Intracranial Hypertension in Acute Liver Failure: Pathophysiological Basis of Rational Management

Rajiv Jalan, M.D., FRCPE[1]

ABSTRACT

Increased intracranial pressure (ICP) in patients with acute liver failure (ALF) remains a major cause of morbidity and mortality. Conventional methods of ammonia reduction such as the use of lactulose do not improve outcome, and metabolic substrates such as L-ornithine L aspartate may offer more promise. Mannitol remains the mainstay of therapy. An important role for cerebral hyperemia in the pathogenesis of increased ICP has led to a reevaluation of established therapies such as hyperventilation, N-acetylcysteine, thiopentone sodium, and propofol. Recent studies have focused on the role of systemic inflammatory response in the pathogenesis of increased ICP and support the use of antibiotics prophylactically. Moderate hypothermia reduces ICP in patients with uncontrolled intracranial hypertension and prevents increases in ICP during orthotopic liver transplantation (OLT). Advances in understanding the pathophysiological basis of intracranial hypertension in ALF have outstripped appropriate testing of the newly generated ideas in appropriate clinical trials, and more effort should be mounted at a national level to organize the appropriate multicenter studies required.

KEYWORDS: Acute liver failure, intracranial pressure, cerebral blood flow, ammonia, orthotopic liver transplantation, hepatic encephalopathy

Objectives: On completion of this article, the reader should be able to understand the current thoughts on the (1) prognosis, (2) brain monitoring, and (3) principles of management of patients with increased intracranial pressure in acute liver failure.

The development of hepatic encephalopathy (HE) in patients with acute liver injury is the key event that defines their prognosis.[1–5] HE is characterized by rapid deterioration in the level of consciousness, increased intracranial pressure (ICP), and reduced cerebral perfusion pressure. Neuropathologically, the brain is edematous.[6] As has been detailed in the previous sections, the exact pathophysiological mechanisms underlying the development of brain edema and increased ICP are not entirely clear but are likely to be multifactorial.[7–10] The

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increase in ICP occurs in conjunction 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 splanchnic vasodilatation that results in increased cardiac output and reduced systemic vascular resistance and mean arterial pressure.[11] As a result, most patients in the advanced stage require intensive cardiovascular monitoring and inotropic support. These circulatory disturbances contribute to the occurrence of renal failure requiring renal support with hemofiltration and hemodialysis.[11] ALF results in severe coagulopathy, which needs to be corrected 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.[11] The increase in ICP occurs with this background, and the strategies to manage increased ICP must be considered in this context.

PROGNOSIS OF INCREASED ICP IN ALF

A detailed discussion of the factors defining poor prognosis in ALF is provided elsewhere in this issue.[12] Data in relation to the impact of increased ICP on the outcome of patients with ALF are scanty, but more than 90% mortality is expected in patients in whom ICP cannot be controlled with conventional measures. With OLT, survival rates of up to 80% can be achieved.[3,4] Thirty to 40% of patients with ALF die while waiting for a donor organ to become available, primarily because of the effects of increased ICP. We studied the outcome of 315 patients with acute liver injury due to paracetamol overdose for 7 years (Fig. 1). Of the 80 patients that were in the poor prognosis group, 42 had other contraindications for OLT. Thirty-nine of these patients died, and the immediate cause of death in 14 (35%) patients was brain herniation from elevated ICP. Of the 36 patients that were listed for OLT, 12 died after being removed from the waiting list (for uncontrolled increase in ICP, sepsis, bleeding, or adult respiratory distress syndrome) while waiting for a donor organ to become available. Six of these deaths were from brain herniation (50%). Of those patients who underwent successful OLT, 2 died in the early posttransplant period from the effects of increased ICP. Eighteen of the 235 patients who were in the good prognosis group died. Death in 9 of these patients was the result of brain herniation (50%). These data suggest that, despite our best efforts in management, a significant proportion of patients continue to die from the effects of increased ICP.

MONITORING OF HEPATIC ENCEPHALOPATHY IN ALF

Clinical

Close clinical monitoring of patients and exclusion of the possible effects of concurrent hypoglycemia are the important first steps. Once the patient with ALF develops evidence of HE, he or she should be managed in an intensive care environment to ensure appropriate monitoring and treatment, airway protection, and decisions regarding OLT. It is important to record the mental status, and close attention should be paid to the pupillary

