ELSEVIER

Journal of Hepatology 42 (2005) S115–S123

Journal of Hepatology

www.elsevier.com/locate/jhep

Acute liver failure: current management and future prospects

Rajiv Jalan*

Liver Failure Group, Institute of Hepatology, University College London Medical School, 69-75 Chenies Mews, London WC1E 6HX, UK

Although the development of hepatic encephalopathy (HE) and the associated increase in intracranial pressure (ICP) in patients with acute liver injury is the key event that defines their prognosis [1–5], ALF is associated with dysfunction of multiple organ systems. The circulatory disturbance in ALF is an early manifestation that tends to worsen during the course of the illness and is characterized by generalized vasodilatation which results in increased cardiac output and, reduced systemic vascular resistance and mean arterial pressure [6,7]. These circulatory disturbances contribute to the occurrence of renal failure requiring renal support. ALF results in severe coagulopathy, which needs correction in cases of overt bleeding or for insertion of appropriate monitoring devices. Along with the increased susceptibility to infection this multiorgan failure often culminates in various degrees of adult respiratory distress syndrome requiring artificial ventilatory support [7]. In a study performed over a 7-year period in 315 patients with ALF, the immediate cause of death in those with evidence of severe liver injury was brain herniation from elevated ICP in 35% and most of the other deaths were the result of severe refractory hypotension resulting from supervening sepsis culminating in multiorgan failure. In the last 20 years, emergency liver transplantation has emerged as the 'only' therapeutic intervention of proven benefit for patients with advanced ALF [8].

The management of patients with acute liver injury must begin as soon as the patient presents and as was recently pointed out by Bernuau, early referral to the liver unit is imperitive [9]. The rationale for this suggestion is the following: the etiological diagnosis of the acute liver disease, especially in cases with unusual clinical profile is often delayed and consequently, specific treatments targeting the liver, which is the key organ to be preserved and supported in patients with acute liver disease who still have no evidence of encephalopathy but with severe coagulopathy and thus threatened by ALF, may also be delayed. The clinical evolution of the condition is often so rapid that any chance of recovery may be lost. Classical examples of this issue include all the treatable acute liver diseases such as acetaminophen-induced hepatotoxicity, herpes simplex hepatitis, acute fatty liver of pregnancy, auto-immune hepatitis, hypoxic hepatitis, Budd-Chiari syndrome and the acute form of Wilson's disease [10–13]. In addition, in the uninitiated environment, there is a risk of aggravation of either the destruction of liver tissue or the patient's condition through the use of hepatotoxic, nephrotoxic or neurotoxic substances.

This review will focus upon the current strategies in the management of patients with ALF and focus upon (a) general issues and (b) specific management in relation to circulatory and renal dysfunction and HE. Detailed discussions surrounding liver transplantation and liver support in acute liver failure have been recently reviewed and will not be discussed [8,14].

1. General management

Time is of the essence in the management of patients with ALF because rapid deterioration is a particular feature and it is not unusual to find a patient with ALF and no neurologic or circulatory disturbance progressing to needing inotropic support for hypotension and ventilation, for Grade 3–4 HE. In the most unfortunate situations this rapid deterioration may culminate in a fatal outcome. Therefore, close clinical monitoring is important during the observation period and particularly when moving a patient either between hospitals or between different wards. Most of the patients with ALF will require liberal volume expansion. The choice of fluid is not crucial and usually a mixture of crystalloids and colloids is used. Close attention to acid–base balance and correction of hyperlactatemia is

* Tel.: +44 2076796552; fax: +44 2073800405.
E-mail address: r.jalan@ucl.ac.uk (R. Jalan).

doi:10.1016/j.jhep.2004.11.010

important because they can impact upon circulatory function and also aggravate cerebral hyperemia [15,16]. Hyperthermia should be prevented as it worsens intracranial hypertension [17,18]. Glucose levels need to be maintained to prevent cerebral and systemic effects of hypoglycemia. Hyperglycemia worsens cerebral edema in patients with ALF [19]. Hyponatremia is a bad prognostic sign and values less than 125 mmol/l is an absolute contraindication for liver transplantation and can also worsen brain edema [20,21]. Hypercapnia should be avoided as it induces cerebral hyperemia and increases ICP [22].

Simultaneously, the patients need to be discussed with the local liver transplantation unit and all attempts to identify potential contraindications to transplantation identified. As the patients are often already encephalopathic, it may be difficult to obtain an accurate history and attempts should be made to clarify the history through the family and friends and the primary care physicians. This is essential in order to allow clarifications about alcohol and drug abuse, history of psychiatric disease, previous overdoses, concomitant illnesses and drug history. As one of the important causes of ALF is drug overdoses, a psychiatric assessment early in the course of the illness before the patient has proceeded to develop encephalopathy is useful in making decisions about subsequent transplantation. As stated above, other routine tests to determine suitability for transplantation would be performed in the consultation with the transplant centre. Once a decision to transport the patient to the Liver Unit has been made, it should be appreciated and all attempts should be made to provide as controlled an environment for transfer as possible. This will mean adequate facilities for the control of the airway, often requiring elective mechanical ventilation; large bore central or peripheral venous access and adequate personnel specifically trained to deal with the emergent situations, a patient with ALF often presents. There is some controversy whether antibiotics and or *N*-acetylcysteine should be used prophylactically. The issues are discussed below:

Prophylactic antibiotics. The rationale for the use of prophylactic antibiotics is twofold. First, patients with ALF have a very high risk of infection and indeed sepsis from bacterial and/or fungal infection accounts for death in up to 75% patients. Second, there is increasing evidence that systemic inflammatory response is important in the pathogenesis of increased ICP in ALF. At present, it is not clear what component of the observed inflammatory response is due to the release of humoral substances from the necrotic liver and what component is due to additional infection [23–25]. However, there are no controlled data in the literature addressing the question whether early use of antibiotics is associated with reduced incidence of HE and indeed mortality. Whether such a progression is reduced by the use of antibiotics has not been demonstrated. As the prophylactic use of parenteral and enteral antibiotics are associated with lower rates of infection ($P<0.005$) [26], these data suggest—in an indirect manner—that prophylactic antibiotics may reduce the incidence of intracranial hypertension. This needs confirmation is suitably randomized controlled clinical trials.

