

Vasodilatation due to loss of vascular tone leads to systemic hypotension, low effective arterial blood volume and high cardiac output. Intravascular volume depletion will contribute to impaired tissue perfusion with decreased oxygen utilization and shunting on a microcirculatory level. The combination of increased anaerobic metabolism and poor lactate clearance is the reason for often profound hyperlactatemia. Both the gut and the liver have been shown to be net producers of lactate in ALF [51]. The pathogenesis of haemodynamic changes appears to be multifactorial, but severe SIRS and sepsis play a paramount role. In addition, cytokine release from the failing liver appears to be partly responsible for the observed haemodynamic disturbances [33]. Adequate monitoring of intravascular volume status and aggressive fluid resuscitation are first line interventions. Injudicious administration of fluids however can be detrimental as it increases the risk of cerebral edema and may induce or worsen acute lung injury. Volumetric indices of preload are preferred over pressure derived variables and all requisites for the successful use of dynamic indicators of fluid responsiveness are commonly present in ALF patients [52]. Refractory hypotension frequently mandates high dose vasopressor support. Norepinephrine is preferred over epinephrine, the latter being associated with deleterious effects on splanchnic blood flow and acid base balance. These side effects may be reversible and not relevant in general ICU patients [53]; however, they are of major concern in patients with ALF. Vasopressin and analogs have been successfully used in patients with septic shock [54], but their use in ALF is currently investigational.

ALF is frequently accompanied by 'relative adrenal dysfunction'. A short Synacthen test should be performed in patients who require vasopressor support. Those with a subnormal response may benefit from administration of 'stress doses' of hydrocortisone 200–300 mg/day for a duration of 7–10 days [55].

Subclinical myocardial injury as evidenced by elevated troponin I levels has recently been shown to frequently complicate ALF [56•]. Two-thirds of 187 patients with ALF enrolled in the ALFSG registry had significantly elevated troponin levels (above 0.1 ng/ml). The percentage was equally distributed between diagnostic groups, and associated with a significant increase in morbidity and mortality. Unfortunately no data on cardiac imaging or invasive cardiac output monitoring was provided. Echocardiographic evidence of a high incidence of impaired systolic function or regional wall motion abnormalities in this population appears to be lacking.

Respiratory failure

Patients with ALF and high-grade hepatic encephalopathy require airway protection and controlled mechanical ventilation (CMV). Hypoxemia is usually not the

primary reason for intubation and CMV; however, a significant proportion of patients develop complications leading to deterioration in alveolar gas exchange during their disease course. Commonly encountered respiratory problems are due to pleural effusions, atelectasis, poor compliance of the respiratory system due to raised intra-abdominal pressure (IAP) or chest wall edema. Intrapulmonary shunting appears to occur frequently in ALF caused by ischemic hepatitis [57•]. ALI and ARDS have been shown to complicate the course of acetaminophen-induced ALF in up to 30% of cases [58], mainly affecting patients with ICH and those in need of vasopressor therapy. Aggressive therapy to prevent or treat ICH such as heavy sedation, induced hypothermia and avoidance of regular bronchial toilette increase the risk of pulmonary and extrapulmonary sepsis and subsequent development of ARDS.

Hypoxemia is a feared complication of ALF and high FiO_2 requirements will frequently lead to removal of patients from the transplant list.

We could recently show in a mixed cohort of patients with ALF that hypoxia is nonspecific for the diagnosis of ALI. A low PaO_2/FiO_2 was not associated with poor outcome and frequently transient in nature. A low invasive approach of measuring extravascular lung water index via the transpulmonary thermodilution technique (Pulsion) may aid in the differential diagnosis of hypoxia in this setting [59].

In applying protective ventilation strategies to ALF patients, pulmonary and cerebral needs have to be balanced. Normocapnia can usually be achieved despite the use of low tidal volumes (6–8 ml/kg predicted body weight) and the avoidance of high tidal volumes in the absence of ALI appears to be justified, as it may protect the lungs from ventilator induced lung injury [60]. Moderate levels of positive end-expiratory pressure (PEEP) are usually well tolerated and do not lead to significant rise in ICP. In fact prevention of alveolar de-recruitment and hypoxemia through the use of PEEP can decrease ICP.