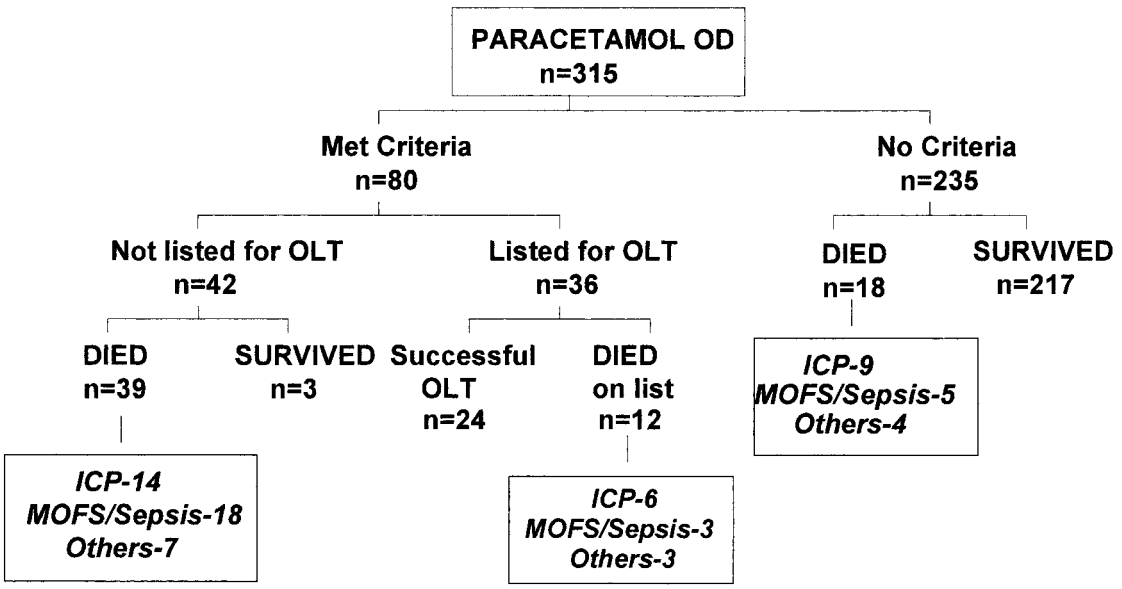

Figure 1 The outcome of patients with acute liver injury because of paracetamol overdose presenting to a single Liver Unit (Scottish Liver Transplantation Unit, database, 1993–1999). The major cause of mortality in the patients who have poor prognosis and are not suitable candidates for OLT is increased ICP and multiorgan failure (MOFS). Similarly, 50% of deaths in the patients who are in the good prognosis group and those awaiting an organ for transplantation are also from increased ICP.

size and reaction to light. Once the patient progresses to Grade III HE (using the West Haven criteria),[13,14] it is often impossible to manage the patient without sedation, and it is at this stage that a formal decision is made to electively intubate and mechanically ventilate the patient. The choice of the sedative used will vary, but present evidence supports the use of propofol (discussed later).[15] In addition, it is important to appreciate that fever, psychomotor agitation, and arterial hypertension are frequently observed preceding the episodes of severe intracranial hypertension. When the patients reach this stage, it is necessary to decide whether an ICP monitor should be inserted.

The Risks of ICP Monitoring

When using an ICP monitor, the risks of insertion have to be acceptable and the question as to whether alternatives would provide the same information needs to be answered. Because we are trying to treat an increase in ICP, intuitively it would seem rational to measure the level. However, there is ongoing debate about whether ICP monitors should be used routinely and in which patients and when they should be inserted.[16,17] Undoubtedly, their use does carry an element of risk given that patients with ALF have a severe coagulopathy. Indeed, Blei et al[18] performed a survey of complications associated with ICP monitoring among centers performing liver transplantation in the United States (n = 262 patients). Epidural transducers were the most commonly used device and had the lowest complication rate (3.8%). Subdural and parenchymal monitors were associated with complication rates of 20 and 22%, respectively. Fatal hemorrhage occurred in 1% of patients undergoing epidural ICP monitoring, whereas subdural and intraparenchymal devices had fatal hemorrhage rates of 5 and 4%, respectively. They also noted that although epidural transducers were safer, the measurements varied more and were less precise than the other devices were.[18] This study was, however, retrospective, with all the inherent difficulties; the number of ALF patients being managed in individual centers was few, and there was no specific protocol for correction of the coagulation parameters.

Data from individual centers are rather different. Daas et al[19] observed hemorrhage in 1 patient of the 11 with inserted ICP monitors. In the study by Lidosfsky et al,[20] no complications of ICP monitoring were observed in 23 patients. They concluded that they were able to institute appropriate treatment in cases of increases in ICP and even allowed the removal of 6 patients who had uncontrolled intracranial hypertension from the waiting list for OLT. Ascher et al[3] monitored ICP in 42 patients with ALF who were candidates for OLT and showed a survival of 92%. They suggested that the unusually good results were due to their aggressive approach to monitoring and treatment of increased ICP.[3] Lee et al recently reported their experience in the use of subdural ICP monitors in 161 patients with ALF at the First UK Liver Failure Group meeting (unpublished, September 2002). Subdural hematoma occurred in 3 of the patients, with death as a result in 1 patient. The risks of bleeding can be minimized if the coagulation is corrected, and the addition of the recombinant factor VIIa to fresh frozen plasma (FFP) is undoubtedly helpful. In a recently reported clinical trial in patients with ALF, the coagulation profile could be corrected to levels that were acceptable for insertion of ICP monitors in all 8 patients, compared with 3 of the 8 who were administered FFP.[21]

Other monitoring devices that are used either alone or in conjunction with an ICP monitor include a reverse jugular catheter for measuring oxygen saturation in the jugular bulb,[22] transcranial Doppler to measure cerebral blood flow (CBF) velocity,[23] continuous electroencephalogram (EEG) monitoring to detect subclinical seizure activity,[24] near infrared spectroscopy to measure cerebral oxygenation,[25] cerebral microdialysis to measure brain biochemistry,[26] and imaging techniques that measure brain water.[27] These newer modalities provide additional pathophysiological measurements, and no direct comparison data with ICP level are as yet available.

When to Insert an ICP Monitor

The question therefore is, should ICP monitors be inserted and when can we use the "other" modalities to determine the timing of insertion of the monitor. In order to improve the risk-benefit ratio, insertion of the ICP monitor should be performed when estimates of pressure are likely to be of value in management. For the monitor to be inserted safely, the patient needs to be sedated, and therefore the appropriate timing is likely to be after he or she has deteriorated to Grade III-IV HE and is being mechanically ventilated. In a recently published study in patients with ALF, it was suggested that an arterial ammonia concentration of greater than 150 μmol/L predicted those who were likely to die from brain herniation, suggesting that this measurement may be used as a cutoff in deciding who should have an ICP monitor.[28] However, it is not possible from the data presented in that study to comment on the relationship between ICP and ammonia concentrations.