N-acetylcysteine. A number of clinical studies support a role for *N*-acetylcysteine in ALF. In patients with paracetamol overdose, who presented late, the mortality was 37% in patients who received *N*-acetylcysteine compared with 58% in the controls. In patients given *N*-acetylcysteine, progression to grade III–IV HE was also lower (51 vs. 75%) [27]. In another controlled trial in paracetamol induced ALF, survival was significantly higher in the *N*-acetylcysteine treated group compared with controls (48 vs. 20%; $P<0.04$) [28]. The improvement in survival was thought to be related to an increase in cardiac output, oxygen extraction ratio and oxygen consumption [29]. This effect of *N*-acetylcysteine could not be confirmed in another study during the first 5 h of a standard infusion regime in 11 ALF patients. They did not observe any clinically relevant improvements in global oxygen consumption, or in clinical markers of tissue hypoxia following infusion of *N*-acetylcysteine [30]. The jury on the value of *N*-acetylcysteine administration in the later stages of ALF is out and a multicenter trial is currently underway in the US examining this question. The drug should be discontinued in case of systemic hypotension or severe intracranial hypertension as its use can aggravate hypotension. Having said this, it is quite clear that, in case of paracetamol poisoning, irrespective of whether they present early, late or if there is any concern about the exact timing of the overdose, *N*-acetylcysteine should be administered as it may prevent the progression to full blown ALF.

2. Specific management issues

2.1. Circulatory and renal dysfunction: pathophysiologic basis and management

2.1.1. Pathophysiology

Acute liver failure (ALF) is hemodynamically characterized by a hyperdynamic circulation with high cardiac output, low mean arterial pressure (MAP), and low systemic vascular resistance (SVR) [31,32]. This reduction in MAP often requires intervention with inotropes and the dependence of the circulation on vasoactive drugs is a bad prognostic sign. In the fully developed syndrome the patients become refractory to inotropes and the immediate cause of death in up to 70% patients in ALF is severe circulatory failure [7].

There are very few studies that have systematically studied the hemodynamic and renal disturbances during the early phase of ALF. Unlike cirrhosis, the vasodilatation does not appear to be restricted to the splanchnic area and at least in the early phase of the illness (but when vasodilatation is already manifest) the vasodilatation is generalized

including the muscle and the kidneys [33]. However, during the later stages of the disease, studies in a galactosamine rat model showed decreased renal blood flow and increased renal vascular resistance [34,35]. A hypothetical paradigm for the circulatory disturbance is that there is generalized vasodilatation at the initial phase, which produces profound activation of the neurohormonal system culminating in vasoconstriction of the regional vascular beds. This hypothesis will need to be tested in future studies. Also of importance is the observation from studies in animals that the renal dysfunction was manifest even when the renal blood flow was normal suggesting that other factors may be important in initiating the renal dysfunction in acute liver failure [33,36]. The pathophysiologic mechanisms underlying these hemodynamic disturbances are unclear but increased nitric oxide production and cGMP has been demonstrated during the later stages of the disease [37]. Unlike cirrhosis, nitric oxide does not seem to be involved as a factor initiating the vascular disturbances. The differences in the pathophysiological factors underlying the development of the circulatory disturbances in ALF compared with cirrhosis suggests that therapeutic strategies that have been developed for the treatment of patients with cirrhosis cannot be directly applied to ALF patients (Fig. 1).

2.1.2. Aim of circulatory support

Given the fact that the patients have such markedly deranged circulation it is important to use monitoring devices which are able to provide information about changes in mean arterial pressure, the filling status of the patient, the cardiac output and the state of oxygenation. The blood pressure should be maintained within a narrow range to achieve a cerebral perfusion pressure of >50 mmHg but <65 mmHg to prevent cerebral hypoperfusion on the one hand and further cerebral hyperemia on the other [38,39]. Unfortunately, it is not clear whether the goal of therapy in as far as the circulation is concerned should be (as is currently thought) to chase the cerebral perfusion pressure or whether some other end point such as oxygen utilization is more relevant.

	Acute Liver Failure	Advanced Cirrhosis
Systemic Vascular Resistance	↓↓↓	↓↓
Cardiac Output	↑↑↑	↑↑
Mean Arterial Pressure	↓↓↓	↓
Muscle Blood Flow	?=↑↓	↓
Renal Blood Flow	?= ↑↓	↓
Splanchnic Blood Flow	↑	↑↑
Severe Hypotension + Vascular Collapse	++	±

Fig. 1. Cartoon depicting the current state of knowledge in relation to the systemic and regional blood flow in patients with acute liver failure compared with those with cirrhosis. It is noteworthy that data about individual organ blood flow in acute liver failure are not available. Current hypotheses support the hypothetical paradigm that in the initial phase there is generalized vasodilatation which produces profound activation of the neurohormonal system culminating in vasoconstriction of the regional vascular beds.