Limiting plateau pressures to less than 30 cm H_2O may be difficult and unnecessary in patients with significant chest wall edema or raised IAP as pleural pressure will increase under these conditions. Consequently plateau pressure will be a poor reflection of transpulmonary pressure. For this reason we recommend the routine measurement of IAP in ALF patients.

Weaning of CMV may be facilitated by tracheostomy insertion. The percutaneous approach is usually safe and well tolerated even in the presence of severe coagulopathy [61].

Renal failure

The incidence of renal failure in ALF is as high as 50–80%. Causes are multifactorial and include direct drug hepatotoxicity (paracetamol, NSAIDs), hepatorenal syndrome, and most frequently acute tubular necrosis due to profound hypovolemia and hypotension. Intra-abdominal hypertension (IAH) and development of abdominal compartment syndrome, due to ascites, intra-abdominal haemorrhage or severe abdominal and gut wall edema, is an often overlooked cause for renal impairment in ALF.

Management of renal failure requires appropriate volume resuscitation and treatment of hypotension to target an adequate renal perfusion pressure. Renal perfusion pressure aims may need to be adjusted according to IAP in case of IAH.

Continuous forms of haemofiltration or dialysis are preferred over intermittent haemodialysis, the latter being associated with haemodynamic instability, increase in ICP and reduction in CPP [62]. Extrapolating evidence from the acute renal failure literature ultrafiltration rates of at least 35 ml/kg/h should be used [63]. Most centres use bicarbonate buffered replacement solution as the failing liver is unable to metabolize lactate or acetate into bicarbonate.

High-volume continuous veno-venous haemofiltration (HVCVVHF; above 90 ml/kg/h ultrafiltration rate) has been shown to reduce vasopressor requirements in septic shock [64] possibly due to modulation of pro-inflammatory mediators according to a 'peak concentration hypothesis'. A preliminary investigation in patients with ALF showed similar benefits. This forms the basis for the use of HVCVVHF to bridge patients with severe haemodynamic and metabolic failure to transplantation [65]. The extended use of this resource intense modality in patients not listed for transplant is, however, questionable.

Higher ultrafiltration volumes or the use of continuous haemodialysis may also aid in ammonia reduction. Both extracorporeal systems have shown net ammonia clearance in children with inborn errors of metabolism [66].

Nutritional aspect

Despite the well-known metabolic abnormalities of ALF and their role in the development of complications, data on the nutritional aspects of care for these patients is scarce.

Hypoglycaemia, due to loss of hepatic glycogen stores, impaired gluconeogenesis and hyperinsulinism, is frequently a presenting clinical complication. Continuous intravenous glucose infusion is common practice at least until feeding is established. Implementation of tight glucose control is controversial in ALF; however,

hyperglycaemia should be avoided as it may contribute to poor ICP control [67].

ALF patients are catabolic despite the significant loss of hepatocyte mass, with supranormal energy expenditure compared to healthy controls [68]. Protein catabolism, muscle wasting, amino acid losses and vitamin deficiency all negatively impact on immune function.

Hypophosphatemia is frequently observed in patients on HVCVVHF and requires prompt replacement; it may, however, be an indication of increased hepatic ATP production during liver regeneration and serve as a good prognostic indicator especially in acetaminophen induced ALF [69].

Feeding is usually commenced within 24 h following ICU admission with a target caloric aim of 25–30 kcal/kg/day. Many centres prefer the enteral over the parenteral route; however, if enteral nutrition is poorly tolerated parenteral nutrition is a reasonable alternative. The fear of parenteral nutrition-induced liver toxicity appears to be unfounded with the use of newer hypocaloric regimens [70]. There is currently no evidence suggesting that normal protein intake of approximately 1 g/kg/day worsens hyperammonemia and hepatic encephalopathy. The use of immunonutrition containing glutamine should, however, be avoided given glutamine's central role in the development of cerebral edema in ALF.

A discussion of liver support systems is beyond the scope of this review, suffice to say that no convincing phase 3 trial has thus far shown efficacy of these devices [71].