We have studied a cohort of patients with ALF in whom we inserted ICP monitors when they were mechanically ventilated for Grade III-IV HE and before they received any specific treatment for increased ICP. We observed that 54% had elevated ICP requiring specific treatment. Of the other 46% of patients, 30% went on to develop surges of increased ICP. Arterial ammonia concentrations were measured in these patients, but we were unable to define a specific cutoff that predicted which patients were likely to have an elevated ICP. As has been suggested in the previous sections, patients with ALF have derangements in cerebral circulation.[8] We

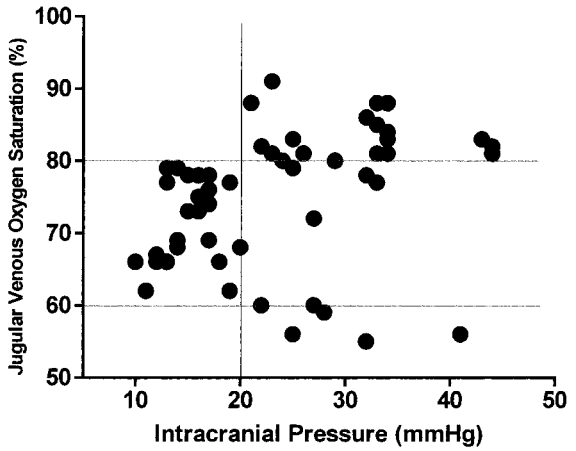

Figure 2 The figure shows the relationship between venous oxygen saturation and ICP. The measurements were made soon after insertion of the ICP monitor before any specific therapy for increased ICP was instituted. Jugular venous oxygen saturation of < 60% or > 80% have relatively high sensitivity and specificity in predicting those who are likely to have increased ICP.

therefore explored whether measurement of jugular venous oxygen saturation would predict those who were likely to have an increased ICP. We observed that if a jugular venous oxygen saturation was either > 80% or < 60%, the sensitivity and specificity of having elevated ICP was high (Fig. 2). However, commensurate changes in jugular venous oxygen saturation did not correlate with reduction in ICP, suggesting that although jugular venous oxygen saturation may be useful in identifying those that have increased ICP, it is not useful in evaluating progression or response to treatment.

Which Group of Patients Should Have ICP Monitoring

The cases that need particular attention are those who are candidates for OLT and those who are in the good prognosis group but have severe encephalopathy. In monitoring the former group, the aim is to make sure that rises in ICP, both before and during OLT, can be treated appropriately and that those with uncontrollable increases in ICP are excluded from OLT.[29,30] For the patients with severe encephalopathy but who do not fulfill criteria for poor prognosis, it is possible that deaths from increased ICP can be prevented by aggressive therapy, allowing a longer period of time for the liver to recover. In the patient group including those who fulfill the criteria for poor prognosis but who are not candidates for OLT, the relevance of monitoring is debatable, given that more than 90% will die. The counter argument is that the only way to improve their survival is to avert deaths from causes that could be treated, such as an increased ICP.

Given the relatively small number of patients with ALF, it is extremely difficult to design a suitable randomized controlled trial to determine when and how ICP monitors should be used. The reliability of data obtained from an epidural catheter is questionable; a subdural catheter is preferable.[18] At present, information about elevated ICP cannot be reliably obtained from any other form of monitoring, and ICP monitoring remains the "gold standard" against which newer pathophysiological measurements should be compared. The small risks of insertion can be minimized by the additive use of recombinant factor VIIa in correcting the coagulopathy at the time of placement and by early referral of patients to centers that have considerable experience with this procedure and the other aspects of intensive care for ALF.

PATHOPHYSIOLOGICAL BASIS OF ALF: TARGETS FOR THERAPY

As has been highlighted by others,[7–10] the exact pathogenesis of intracranial hypertension in ALF is not entirely clear, but it is likely that a number of interrelated factors contribute. Ammonia-related neurotoxicity and brain edema are possibly the first event and are therefore an important target for therapy.[31] CBF autoregulation is lost in patients with ALF, resulting in cerebral hyperemia, and in the advanced stages, there is an associated loss of oxygen and glucose extraction by the brain.[32] There is also an increasing body of literature suggesting that the systemic inflammatory response may play an important modulating role and contribute to the altered CBF and cellular bioenergetics.[33–35] The alterations in ammonia metabolism and its effects on the Krebs cycle result in increased brain lactate, and alterations in the reuptake mechanisms result in an increase in extracellular glutamate that initiate further brain swelling.[26,36–38] Targets for therapy include (1) ammonia and brain swelling, (2) CBF and metabolism, (3) inflammatory response, and (4) treatments that affect multiple pathways (Fig. 3). 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 the following section deals with the measures currently used.