2.1.3. Use of vasopressors

A particular problem in the management of hypotension in ALF is the fact that these patients have lost cerebral blood flow autoregulation [7,40]. The direct implication of this pathophysiological derangement is that an increase in mean arterial pressure results in an increase in cerebral perfusion pressure, which in turn would increase cerebral blood flow that has the potential to increase intracranial pressure. It is therefore important to have just 'enough' perfusion of the end-organs. There are no controlled studies addressing whether a given vasopressor is better than another but the management of patients will be critically dependent upon the need for expansion of the plasma volume on the one hand and vasopressor support on the other. As pathophysiological basis of the circulatory disturbance is one of vasodilatation and increased cardiac output, the preferred drug for vasopressor support is noradrenaline. There is at present no evidence for the use of adrenaline, dobutamine or dopamine.

Terlipressin (a vasopressin analogue) is widely used in patients with cirrhosis for the treatment of hepatorenal syndrome. Recently, it has been shown to be a powerful vasopressor agent for treating patients with hypotension from severe sepsis [41]. However, the role of terlipressin in the management of hypotension in ALF is not clear. Terlipressin acts through the V_1 and the V_2 receptors. V_1 receptors are distributed in the systemic circulation and mediate vasoconstriction. The V_2 receptors are distributed in the cerebral vasculature and in contrast mediate cerebral vasodilatation. Studies in an animal model of cerebral edema have revealed that administration of vasopressin results in worsening of cerebral hyperemia and consequently severity of brain swelling suggesting that terlipressin may accentuate intracranial hypertension in ALF [42]. In a pilot study, we evaluated cerebrovascular hemodynamic effect of administration of a small dose of a single bolus of terlipressin to patients with ALF and Grade IV HE. In this study, the low dose of terlipressin that was administered did not produce any significant changes in systemic hemodynamics but was associated with the increases in CBF and consequently ICP [6]. The mechanism of this apparent increase in CBF following administration of terlipressin may be the result of its action upon the V_2 receptors, which is known to modulate cerebral vasodilatation through a nitric oxide dependent mechanism. Until results of further studies in the more advanced stages are available, terlipressin should be used with extreme caution in patients with ALF.

2.1.4. Adrenocortical insufficiency

In septic shock, adrenal insufficiency, defined using the short synacthen test was shown to be associated with more

severe stages of hypotension [43]. In a recent study the short synacthen test was performed in 45 patients with acute liver dysfunction. Abnormal tests were common, occurring in 62% of patients. Those who required noradrenaline for blood pressure support had a significantly lower increment following synacthen compared with patients who did not. In the patients who died or underwent liver transplantation the increment and peak were lower than in those who survived [44]. As a follow on from this observation, the authors reviewed their experience of administration of corticosteroids in hypotensive liver failure in 20 patients and showed that supraphysiological doses of corticosteroids reduced norepinephrine requirements but did not improve survival [45]. It is possible that the lack of any significant benefit in this study may have been related to the selection of patients for administration of the corticosteroids; all hypotensive patients were treated with corticosteroids rather than in those that had poor response to synacthen. The translation of this important clinical observation will require development of techniques for bedside assessment of adrenocortical insufficiency and a suitable randomized clinical trial.

2.1.5. Renal support

In patients with advanced stages of ALF, renal failure is common and up to 70–80% will require some form of extracorporeal renal support in those who have circulatory disturbances and cerebral edema [7,46,47]. Extracorporeal renal support also provides the opportunity to manage cerebral edema better allowing removal of fluid and reducing ammonia concentration. Several lines of investigation indicate that in patients with ALF complicated by oliguric renal failure it may be safer to use continuous hemofiltration rather than intermittent hemodialysis. In one of the early studies, intermittent therapy was associated with an increase in ICP from 8.4 ± 1.5 mmHg prior to treatment to 12.6 ± 1.8 mmHg on completion ($P < 0.05$). However, during continuous therapy, the mean ICP was 15.6 ± 5.2 mmHg prior to treatment and this fell to 11.7 ± 2.3 mmHg at 4 h [46]. In addition, continuous hemofiltration was associated with significantly greater cardiovascular stability and significantly higher cerebral perfusion pressures compared with intermittent renal replacement therapy [47,48]. The mechanism underlying the better neurologic tolerance of continuous hemofiltration compared with intermittent therapy is likely to be through the rapid water shifts that are encountered with intermittent haemodialysis [49].

2.2. Intracranial hypertension: pathophysiologic basis and management

The exact pathogenesis of intracranial hypertension in ALF is not entirely clear but a number of inter-related factors are thought to be responsible [50]. Ammonia related brain edema is possibly the first event [51]. CBF autoregulation is lost in patients with ALF resulting in cerebral hyperemia [40,52]. Recent literature has suggested that the systemic inflammatory response may play an important modulating role [23–25]. The alterations in ammonia metabolism and its effects upon cellular bioenergetics increases brain lactate and alters reuptake mechanisms resulting in increases in extracellular glutamate which contribute to further brain swelling [53–55]. The relative lack of randomized controlled clinical trial data makes it difficult to provide an evidence-based argument for the use of any particular form of therapy and Section 3 deals with the measures currently used. The main pathophysiological targets of current therapies are summarized in Fig. 2.