Conclusion

Despite recent advances in supportive care, which have led to a consistent improvement in outcome, ALF remains a devastating disease process. It is unlikely that supportive therapy will improve to an extent where patients can be successfully 'bridged' to hepatic regeneration and full recovery. Our increasing understanding of the pathophysiological basis of organ dysfunction complicating ALF may, however, lead to further advances in therapy and a growing number of patients surviving to successful liver transplantation – the only curative treatment to date.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 235).

1 Trey C, Lipworth L, Davidson CS. Halothane and liver damage. N Engl J Med 1969; 280:562–563.

2 Lee WM. Acute liver failure in the United States. Semin Liver Dis 2003; 23: 217–226.

3 Keays R, Harrison PM, Wendon JA, *et al.* Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ 1991; 303:1026–1029.

4 Harrison PM, Wendon JA, Gimson AE, *et al.* Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991; 324:1852–1857.

5 Lee WM, Rossaro L, Fontana RJ, *et al.* Intravenous *N*-acetylcysteine improves spontaneous survival in early stage nonacetaminophen acute liver failure [abstract]. Hepatology 2007; 46 (Suppl 1):268A.

6 Niemi TT, Munsterhjelm E, Pöyhiä R, *et al.* The effect of *N*-acetylcysteine on blood coagulation and platelet function in patients undergoing open repair of abdominal aortic aneurysm. Blood Coagul Fibrinolysis 2006; 17: 29–34.

7 Heller AR, Groth G, Heller SC, *et al. N*-acetylcysteine reduces respiratory burst but augments neutrophil phagocytosis in intensive care unit patients. Crit Care Med 2001; 29:272–276.

8 Castro MA, Fassett MJ, Reynolds TB, *et al.* Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol 1999; 181:389–395.

9 Tillmann HL, Hadem J, Leifeld L, *et al.* Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat 2006; 13:256–263.

10 Broussard CN, Aggarwal A, Lacey SR, *et al.* Mushroom poisoning-from diarrhea to liver transplantation. Am J Gastroenterol 2001; 96:3195–3198.

11 Ichai P, Duclos-Vallee JC, Guettier C, *et al.* Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007; 13:996–1003.

12 O'Grady J, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97:439–445.

13 Bernal W, Donaldson N, Wyncoll D, Wendon J. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure. Lancet 2002; 359:558–563.

14 Rehm M, Orth V, Scheingraber S, *et al.* Acid-base changes caused by 5% albumin versus 6% hydroxyethyl starch solution in patients undergoing acute normovolemic hemodilution: a randomized prospective study. Anesthesiology 2000; 93:1174–1183.

15 Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy – a prospective audit. Intensive Care Med 1999; 25:481–485.

16 Rolando N, Wade J, Davalos M, *et al.* The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000; 32:734–739.

17 Vaquero J, Polson J, Chung C, *et al.* Infection and the progression of hepatic encephalopathy in acute liver failure. Gastroenterology 2003; 125:755–764.

18 •• Antoniades CG, Berry PA, Davies ET, *et al.* Reduced monocyte HLA-DR expression: a novel biomarker of disease severity and outcome in acetaminophen induced acute liver failure. Hepatology 2006; 44:34–43.
Important investigation into the prognostic role of HLA-DR expression on monocytes in ALF. The findings of this study support the theory that immune paralysis may be instrumental in the high incidence of sepsis and MOF in this population.

19 Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis 1996; 16:389–402.

20 De Jonge E, Schultz MJ, Spanjaard L, *et al.* Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 2003; 362:1011–1016.

21 Rolando N, Gimson A, Wade J, *et al.* Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant hepatic failure. Hepatology 1993; 17:196–201.

22 Koeman M, Van der Ven AJ, Hak E, *et al.* Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 2006; 173:1348–1355.

23 Bleasedale SC, Trick WE, Gonzales IM, *et al.* Effectiveness of chlorhexidine bathing to reduce catheter-associated bloodstream infections in medical intensive care unit patients. Arch Intern Med 2007; 167:2073–2079.

24 Clemmesen JO, Larsen FS, Kondrup J, *et al.* Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999; 29:648–653.

25 Tofteng F, Hauerberg J, Hansen BA, *et al.* Persistent arterial hyperammonemia •• increases the concentration of glutamine and alanine in the brain and correlates with intracranial pressure in patients with fulminant hepatic failure. J Cereb Blood Flow Metab 2006; 26:21–27.