General Measures

It is important to note that patients with ALF can decompensate very rapidly, often within a matter of hours, and have a catastrophic event related to their airway and respiration, circulation, or brain herniation. As already mentioned, close clinical monitoring is important during the observation period and particularly when moving a patient between either hospitals or wards. 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.[29,30] Vasopressin and its analogues such as glypressin should be avoided because

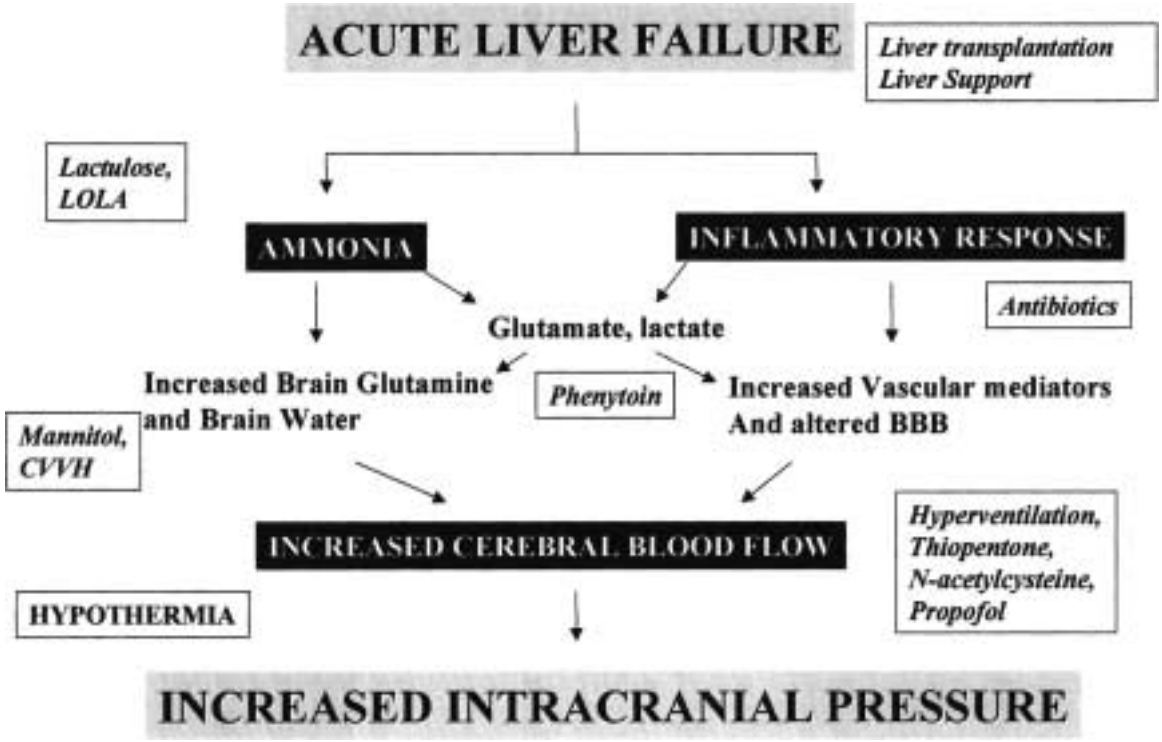

Figure 3 The various therapeutic modalities available and the sites in the pathophysiological cascade on which they act. (LOLA, L-ornithine L aspartate; CVVH, continuous venovenous hemofiltration)

they may worsen hyperammonemia and also increase ICP through increases in CBF.[39,40] Hyperthermia should be prevented because it worsens intracranial hypertension.[41,42] Glucose levels need to be maintained to prevent cerebral and systemic effects of hypoglycemia. Hyperglycemia worsens cerebral edema in patients with ALF.[43] Hyponatremia can also worsen brain edema and should be prevented or corrected.[44,45] Hypercapnia should be avoided because it induces cerebral hyperemia and increases ICP.[46] Close attention to acid-base balance and correction of hyperlactatemia is important because it can worsen cerebral hyperemia.[26,38] Patients requiring renal support should have continuous venovenous hemofiltration rather than hemodialysis to prevent rapid fluid shifts.[47]

Ammonia and Brain Swelling

AMMONIA-REDUCING STRATEGIES

There are no randomized controlled clinical trials of ammonia-reducing strategies such as lactulose, branched amino acids, or nonabsorbable antibiotics in ALF patients. However, a recently reported study from the database of the U.S. ALF group compared the outcome of 70 patients with ALF who received lactulose with data from 47 patients who did not receive the drug. Despite the retrospective nature of the study, the patients were well-matched for their demographics and coma score. There was no significant difference between the groups in the severity of HE, length of stay in the intensive care unit, rate of infections, percentage of patients that underwent OLT, and percentage of patients who died during follow-up.[48] The routine use of lactulose cannot therefore be recommended.

L-ornithine L-aspartate is a mixture of two amino acids that has been shown in controlled clinical trials to reduce blood ammonia concentrations by increasing ammonia detoxification in the muscle and to reduce the severity of HE in cirrhosis.[49] Although there are no data in humans with ALF, studies in experimental models of ALF suggest that the administration of this agent early in the course of illness may prevent the occurrence of brain edema.[50] Because of the good safety profile of this drug, its further evaluation in ALF through a randomized controlled clinical trial would seem worthwhile.