Minimal intervention, and extreme care when moving or turning a patient underlie the general principles of management. Patients should be nursed head up by about 10–15%. There is ongoing discussion at present about how best to monitor patients with ALF from the neurologic point of view [7]. Clearly, the most effective goal of management is control of ICP; therefore the use of ICP monitors seems logical. However, its routine use in ALF has to be balanced against the risk of bleeding. Having said this, the risks can be reduced to minimal levels by close attention to correction of coagulation and judicious use of recombinant factor VII [56]. We have recently suggested that it may be possible to select patients for insertion of ICP monitors based upon measurements using reverse jugular oxygen saturation. We showed that oxygen saturation of $<65\%$ or greater than 80% predicted a high likelihood of a high ICP [7]. The complexity of monitoring using reverse jugular catheters, ICP monitors and, emerging new techniques such as continuous EEG monitors and microdialysis techniques supports the notion that such patients should be managed in experienced centers.

2.2.1. Ammonia and brain swelling

Ammonia reducing strategies. There are no randomized controlled clinical trials of lactulose in ALF. A recent retrospective study compared the outcome of 70 patients with ALF who received lactulose with data from 47 patients who did not receive the drug. There was no significant

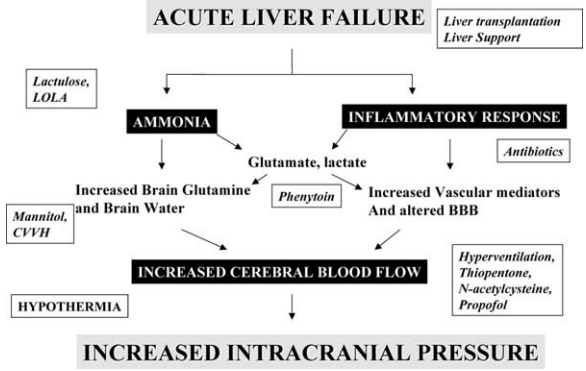

Fig. 2. Therapeutic strategies for the management of intracranial hypertension in acute liver failure based upon the proposed pathophysiological mechanisms. LOLA: L-ornithine L-aspartate; CVVH: continuous veno-venous hemofiltration [reproduced with permission from Jalan R, Semin Liv Dis 2003; 23 (3): 271–82].

difference between the groups in the severity of HE, stay in the intensive care unit, rate of infections, the percentage of patients that underwent OLT and the percentage of patients who died during follow up [57]. The routine use of lactulose cannot therefore be recommended.

L-ornithine L-aspartate is a mixture of two amino acids, which has been shown in controlled clinical trials to reduce blood ammonia concentrations by increasing ammonia detoxification in the muscle and the severity of HE in cirrhosis [58]. Although there are no data in humans with ALF, studies in experimental models of ALF suggests that the administration of this agent early in the course of illness may prevent the occurrence of brain edema [59]. Its further evaluation in ALF seems worthwhile.

Reduction of brain edema. The mainstay for the treatment of increased ICP in ALF is mannitol. Its use is associated with an increase in the osmolality of the capillaries in the brain and this results in movement of water according to Starling's law. In patients with ALF, mannitol was shown to reduce episodes of cerebral edema significantly more frequently compared with those who did not receive this ($P<0.001$). In those that received mannitol, the survival was significantly higher than those who did not receive it (47.1 and 5.9%, respectively, P 0.008) [60]. However, in patients with renal failure repeated administration results in an increase in plasma osmolality and loss of efficacy. Plasma osmolality needs to be measured if more than two doses are used to ensure it is less than 320 Osm/l. In order to be able to use mannitol repeatedly, fluid can be taken off with hemofiltration, which, by itself reduces ICP. Although controlled data are lacking in the literature, reduction of blood volume (upto 500 ml) with hemofiltration is effective in reducing the ICP [7].

Hypertonic saline. Based upon principles similar to the use of mannitol, hypertonic saline has been evaluated in a small controlled clinical trial to try and prevent the occurrence of increases in ICP. Hypertonic saline (30%) via infusion to maintain serum sodium levels of 145–155 mmol/l was compared with a control group in 30 ALF patients. ICP decreased significantly relative to baseline over the first 24 h in the treatment group but not in the control group. The incidence of severe increases in ICP to values of 25 mmHg or greater, was significantly higher in the control group [61]. These results are provocative but before adoption into clinical practice, these results should be confirmed in another study. Importantly, as was pointed out in the accompanying editorial, some potential adverse effects of hypertonic saline should be considered such as multiple small hemorrhages, vein thromboses, brain shrinkage with obliteration of sulci, demyelination of the pons, induction of hyperchloremic acidosis, hematologic abnormalities, aggravation of coagulopathy and red cell lysis [62].

Sodium flux. Phenytoin acts upon the Na/K ATPase and this was used to test whether the frequency of subclinical fitting in ALF could be reduced. In a randomized study no significant differences in frequency of subclinical seizures (30 and 45%, respectively) were observed or the occurrence of increase in ICP was observed (25 and 50%, respectively). However, cerebral edema at autopsy was lower in the phenytoin-treated patients ($P<0.03$) [63]. In another clinical trial from India, no benefit of using prophylactic phenytoin on the incidence of cerebral edema or in survival was observed suggesting that in the absence of new trial data, its use cannot be justified [64].

