Preventing cerebral oedema in acute liver failure: the case for quadruple-H therapy

S. J. WARRILLOW*, R. BELLOMO†
Department of Intensive Care, Austin Health, Heidelberg, Victoria

SUMMARY
Severe cerebral oedema is a life-threatening complication of acute liver failure. Hyperammonaemia and cerebral hyperaemia are major contributing factors. A multimodal approach, which incorporates hyperventilation, haemodiafiltration, hypernatraemia and hypothermia (quadruple-H therapy), may prevent or attenuate severe cerebral oedema. This approach is readily administered by critical care clinicians and is likely to be more effective than the use of single therapies. Targeting of PaCO₂ in the mild hyperventilation range, as seen in acute liver failure patients before intubation, aims to minimise hyperaemic cerebral oedema. Haemodiafiltration aims to achieve the rapid control of elevated blood ammonia concentrations by its removal and to reduce production via the lowering of core temperature. The administration of concentrated saline increases serum tonicity and further reduces cerebral swelling. In addition, the pathologically increased cerebral blood-flow is further attenuated by therapeutic hypothermia. The combination of all four treatments in a multimodal approach may be a safe and effective means of attenuating or treating the cerebral oedema of acute liver failure and preventing death from neurological complications.

Key Words: cerebral oedema, acute liver failure

Acute liver failure (ALF) is a relatively uncommon reason for admission to intensive care in Australia, with approximately 50 patients cared for annually¹. These patients tend to be young, have good pre-morbid health and yet are dramatically ill. Mortality rates with best supportive care have been reported as up to 80%, and liver transplantation is the only proven treatment for patients dying of ALF²,³. Co-ordinated management strategies have not been well studied and treatment is often centre-specific⁴. Severe cerebral oedema is a key clinical problem and a major cause of death in ALF⁷–¹⁰. Important risk factors and underlying pathophysiological processes have been identified, which may contribute to cerebral oedema complicating severe hepatic encephalopathy⁹. No single element of current treatment strategies is likely to provide demonstrable improvements in patient outcome when evaluated in isolation. However, it is possible that the co-ordinated implementation of a multimodal ‘bundle of care’ targeting the pathophysiology of cerebral oedema would protect such patients from a neurological death.

Pathophysiology of cerebral oedema in ALF

Brainstem herniation is a common cause of death in ALF¹²,¹³ and occurs because of severe cerebral swelling causing refractory intracranial hypertension¹⁴. Classic features of severe cerebral oedema with resultant intracranial hypertension are difficult to reliably detect in the context of hepatic coma¹⁵,¹⁶, and it is reasonable to assume its presence in the deeply encephalopathic patient and treat in a proactive manner to prevent neurological death.

The pathophysiology of ALF-associated cerebral oedema is complex, but the accumulation of metabolic toxins, especially ammonia, is considered a key factor¹⁷,¹⁸. Loss of cerebral vascular autoregulation is a second important contributing process¹⁸,¹⁹. Both are amenable to therapeutic intervention¹⁸,¹⁹,²⁰–²⁴, and the application of a synergistic suite of interventions that impact on several steps of this process is likely to confer benefit²⁵.

Toxic injury to astrocytes

ALF results in the accumulation of a range of neurotoxins, especially ammonia. Ammonia is a key
Figure 1: The hepatic urea cycle is responsible for the majority of ammonia detoxification and hyperammonaemia is inevitable in the case of extreme loss of liver function. \( \text{NH}_3 = \text{ammonia} \), \( \text{NH}_4^+ = \text{ammonium} \).