REDUCTION OF BRAIN EDEMA

In animal models of ALF, the administration of a glutamine synthase inhibitor prevents the occurrence of brain edema, but this strategy is not possible in humans because glutamine is an important metabolic intermediate.[51] The mainstay for the treatment of increased ICP is mannitol, which is administered intravenously as a bolus in a dose of 1 to 2 mg/kg as a 20% solution. Its use is based on the principle that mannitol administration results in an increase in the osmolality of the capillaries in the brain, and this results in movement of water, accord-

ing to Starling's law. Canalese et al[52] studied 34 patients with ALF and showed that the episodes of cerebral edema resolved significantly more frequently in the 17 patients who received mannitol than it did in the 17 patients who did not (44 of 53 and 16 of 17, respectively, $p < 0.001$). In those who received mannitol, the survival rate was significantly higher than it was in those who did not receive it (47.1 and 5.9%, respectively, $p < 0.008$).[53] There are, however, problems with its use, particularly in those patients who have renal failure, because repeated administration results in an increase in plasma osmolality and consequent loss of efficacy. Plasma osmolality needs to be measured if more than 2 doses are used to ensure that 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 (up to 500 mL) with hemofiltration is effective in reducing the ICP.

N-METHYL-D-ASPARTATE ANTAGONISM AND SODIUM FLUX

The use of inhibitors of the glutamate N-methyl-D-aspartate receptor memantine is based on data from studies on experimental animals with ALF, suggesting that hyperammonemia results in an increase in extracellular glutamate concentrations that act on the N-methyl-D-aspartate receptors, leading to an increase in sodium flux into the cell and brain swelling.[37] Although there are no data of its use in patients with ALF, pretreatment of rats with portacaval shunt resulted in a reduction in brain swelling and ICP.[53]

Phenytoin, which acts on the Na/K adenosine triphophatase (ATPase) has undergone a randomized clinical trial in 42 ALF patients admitted with Grade III-IV HE. In addition to ICP monitoring, the patients underwent continuous EEG monitoring. Although there were no significant differences in frequency of subclinical seizure in the two groups (30 and 45%, respectively) or in the increase of ICP (25 and 50%, respectively), the autopsy examinations available in 19 patients showed signs of cerebral edema in only 22% of the phenytoin-treated patients compared with 70% of the controls ($p < 0.03$).[24] These data provide the rationale for the use of phenytoin in ALF as prophylaxis in those who have reached Grade III-IV HE.

Cerebral Blood Flow and Metabolism

HYPERVENTILATION

In patients with ALF, loss of CBF autoregulation contributes to cerebral vasodilatation.[7,8,32] The induction of arterial hypocapnia by hyperventilation resulted in the restoration of cerebral vascular autoregulation.[54] Ede et al[55] performed a controlled clinical evaluation of hyperventilation in ALF. Twenty patients were electively hyperventilated to maintain $PaCO_2$ between 3.5 and 5 kPa. In the other 35 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. They observed no significant reduction in the number of episodes of cerebral edema in the hyperventilated patients (4.8 episodes per 24 hours) compared with the controls (5.3 episodes per 24 hours), and hyperventilation did appear to delay the onset of coning.[55] Their results suggest that hyperventilation may reduce ICP acutely but cannot be recommended for prolonged use.

N-ACETYLCYSTEINE

Although N-acetylcysteine is used widely in the United Kingdom in the later stages of ALF (in contradistinction to its use as an antidote to paracetamol poisoning when administered within 24 hours), its use is difficult to justify on pathophysiological grounds because its vascular effects are those of vasodilatation.[56] A number of clinical studies support a role for this drug. Harrison et al[57] investigated the administration of N-acetylcysteine in patients with paracetamol overdose who presented up to 36 hours afterwards and showed that 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 lower (51% versus 75%).[57] Keays et al[58] performed a randomized controlled trial in paracetamol-induced ALF and showed that survival was significantly higher in the N-acetylcysteine–treated group than it was in the controls (48% versus 20%; $p < 0.04$). The N-acetylcysteine–treated patients had a lower incidence of cerebral edema (40% versus 68%; $p < 0.05$).[58] In a subsequent study, they suggested that the improvement in survival was related to an increase in cardiac output, oxygen extraction ratio, and oxygen consumption, and it was proposed that the therapeutic benefit was caused by a reduction of tissue hypoxia.[59] Because the Fick method was used to determine the relationship between oxygen delivery and oxygen consumption from the cardiac output and arteriovenous oxygen content data, there is considerable potential for measurement error. In order to answer this question carefully, Walsh et al[60] studied the hemodynamic effects of N-acetylcysteine during the first 5 hours of a standard infusion regime in 11 ALF patients and simultaneously measured oxygen consumption using a method based on respiratory gas analysis. They were unable to confirm that N-acetylcysteine infusion resulted in clinically relevant improvements in global oxygen consumption or in clinical markers of tissue hypoxia.[60] The jury is still out on the value of N-acetylcysteine administration in the later stages of ALF, and a multicenter trial is

currently underway in the United States to examine this question. The drug should be discontinued in case of systemic hypotension or severe intracranial hypertension.

THIOPENTAL SODIUM

The use of this agent was prompted by the observation that its administration results in cerebral vasoconstriction, possibly by inhibition of nitric oxide synthase, which is thought to be important in the pathogenesis of increased ICP in ALF. In 13 patients who had increased ICP that was unresponsive to standard medical therapy, the dosage of thiopental was adjusted upward until the ICP fell to within normal limits or until there were adverse hemodynamic changes. In each case, the ICP was reduced by administration of 185 to 500 mg thiopental over 15 minutes. Five of the patients made complete recovery, and there were only 3 deaths from intracranial hypertension.[61] However, thiopentone sodium is not an easy drug to use, and its administration to patients with ALF is associated with significant hemodynamic disturbances that may require additional inotropes. Some of the benefit from reduction in ICP may be offset 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 multiple mechanisms that include inhibition of the endothelial cyclooxygenase pathway, alterations in extracellular pH, and reduction in cerebral temperature.[62] Its use has been investigated in a single patient with ALF in whom administration of 25 mg of indomethacin resulted in normalization of ICP.[63] Although the results are interesting and confirmed by data from studies in an animal model,[64] indomethacin is toxic for the kidneys and the gut and cannot be recommended for use in patients with ALF. Studies using the cyclooxygenase-2 inhibitors are awaited.