2.2.2. Cerebral blood flow and metabolism

Hyperventilation. The use of hyperventilation is based upon the observation that it restores CBF autoregulation [65]. In a controlled clinical evaluation of hyperventilation in ALF 20 patients were electively hyperventilated to maintain PaCO2 between 3.5 and 5 kPa. In 35 control patients, mechanical ventilation was instituted only if severe hypoxia or hypercapnia occurred. Cerebral edema, diagnosed clinically or by a rise in ICP to greater than 30 mmHg, occurred in 85% of hyperventilated patients and in 86% of controls. No significant reduction in the number of episodes of cerebral edema was observed in the hyperventilated patients (4.8 episodes/24 h) compared with the controls (5.3 episodes/24 h) [66]. Hyperventilation may reduce ICP acutely but should not be used over a prolonged period.

Thiopental sodium. Its administration results in cerebral vasoconstriction possibly by inhibition of nitric oxide synthase. No controlled trial data are available. Its use is mainly in patients who have increased ICP that is unresponsive to standard medical therapy. In 13 such patients, ICP was reduced by administration of 185–500 mg thiopental over 15 min. Five of the patients made complete recovery and there were only three deaths from intracranial hypertension [67]. However, thiopentone sodium administration to patients with ALF is associated with significant hemodynamic disturbances, which may require additional inotropes. Some of the benefit from reduction in ICP may be off-set by a reduction in mean arterial pressure and thereby cerebral perfusion pressure. Its use should be limited to episodes of catastrophic increases in ICP particularly in relation to OLT.

Indomethacin. Indomethacin induces cerebral vasoconstriction through inhibition of the endothelial cyclooxygenase pathway, alterations in extracellular pH and reduction in cerebral temperature [68]. Following initial positive results of its use in a patient with ALF and in an animal model [69], indomethacin has been tested in patients with ALF. In 12 patients with ALF and brain edema, indomethacin was administered at a dose of 25 mg intravenously. This was associated with a reduction in ICP from 30 (7–53) to 12 (4–33) mmHg ($P<0.05$) without any deleterious effects on cerebral perfusion. Interestingly, the administration of indomethacin did not correct CBF autoregulation [70]. Although the results are interesting and may have some use in patients who do not respond to other forms of treatment, indomethacin is toxic for the kidneys, platelets and the gut

and cannot be recommended for routine use in patients with ALF without more data.

Propofol. Propofol in a dose of 6 mg/kg/h reduces CBF through metabolic suppression. Its use was investigated in seven patients with ALF. The patients were managed with an infusion rate of 50 μg/kg/min of propofol. ICP was elevated in three of seven patients and remained controlled during the course of the illness in six of seven patients. One of the patients died from increased ICP and one during OLT [71]. Early data on the use of propofol in ALF are encouraging and support a fuller evaluation. The current literature supports its use as the sedative of first choice in ALF as it may also protect from intracranial hypertension.

2.2.3. Systemic inflammatory response

There is increasing evidence that systemic inflammatory response is important in the pathogenesis of increased ICP in ALF [7,23–25,55]. Hence, reduction in inflammatory response may be a strategy to prevent/treat intracranial hypertension in ALF.

Dexamethasone. There are no trials of steroids in ALF but in a relatively old study cerebral edema developed in 34 patients with similar frequency in those treated with and without dexamethasone (32 mg stat, 8 mg qds), (16 of 21 and 18 of 23, respectively). Survival was unaffected [60].

Hepatectomy. The use of hepatectomy in patients awaiting OLT is based upon the concept that the 'necrotic liver' is the source of unknown humoral substances that contribute to increased ICP. Ringe et al. performed hepatectomy with portacaval shunting in 32 patients. They observed stabilization of the cardiovascular and cerebrovascular state with 19 of 32 patients being successfully transplanted, 6–41 h afterwards [72]. In a single case, we have recently shown that the removal of the liver in an ALF patient resulted in improved ICP possibly through a reduction in CBF, nitric oxide and liver derived pro-inflammatory cytokines [24]. At present there is no role for this rather heroic intervention, except if there is a 'true' failure of every other approach.

2.2.4. Mild hypothermia

Mild-moderate hypothermia has been extensively studied in head injured patients and its use has been explored in a number of animal models of ALF. Peignoux et al. [73], Eguchi et al. [74] and Traber et al. [75] showed that hypothermic rats (32–33 °C) with ALF had significantly less brain water, reduced duration of encephalopathy and less clinical neurological deterioration compared with the euthermic rats. The proposed mechanisms impact upon all the major proposed pathogenic mechanisms of development of increased ICP in ALF. There are no controlled data of the use of hypothermia in ALF and most of the studies have been in ALF patients that have failed to respond to standard medical therapy.

The effect of moderate hypothermia (32–33 °C) in ALF patients is quite dramatic. Reduction in ICP in patients who have otherwise failed to respond to standard medical therapy is almost universal and recent data suggest that it may be effective in patients with established pupillary abnormalities and patients can be cooled for upto 5 days (median, 30 h). Rewarming a patient is associated with rebound increases in ICP, and therefore due care is necessary if this is to be undertaken [76]. Following our initial report on seven patients [76] providing proof of principle that hypothermia reduces ICP, we have recently reported a study on 14 patients who had ALF and uncontrolled increase in ICP and were awaiting OLT [77]. Thirteen were successfully bridged to OLT with a mean of about 32 h of cooling. Prior to cooling the ICP was elevated at a mean of 36 mmHg and this was reduced to a mean of 16 mmHg at 4 h, which was sustained at 24 h ($P<0.001$), Table 1. During prolonged cooling, some patients do get increases in ICP, which has been shown in most patients to respond to further doses of mannitol. Although hypothermia can increase the risk of bleeding no such complication was encountered. Patients with ALF have a tendency to infection and theoretically hypothermia can increase that risk. Appropriate cultures and antibiotic therapy are essential. As stated above, hypothermia achieves its effect on ICP by impacting upon ammonia and its brain metabolism, cerebral blood flow and its autoregulation, reduction in inflammatory response and its markers such as nitric oxide, pro-inflammatory cytokines and markers of oxidative stress [77,78]. In addition to the neurologic effects hypothermia was associated with significant improvement in cardiovascular hemodynamics manifested by increased mean arterial pressure and systemic vascular resistance and reduced noradrenaline requirements (Table 1) [77]. Recently, we have shown that hypothermia (35 °C) can prevent the occurrence of increases in ICP in ALF patients who fulfilled criteria for poor prognosis and had Grade IV HE. Prior to