Large single-centre investigation into the predictive role of arterial ammonia for the development of encephalopathy and ICH. Although severely elevated levels were specific for ICH they lacked sensitivity. Other factors were independently associated with ICH such as age and noncerebral organ failure.

26 Bernal W, Hall C, Karvellas CJ, *et al.* Arterial ammonia and clinical risk • factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007; 46:1844–1852.

Large single-centre investigation into the predictive role of arterial ammonia for the development of encephalopathy and ICH. Although severely elevated levels were specific for ICH, they lacked sensitivity. Other factors were independently associated with ICH, such as age and noncerebral organ failure.

27 Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for • complications and outcome in acute liver failure. Gut 2006; 55:98–104.

Interesting observational study from the Indian subcontinent linking admission ammonia levels with overall outcome.

28 Vaquero J, Chung C, Blei AT. Cerebral blood flow in acute liver failure: a finding in search of a mechanism. Metab Brain Dis 2004; 19:177–194.

29 Wendon JA, Harrison PM, Keays R, Williams R. Cerebral blood flow and metabolism in fulminant liver failure. Hepatology 1994; 19:1407–1413.

30 Aggarwal S, Kramer D, Yonas H, *et al.* Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. Hepatology 1994; 19:80–87.

31 Durham S, Yonas H, Aggarwal S, *et al.* Regional cerebral blood flow and CO_2 reactivity in fulminant hepatic failure. J Cereb Blood Flow Metab 1995; 15: 329–335.

32 Jalan R, Pollock A, Shah SH, *et al.* Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure. J Hepatol 2002; 37:536–538.

33 Wright G, Shawcross D, Olde Damink SW, *et al.* Brain cytokine flux in acute liver failure and its relationship with intracranial hypertension. Metab Brain Dis 2007; 22:375–388.

34 Ranjan P, Mishra AM, Kale R, *et al.* Cytotoxic edema is responsible for raised intracranial pressure in fulminant hepatic failure: *in vivo* demonstration using diffusion weighted MRI in human subjects. Metab Brain Dis 2005; 20:181–192.

35 Cremer OL, Moons KG, Bouman EA, *et al.* Long-term propofol infusion and cardiac failure in adult head-injured patients. Lancet 2001; 357:117–118.

36 Ellis AJ, Wendon JA, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. Hepatology 2000; 32:536–541.

37 Sperry RT, Bailey PL, Reichmann MV. Fentanyl and sufentanyl increase intracranial pressure in head trauma patients. Anesthesiology 1992; 77: 416–420.

38 Shawcross DL, Davies NA, Mookerjee RP, *et al.* Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. Hepatology 2004; 39:471–475.

39 Eefsen M, Dethloff T, Frederiksen HJ. Comparison of terlipressin and •• noradrenalin on cerebral perfusion, intracranial pressure and extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. J Hepatol 2007; 47:381–386.

Contrary to a previous investigation the authors found no increase in ICP with the use of the vasopressin analog terlipressin. The increase in CBF was similar during norepinephrine and terlipressin therapy. There was no evidence of increase in cerebral metabolic rate for oxygen on microdialysis.

40 Vaquero J, Fontana RJ, Larson AM, *et al.* Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl 2005; 11:1581–1589.

41 Shami VM, Caldwell SH, Hespenheide EE, *et al.* Recombinant factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl 2003; 9:138–143.

42 Lidofsky SD, Bass NM, Prager MC, *et al.* Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. Hepatology 1992; 17:1–7.

43 Davies MH, Mutimer D, Lowes J, *et al.* Recovery despite impaired cerebral perfusion in fulminant hepatic failure. Lancet 1994; 343:1329–1330.

44 Canalese J, Gimson AES, Davis C, *et al.* Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut 1982; 23:625–629.

45 Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004; 39:464–470.

46 Strauss G, Hansen BA, Knudsen GM, Larsen FS. Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure. J Hepatol 1998; 28:199–203.

47 Jalan R, Olde Damink SW, Deutz NE, *et al.* Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology 2004; 127:1338–1346.

48 Bernal W, Auzinger G, Sizer E, *et al.* Variation in blood ammonia concentration with site of measurement and evidence of brain and muscle uptake in patients with acute liver failure. Liver Int (in press).