PROPOFOL

Propofol is a highly lipophilic drug and is rapidly distributed with the blood volume and brain and has a high metabolic clearance. In addition, propofol in a dose of 6 mg/kg per hour 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 per minute of propofol. The ICP at insertion was elevated in three of seven patients, but remained within normal limits in six of seven patients. One of the patients died from increased ICP, and one died during OLT.[15] 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 because it may also protect from intracranial hypertension.

Systemic Inflammatory Response

As has been highlighted in the previous sections, 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.[7,8,33–35]

DEXAMETHASONE

The use of steroids in ALF is based on the notion that inflammatory response is important in the progression of intracranial hypertension. A relatively old study addresses this question.[52] Cerebral edema developed in 34 patients with similar frequency in those treated with and without dexamethasone (32 mg stat, 8 mg every day), (16 of 21 and 18 of 23, respectively). Survival figures were also unaffected.[52]

HEPATECTOMY

The use of hepatectomy in patients awaiting OLT is a rather dramatic intervention but may be of value in desperate situations in which all the available treatments have been applied and the patient continues to deteriorate. It is based on the concept that the "necrotic liver" is the source of unknown humoral substances that contribute to increased ICP. In 32 patients with ALF who were likely to die while awaiting OLT, Ringe et al[65] performed hepatectomy with portacaval shunting. They observed stabilization of the cardiovascular and cerebrovascular state, with 19 of 32 patients having successful transplants, 6 to 41 hours after.[65] We have recently shown in a single case 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 proinflammatory cytokines (Fig. 4).[34]

ANTIBIOTICS

There are no controlled data in the literature addressing whether early use of antibiotics is associated with reduced incidence of HE. As referred to earlier, Rolando et al[33] have suggested that systemic inflammatory response as a result of microbial infection is likely to be important in those who progress to advanced stages of HE. Whether such a progression is reduced by the use of antibiotics has not been demonstrated. Because the prophylactic use of parenteral and enteral antibiotics is associated with lower rates of infection ($p < 0.005$),[66] these data suggest—in an indirect manner—that prophylactic antibiotics may reduce the incidence of intracranial hypertension. The choice of the antibiotic should be decided by local microbiology.

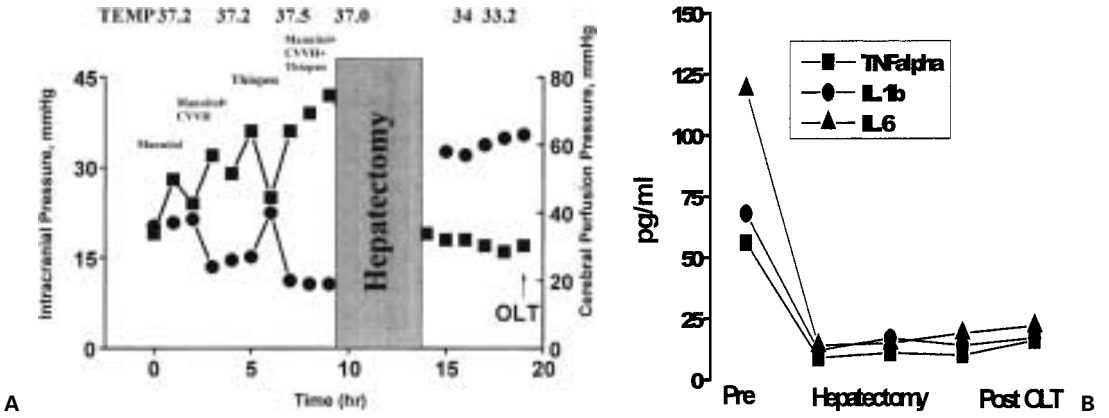

Figure 4 The changes in (A) ICP (represented by open squares) and cerebral perfusion pressure (represented by open circles) and (B) the proinflammatory cytokine profile in a single patient who underwent hepatectomy. It is interesting to note that the hepatectomy resulted in concomitant hypothermia and raises the question whether the improvement noted after hepatectomy was modulated at least in part through the effects of hypothermia (data from Jalan et al[34]).

Affecting Multiple Pathways—Mild Hypothermia

Both the biological and the nonbiological extracorporeal liver support systems that affect multiple pathways have marked effects on ICP. Similarly, OLT reverses liver failure, thereby leading to improvement in ICP (although the ICP may remain elevated for 12 to 24 hours) and will not be discussed further.

Mild to moderate hypothermia has been extensively studied in patients with head injuries, and its use has been explored in a number of animal models of ALF. Peignoux et al,[67] Eguchi et al,[68] and Traber et al[69] showed that hypothermic rats (32 to 33°C) with ALF had significantly less brain water, reduced duration of encephalopathy, and less clinical neurological deterioration compared with euthermic rats. Brain edema was accompanied by an increase in CBF in the control rats, which was not observed in the hypothermic animals, suggesting that the beneficial effects of hypothermia may be through a reduction in cerebral hyperemia, which is important in the pathogenesis of intracranial hypertension in ALF. In another study, Rose and colleagues[70] observed similar protection and suggested that this protective effect was due to a reduction of cerebrospinal fluid ammonia and extracellular glutamate concentrations. The preceding studies provided the rationale for the evaluation of the role of hypothermia in patients with ALF.