Table 1
Effect of hypothermia on cardiovascular and cerebral haemodynamics

	Pre-cooling	4 h	10–24 h
Intracranial pressure (mmHg)	36.5 (2.7)	16.3 (0.7)***	16.8 (1.5)***
Cerebral blood flow (ml/100 g/min)	78.2 (9.7)	46.5 (3.8)***	44.0 (1.9)***
Mean arterial pressure (mmHg)	76.6 (3.6)	82.8 (2.2)**	84.9 (2.1)***
Systemic vascular resistance (dyn s/cm^{-5})	503.8 (41)	671.4 (48.4)*	716.8 (43.3)**
Cardiac output (l/min)	11.3 (0.7)	9.2 (0.5)*	8.7 (0.5)**
Noradrenaline requirement (μg/kg/min)	0.5 (0.1)	0.2 (0.1)*	0.1 (0.0)**
Cerebral perfusion pressure (mmHg)	40.1 (2.9)	66.4 (2.8)***	67.2 (2.8)***

Note: the increase in mean arterial pressure and therefore the cerebral perfusion pressure is not associated with an increase in intracranial pressure indicating that hypothermia restores CBF autoregulation. [Data from Jalan et al. Gastroenterology 2004; 127: 1338–46]. Difference over time tested using one-way ANOVA with Bonferroni correction; *$P<0.05$, **$P<0.01$, ***$P<0.001$.

cooling, the ICP was elevated at a mean of 17.6 (2.7) mmHg and this was reduced to 15.2 (0.9) mmHg at 4 h, which was sustained at 24 h (15.9 (1.3) mmHg) ($P < 0.05$). There were no significant changes in CBF during the cooling period [unpublished data]. During the dissection and reperfusion phases of OLT in ALF patients, increases in ICP are inevitable and current therapies are limited to using barbiturates as treatment with its attendant difficulties. When the patients were maintained hypothermic during the transplantation procedure, the rises in ICP observed in the patients maintained normothermic during the dissection and the reperfusion phases was abolished. Furthermore, in this small study, we did not observe and major complications of hypothermia during the surgery [79].

The use of hypothermia in ALF is particularly promising and data for it strongly supports its use in patients with uncontrolled intracranial hypertension, particularly as a bridge to OLT. In patients, who have severe HE but do not have increased ICP, mild hypothermia reduces the risk of developing increases in ICP, but a lot more data are needed before recommendation for widespread usage can be made. A large clinical trial of hypothermia is being planned in the United States and selected centers in Europe.

3. Summary and future prospects

The multiorgan failure presented by patients with ALF is one of the most challenging management problems in clinical medicine and requires very close co-operation between the intensivist, the hepatologist, the neurologist and the surgeon. There are major issues regarding training of nurses and support networks from hematology, virology, biochemistry and radiology. Results can only be improved if there is a realization in the community hospitals that patients need to be referred early and the focus being shifted from responding to a patient in multiorgan failure to prevention of progression to multiorgan failure. Our knowledge about the pathophysiologic basis of the neurologic syndrome presented by a patient with ALF has advanced considerably and newer agents are aimed at drugs to reduce ammonia and its brain uptake, alter brain glutamine and glutamate metabolism and possibly use anti-inflammatory cytokine therapy. Our understanding of the pathophysiologic basis of hemodynamic disturbance, immune dysfunction and multiorgan failure is at a rudimentary stage and further understanding of the molecular basis of these circulatory disturbances is likely to improve our ability to manage these patients. Given the relatively small number of patients with ALF, it will be important in the future to organize ourselves in collaborative groups in order to explore the place of existing treatments and newer therapeutic modalities in appropriate multicenter studies.

Acknowledgements

The outline of this review is based upon two previous reviews. Jalan R. Semin Liv Dis. 2003; 23: 271–82; Jalan R. Neurochemistry International, 2004 (in press). I am grateful to the members of the Liver Failure Group, UCL and also to my collaborators, for helpful advice and thoughts, which have contributed to this review.