49 Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion, and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. J Cereb Blood Flow Metab 2004; 24:798–804.

50 Rozga J, Podesta L, LePage F, *et al.* Control of cerebral edema by total hepatectomy and extracorporeal liver support in fulminant hepatic failure. Lancet 1993; 342:898–899.

51 Murphy ND, Kodakat SK, Wendon J, *et al.* Liver and intestinal lactate metabolism in patients with acute liver failure undergoing liver transplantation. Crit Care Med 2001; 29:2111–2118.

52 Pinsky MR, Payen D. Functional hemodynamic monitoring. Crit Care 2005; 9:566–572.

53 Annane D, Vignon P, Renault A, *et al.* Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007; 370:676–684.

54 Dünser MW, Mayr AJ, Ulmer H, *et al.* Arginine vasopressin in advanced vasodilatory shock: a prospective, randomized, controlled study. Circulation 2003; 107:2313–2319.

55 Harry RA, Auzinger G, Wendon JA. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 2002; 36:395–402.

56 Parekh NK, Hynan LS, De Lemos J, *et al.* Elevated troponin I levels in acute • liver failure: is myocardial injury an integral part of acute liver failure? Hepatology 2007; 45:1489–1495.

Interesting study investigating the role of covert myocardial injury in ALF and its role in relation to outcome.

57 Fuhrmann V, Madl C, Mueller C, *et al.* Hepatopulmonary syndrome in patients • with hypoxic hepatitis. Gastroenterology 2006; 131:69–75.

This is the first time that a high incidence of hepatopulmonary syndrome was reported outside the setting of chronic liver disease in a subgroup of patients with ALF. It remains to be seen if some degree of intrapulmonary shunting complicates all forms of ALF.

58 Baudouin SV, Howdle P, O'Grady JG, *et al.* Acute lung injury in fulminant hepatic failure following paracetamol poisoning. Thorax 1995; 50:399–402.

59 Auzinger G, Sizer E, Bernal W, *et al.* Incidence of lung injury in acute liver failure: diagnostic role of extravascular lung water index. Crit Care 2004; 8 (Suppl 1):40.

60 Schultz MJ, Haitsma JJ, Slutsky AS, *et al.* What tidal volumes should be used in patients without acute lung injury? Anesthesiology 2007; 106:1226–1231.

61 Auzinger G, O'Callaghan GP, Bernal W, *et al.* Percutaneous tracheostomy in patients with severe liver disease and a high incidence of refractory coagulopathy: a prospective trial. Crit Care 2007; 11:R110.

62 Davenport A, Will EJ, Davison AM. Continuous versus intermittent forms of haemofiltration and/or dialysis in the management of acute renal failure in patients with defective cerebral autoregulation at risk of cerebral oedema. Contrib Nephrol 1991; 93:225–233.

63 Ronco C, Bellomo R, Homel P, *et al.* Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000; 356:26–30.

64 Honore PM, Jamez J, Wauthier M, *et al.* Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 2000; 28:3581–3587.

65 Bernal W, Wong T, Wendon J. High-volume continuous veno-venous haemofiltratiom in hyper-acute liver failure: a pilot study. Crit Care 1999; 3 (Suppl 1):212.

66 Lai YC, Huang HP, Tsai IJ, *et al.* High-volume continuous venovenous hemofiltration as an effective therapy for acute management of inborn errors of metabolism in young children. Blood Purif 2007; 25:303–308.

67 Kodakat S, Gopal P, Wendon J. Hyperglycemia is associated with intracranial hypertension in patients with acute liver failure. Liver Transpl 2001; 7 (Suppl): C21.

68 Walsh TS, Wigmore SJ, Hopton P, *et al.* Energy expenditure in acetaminophen-induced fulminant hepatic failure. Crit Care Med 2000; 28:649–654.

69 Schmidt LE, Dalhoff K. Serum phosphate is an early predictor of outcome in severe acetaminophen-induced hepatotoxicity. Hepatology 2002; 36:659–665.

70 Salvino R, Ghanta R, Seidner DL, *et al.* Liver failure is uncommon in adults receiving long-term parenteral nutrition. JPEN J Parenter Enteral Nutr 2006; 30:202–208.

71 Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure. A systematic review. JAMA 2003; 289:217–222.