UNCONTROLLED INTRACRANIAL HYPERTENSION

Data from our first seven patients have been fully published.[71] We have now treated a total of 20 patients with ALF who fulfilled the King's College criteria for poor prognosis and had uncontrolled increase in ICP that was refractory to standard treatment. Patients were cooled to 32°C. All 6 patients who were not suitable candidates for OLT died after rewarming. Thirteen of the 14 patients who were candidates for OLT were successfully bridged to OLT with a mean of 31.8 (9.1, range 10 to 118) hours of cooling. Prior to cooling the ICP was elevated at 36.5 (2.7) mmHg and this was reduced to 17.1 (0.9) mmHg at 4 hours, which was sustained at 24 hours (16.3 [1.3] mmHg) ($p < 0.001$) (Fig. 5A). Despite cooling, ICP increased to 48 mmHg in 1 patient who devel-

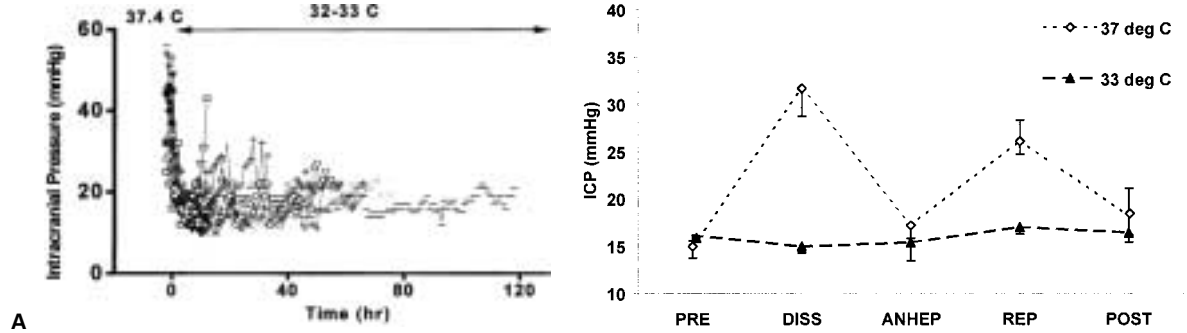

Figure 5 (A) The effects of hypothermia on ICP in 14 patients with ALF and uncontrolled increase in ICP awaiting OLT. Thirteen patients were successfully bridged to OLT and 1 patient (open square) died with increased ICP. (B) This figure shows changes in ICP in patients undergoing OLT. One group (open diamonds) was maintained as normothermic and the other group underwent OLT at a median of 33ºC (open triangle). There were significant increases in ICP in the normothermic patients during the dissection (DISS) and the reperfusion (REP) phases that were not observed in those that were hypothermic. (PRE, before transplant but after anesthesia; ANHEP, anhepatic phase; POST, 2 hours after transplantation). Data from Jalan et al.[73]

oped signs suggestive of cerebral herniation and was removed from the waiting list for OLT. Of the 7 patients who were treated with hypothermia for more than 24 hours, 5 developed transient increases in ICP to greater than 20 mmHg, which responded to additional treatment with mannitol. All had normal neurological recovery apart from 1 patient who required prolonged rehabilitation for muscle weakness because of prolonged hospital admission. Death in the 3 patients after OLT were due to multiorgan failure in 2 patients (possibly from sepsis) and from primary graft nonfunction in 1. CBF was reduced from a mean of 78.2 (9.7) mL/100 g per minute to 46.6 (3.8) mL/100 g per minute at 4 hours after cooling, and this was sustained at 10 to 24 hours (44 [1.8] mL/100 g per minute) ($p < 0.001$). CBF autoregulation was restored with cooling.[72] These effects on ICP and CBF were associated with significant improvement in cardiovascular hemodynamics manifested by increased mean arterial pressure and systemic vascular resistance and reduced noradrenaline requirements.

In addition, moderate hypothermia reduced the arterial ammonia concentration by about 30% and ammonia delivery to the brain by 66%. This was coupled with a reduction in extraction of ammonia by the brain from about 11% to values, which were not significantly different from zero.[71] The brain produced glutamine prior to cooling, and this was reduced to values not different from zero, suggesting that hypothermia inhibits the major ammonia-metabolizing enzyme, glutamine synthetase. In addition, hypothermia reduced proinflammatory cytokines tumor necrosis factor–alpha (TNF-α), interleukin-1β (IL-1β), and IL-6 significantly (R. Jalan, unpublished data, 2003).

PREVENTION OF RISE IN ICP

Five patients with ALF who fulfilled the criteria for poor prognosis and had Grade IV HE but an ICP of < 20 mmHg were included in the study and were cooled to 35°C from the time of mechanical ventilation until OLT, spontaneous recovery, or death. Three of the 4 patients were successfully bridged to OLT, with a mean cooling period of 53.8 hours (median 17.5, range 23 to 119). One of the patients recovered without need for OLT, and 1 patient died 120 hours after inclusion into the study from sepsis and multiorgan failure. Prior to 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