References

[1] Trey C, Davidson CS. In: Popper H, Schaffner F, editors. The management of fulminant hepatic failure. Progress in liver disease, vol. III. New York: Grune and Stratton; 1970. p. 282–298.
[2] O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439–445.
[3] Ascher NL, Lake JR, Emond JC, Roberts JP. Liver transplantation for fulminant hepatic failure. Arch Surg 1993;128:677–682.
[4] Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). Gastroenterology 1995;109:1907–1916.
[5] Hoofnagle JH, Carithers RL, Chapiro C, Ascher NL. Fulminant hepatic failure: summary of a workshop. Hepatology 1995;21: 240–252.
[6] Shawcross DL, Davies NA, Mookerjee RP, Hayes PC, Williams R, Lee A, et al. Worsening of cerebral hyperemia by the administration of terlipressin in acute liver failure with severe encephalopathy. Hepatology 2004;39:471–475.
[7] Jalan R. Intracranial hypertension in acute liver failure: pathophysiological basis of rational management. Semin Liver Dis 2003;23: 271–282.
[8] Bernal W, Wendon J. Liver transplantation in adults with acute liver failure. J Hepatol 2004;40:192–197.
[9] Bernuau J. Acute liver failure: avoidance of deleterious cofactors and early specific medical therapy for the liver are better than late intensive care for the brain. J Hepatol 2004;41:152–155.
[10] Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SHB, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137:947–954.
[11] Riordan SM, Williams R. Fulminant hepatic failure. Clin Liver Dis 2004;4:25–45.
[12] Bernuau J, Benhamou JP. Fulminant and subfulminant hepatic failure. In: Bircher J, Benhamou JP, McIntyre N, Rizzetto M, Rodés J, editors. Oxford textbook of clinical hepatology. Oxford: Oxford University Press; 1999. p. 1341–1372.
[13] Durand F, Bernuau J, Giostra E, Mentha G, Shouval D, Degott C, et al. Wilson's disease with severe hepatic insufficiency: beneficial effects of early administration of D-penicillamine. Gut 2001;48:849–852.
[14] Van de Kerkhove MP, Hoekstra R, Chamuleau RA, Van Gulik TM. Clinical application of bioartificial liver support systems. Ann Surg 2004;240:216–230.
[15] Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [^{1}H–^{13}C] nuclear magnetic resonance study. Hepatology 2003;37:420–428.
[16] Tofteng F, Jorgensen L, Hansen BA, et al. Cerebral microdialysis in patients with fulminant hepatic failure. Hepatology 2002;36: 1333–1340.
[17] Munoz SJ, Moritz MJ, Bell R, et al. Factors associated with severe intracranial hypertension in candidates for emergency liver transplantation. Transplantation 1993;55:1071–1074.

[18] Kodakar SK, Gopal PB, Wendon JA. Intracranial pressure is related to body temperature in acute liver failure. Liver Transpl 2001;7:C87.
[19] Kodakar SK, Gopal PB, Wendon JA. Hyperglycemia is associated with intracranial hypertension in patients with acute liver failure. Liver Transpl 2001;7:C21.
[20] Cordoba J, Gottstein J, Blei AT. Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 1998;29:589–594.
[21] Jalan R, Dabos K, Redhead DN, et al. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol 1997;27:928–933.
[22] Van Hulst RA, Hasan D, Lachmann B. Intracranial pressure, brain pCO_2, pO_2, and pH during hypo- and hyperventilation at constant mean airway pressure in pigs. Intensive Care Med 2002;28:68–73.
[23] Rolando N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. Hepatology 2000;32: 734–739.
[24] Jalan R, Pollok A, Shah S, et al. Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure. J Hepatol 2002;37:536.
[25] Jalan R, Williams R. The inflammatory basis of intracranial hypertension in acute liver failure. J Hepatol 2001;34:940–942.
[26] Rolando N, Gimson A, Wade J, et al. Prospective controlled trial of selective parenteral and enteral antimicrobial regimen in fulminant liver failure. Hepatology 1993;17:196–201.
[27] Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. Lancet 1990;30:1572–1573.
[28] Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. Br Med J 1991;303:1026–1029.
[29] 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.
[30] Walsh TS, Hopton P, Philips BJ, et al. The effect of *N*-acetylcysteine on oxygen transport and uptake in patients with fulminant hepatic failure. Hepatology 1998;27:1332–1340.
[31] Ellis A, Wendon J. Circulatory, respiratory, cerebral, and renal derangements in acute liver failure: pathophysiology and management. Semin Liver Dis 1996;16:379–388.
[32] Trewby PN, Williams R. Pathophysiology of hypotension in patients with fulminant hepatic failure. Gut 1977;18:1021–1026.
[33] Ytrebo LM, Nedredal GI, Langbakk B, Revhaug A. An experimental large animal model for the assessment of bioartificial liver support systems in fulminant hepatic failure. Scand J Gastroenterol 2002;37: 1077–1088.
[34] Javle P, Yates J, Kynaston HG, Parsons KF, Jenkins SA. Hepatosplanchnic haemodynamics and renal blood flow and function in rats with liver failure. Gut 1998;43:272–279.
[35] Anand R, Harry D, Holt S, Milner P, Dashwood M, Goodier D, et al. Endothelin is an important determinant of renal function in a rat model of acute liver and renal failure. Gut 2002;50:111–117.
[36] Ytrebo LM, Sen S, Rose C, Nedredal GI, Davies NA, Williams R, et al. MARS treatment improves renal function independent of systemic haemodynamics in acute liver failure: a randomized controlled study in a pig model. Hepatology 2003;38:1083A.
[37] Schneider F, Lutun P, Boudjema K, Wolf P, Tempe JD. In vivo evidence of enhanced guanylyl cyclase activation during the hyperdynamic circulation of acute liver failure. Hepatology 1994; 19:38–44.
[38] McCashland TM, Shaw BW, Tape E. The American experience with transplantation for acute liver failure. Semin Liv Dis 1996;16: 427–433.
[39] Davies MH, Mutimer D, Lowes J, et al. Recovery despite impaired cerebral perfusion in fulminant hepatic failure. Lancet 1994;343: 1329–1330.
[40] Larsen FS. Cerebral circulation in liver failure: Ohm's law in force. Semin Liver Dis 1996;16:281–292.
[41] O'Brien A, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. Lancet 2002;359:1209–1210.
[42] Chung C, Vaquero J, Gottstein J, Blei AT. Vasopressin accelerates experimental ammonia-induced brain edema in rats after portacaval anastomosis. J Hepatol 2003;39:193–199.
[43] Minneci PC, Deans KJ, Banks SM, Eichacker PQ, Natanson C. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. Ann Intern Med 2004;141:47–56.
[44] Harry R, Auzinger G, Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. Hepatology 2002;36: 395–402.
[45] Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. Liver Int 2003; 23:71–77.
[46] Davenport A, Will EJ, Davison AM, Swindells S, Cohen AT, Miloszewski KJ, et al. Changes in intracranial pressure during hemofiltration in oliguric patients with grade IV hepatic encephalopathy. Nephron 1989;53:142–146.
[47] Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med 1993;21:328–338.
[48] Davenport A. Hemofiltration in patients with fulminant hepatic failure. Lancet 1991;338:1604.
[49] Winney RJ, Kean DM, Best JJ, Smith MA. Changes in brain water with haemodialysis. Lancet 1986;8:1107–1108.
[50] Blei AT, Larsen FS. Pathophysiology of cerebral edema in fulminant hepatic failure. J Hepatol 1999;31:771–776.
[51] Blei AT, Olafsson S, Therrien G, Butterworth RF. Ammonia-induced brain edema and intracranial hypertension in rats after portacaval anastomosis. Hepatology 1994;19:1437–1444.
[52] Jalan R, Olde Damink SW, Hayes PC, Deutz NE, Lee A. Pathogenesis of intracranial hypertension in acute liver failure: inflammation, ammonia and cerebral blood flow. J Hepatol 2004;41:613–620.
[53] Lai JC, Cooper AJ. Brain alpha-ketoglutarate dehydrogenase complex: kinetic properties, regional distribution, and effects of inhibitors. J Neurochem 1986;47:1376–1386.
[54] Michalak A, Rose C, Butterworth J, Butterworth RF. Neuroactive amino acids and glutamate (NMDA) receptors in frontal cortex of rats with experimental acute liver failure. Hepatology 1996;24:908–913.
[55] Zwingmann C, Chatauret N, Leibfritz D, Butterworth RF. Selective increase of brain lactate synthesis in experimental acute liver failure: results of a [^{1}H–^{13}C] nuclear magnetic resonance study. Hepatology 2003;37:420–428.
[56] Shami VM, Caldwell SH, Hespenheide EE, et al. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl 2003;9:138–143.
[57] Alba L, Hay JE, Angulo P, Lee WM. Lactulose therapy in acute liver failure. J Hepatol 2002;36:33 [abstract].
[58] Kircheis G, Nilius R, Held C, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology 1997;25:1351–1360.
[59] Rose C, Michalak A, Rao KV, et al. L-ornithine-L-aspartate lowers plasma and cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure. Hepatology 1999;30:636–640.
[60] Canalese J, Gimson AES, Davis C, et al. Controlled trial of dexamethasone and mannitol for the cerebral edema of fulminant hepatic failure. Gut 1982;23:625–629.
[61] Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology 2004;39:464–470.
[62] Larsen FS. Optimal management of patients with fulminant hepatic failure: targeting the brain. Hepatology 2004;39:299–301.