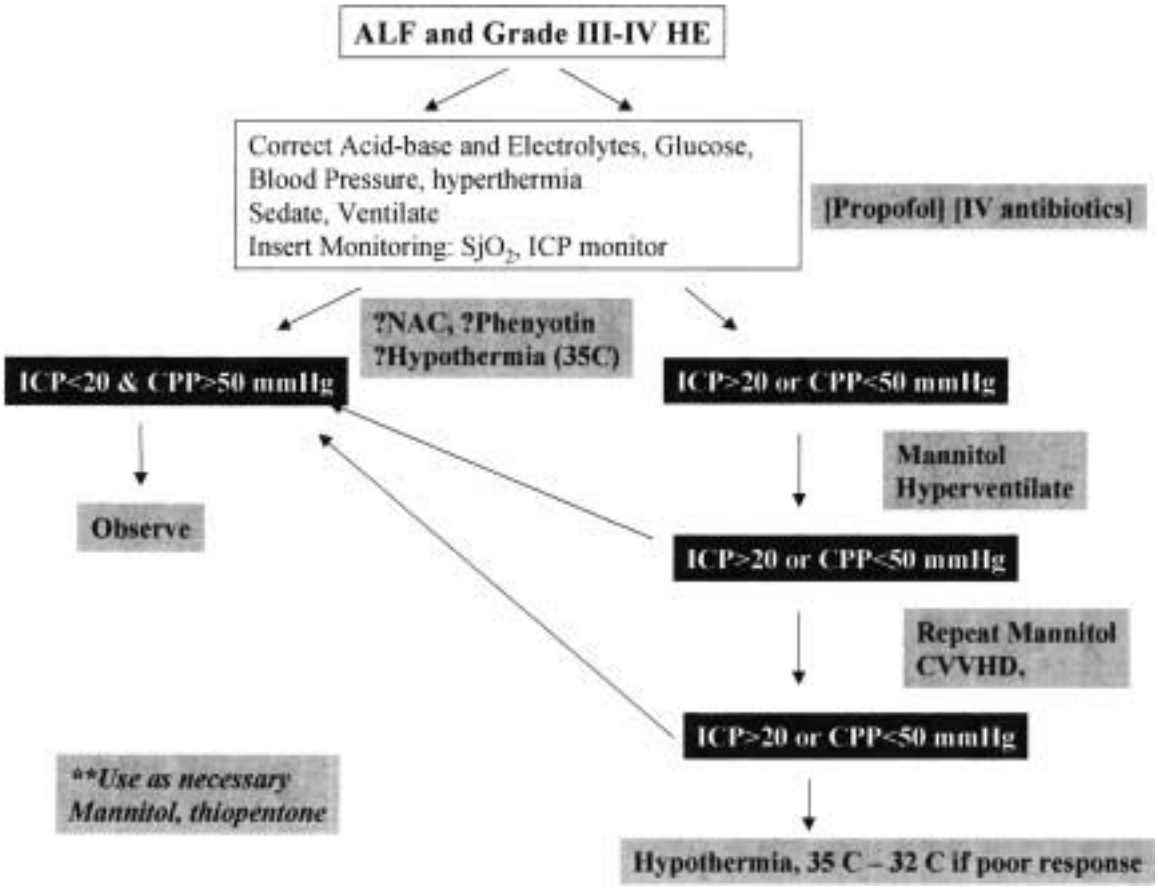

Figure 6 An algorithm for the management of increased ICP in ALF. (NAC, N-acetylcysteine; CPP, cerebral perfusion pressure; CVVHD, continuous venovenous hemodiafiltration); SjO_2, jugular venous oxygen saturation; HE, hepatic encephalopathy; ICP, intracranial pressure.

hours, which was sustained at 24 hours (15.9 [1.3] mmHg) ($p < 0.05$). There were no significant changes in CBF during the cooling period (unpublished data).

PREVENTION OF INCREASE IN ICP DURING OLT

During the dissection and reperfusion phases of the OLT in ALF patients, increases in ICP are inevitable, and current therapies are limited to using barbiturates as treatment, with their attendant difficulties. In this study we compared the changes in ICP between a group that was maintained as hypothermic and another group that was maintained as normothermic during OLT. There were significant increases in ICP in the normothermic group during the dissection and reperfusion phases of the operation, which was not observed in the hypothermic group. The rise in the ICP in the normothermic group was associated with significant increase in CBF, which was not observed in patients in the hypothermic patients (Fig. 5B).[73]

Although the data on the use of hypothermia as therapy for increased ICP in ALF and during OLT are not from randomized controlled studies, they provide evidence of efficacy and safety in patients with uncontrolled ICP and those that are undergoing OLT. In patients who have severe HE but not increased ICP, mild hypothermia reduces the risk of developing increases in ICP. The mechanism by which hypothermia acts in ALF is well worked out and suggests that it reduces ICP by reducing arterial ammonia and its brain metabolism, reducing CBF and restoring its autoregulation, and reducing inflammatory response.

CONCLUSIONS

The mechanisms associated with the development of increased ICP in ALF are complex and likely to be due to multiple interacting factors. Increased ICP is an important cause of death in patients with ALF, and an aggressive approach to monitoring and therapy is essential if outcome is to be improved. An algorithm for the management of patients with advanced stages of HE in ALF is outlined in Figure 6. It is possible that with newer agents that reduce ammonia and its brain uptake and alter brain glutamine and glutamate metabolism and possibly anti-inflammatory cytokine therapy we may start to make further advances toward prevention of intracranial hypertension in ALF. Given the relatively small number of patients with ALF, it will be important in the future to explore the place of existing treatments and newer therapeutic modalities in appropriate multicenter studies.

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ABBREVIATIONS

ALF acute liver failure
CBF cerebral blood flow
ICP intracranial pressure
OLT orthotopic liver transplantation

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