[63] 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.
[64] Bhatia V, Batra Y, Acharya SK. Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure—a controlled clinical trial. J Hepatol 2004;41:89–96.
[65] 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.
[66] Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral edema in fulminant hepatic failure. J Hepatol 1986;2:43–51.
[67] Forbes A, Alexander GJ, O'Grady JG, et al. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. Hepatology 1989;10:306–310.
[68] Jensen K, Ohrstrom J, Cold GE, Astrup J. Indomethacin (Confortid) in severe head injury and elevated intracranial pressure (ICP). Acta Neurochir Suppl (Wien) 1992;55:47–48.
[69] Chung C, Gottstein J, Blei AT. Indomethacin prevents the development of experimental ammonia-induced brain edema in rats after portacaval anastomosis. Hepatology 2001;34:249–254.
[70] 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.
[71] Wijdicks EFM, Nyberg SL. Propofol to control intracranial pressure in fulminant hepatic failure. Transplant Proc 2002;34:1220–1222.
[72] Ringe B, Lubbe N, Kuse E, et al. Total hepatectomy and liver transplantation as two-stage procedure. Ann Surg 1993;218:3–9.
[73] Peignoux M, Bernuau J, Benhamou JP. Total hepatectomy and vascular exclusion in the rat. A comparison, with special reference to the influence of body temperature. Clin Sci 1982;62:273–277.
[74] Eguchi S, Kamlot A, Ljubimova J, et al. Fulminant hepatic failure in rats: survival and effect on blood chemistry and liver regeneration. Hepatology 1996;24:1452–1459.
[75] Traber P, DalCanto M, Ganger D, Blei AT. Effect of body temperature on brain edema and encephalopathy in the rat after hepatic devascularization. Gastroenterology 1989;96:885–891.
[76] Jalan R, Olde Damink SWM, Deutz NEP, Lee A, Hayes PC. Treatment of uncontrolled intracranial hypertension in acute liver failure with moderate hypothermia. Lancet 1999;354:1164–1168.
[77] Jalan R, Olde Damink SWM, Deutz NEP, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. Gastroenterology 2004;127: 1338–1346.
[78] Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. Hepatology 2001;34: 50–54.
[79] Jalan R, Olde Damink SW, Deutz NE, Davies NA, Garden OJ, Madhavan KK, et al. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. Transplantation 2003;75: 2034–2039.