Figure 2: Hyperammonaemia from acute liver failure causes cerebral oedema through cerebral vasodilation, astrocyte swelling and an increase in interstitial fluid volume. The processes involve increases in glutamate concentrations, loss of regulation over crucial enzymes (such as alpha-ketoglutarate and lactate dehydrogenase) and mitochondrial dysfunction. COX = cyclooxygenase, PG = prostaglandins, iNOS = inducible nitric oxide synthase, NO = nitric oxide, \( \text{NH}_3 = \text{ammonia} \).
waste product of nitrogen metabolism. The liver accounts for the majority of ammonia detoxification via the urea cycle and is the major route of clearance (Figure 1). Increased blood ammonia levels cause ammonia concentrations within the brain to rise due to its ready passage across the blood-brain barrier (BBB) via diffusion and through ion channels. High levels of ammonia within the brain cause neuroexcitation and astrocyte swelling via increased glutamine production and release. Other cellular functions adversely affected by high ammonia levels within the astrocyte include calcium regulation, enzymatic function, free radical generation, protein synthesis and mitochondrial performance (Figure 2). While blood ammonia concentrations may have a non-linear and somewhat unpredictable relationship with the severity of encephalopathy in chronic liver disease, very high levels (>117 μmol/l) have been shown to be highly associated with the development of severe cerebral oedema and severe intracranial hypertension in ALF. Other identified risk factors for progression to intracranial hypertension in the setting of severe encephalopathy include prolonged elevations in blood ammonia concentrations, younger age, need for renal replacement therapy and need for vasoactive infusions. The explanation as to why patients with decompensated cirrhosis infrequently develop significant cerebral oedema presumably relates to astrocyte adaptation in chronic hyperammonaemia. ALF also results in increasing concentrations of many other central nervous system (CNS) depressants, false neurotransmitters and inflammatory mediators, which reduce consciousness. While these are likely to worsen encephalopathy and coma, their contribution to cerebral oedema is less well understood. Importantly, however, most, if not all, of these mediators are small water-soluble solutes, which may be removed by extracorporeal therapy.

**Vasogenic oedema**

Cerebral blood flow (CBF) is normally tightly regulated across a wide range of systemic arterial blood pressures. Patients with chronic hepatic encephalopathy have a reduced cerebral metabolic rate (CMR) and concordantly lower CBF. Hepatic encephalopathy from ALF, however, is associated with relative or absolute increases in CBF despite progressive coma. In the case of severe hepatic encephalopathy from ALF, loss of autoregulatory control of CBF results in marked hyperaemia, which, coupled with ammonia-induced disruption of tight junctions throughout the BBB, causes seepage of plasma constituents into the cerebral interstitium. Several mechanisms appear to underlie the development of cerebral hyperaemia. These include increases in neuronal nitric oxide synthase activity resulting in excessive production of nitric oxide, as well as alterations in the activity of other vasodilatory mediators such as prostaglandins and other eicosanoids (Figure 2). This pattern of an absolute and relative increase in CBF (above that driven by systemic arterial blood pressure or required for CMR) is characteristic of ALF-associated severe encephalopathy and does not generally occur in the context of decompensated chronic cirrhosis.

Because increased CBF is an important contributing factor in the development of cerebral oedema, the pursuit of increased systemic arterial blood pressure to achieve a designated cerebral perfusion pressure may paradoxically be deleterious. This is in contrast to the neuro-critical care of patients with CNS injury resulting from severe, closed head injury or from subarachnoid haemorrhage, where vasospasm and cerebral ischaemia may be important pathophysiological factors.

**Monitoring and measurement of cerebral status in ALF**

The development of severe cerebral oedema inevitably results in elevations of intracranial pressure. Once the relatively modest buffering mechanisms are exhausted, intracranial pressure increases as per the Monro-Kellie hypothesis. Predictive factors for intracranial hypertension include Grade III or IV encephalopathy (which will be present in many patients requiring intubation for ALF) and very high levels of blood ammonia. Features of very high intracranial pressure include deep coma, hypertension, bradycardia, dilated pupils and abnormal posturing in response to a painful stimulus. However, such findings are not universal and are, furthermore, unlikely to be clear-cut in the context of a shocked patient exhibiting multiple organ failure. These complexities of clinical assessment make accurate determinations of neurological status extremely challenging in ALF patients, and a range of strategies have been utilised in an attempt to provide an objective guide. Such strategies frequently include direct measurement of intracranial pressure via invasive catheters or solid-state devices. Alternative approaches include techniques which attempt indirect measures of cerebral perfusion and oxygenation, such as jugular venous bulb saturation monitoring, near infrared spectroscopy and transcranial Doppler ultrasound. However, none of these approaches have been shown to favourably impact on outcome and the measurement data obtained are not always readily...
interpretable for guiding management decisions. Furthermore, invasive modalities have uncertain indications and no proven mortality benefit for patients with intracranial hypertension due to liver failure or in other contexts, and yet carry potential risks for these coagulopathic patients (Figure 3).

Electroencephalography has been proposed as a means of detecting subclinical seizures and ischaemia in patients with severe hepatic encephalopathy. Computed tomography may not demonstrate abnormalities until oedema and increases in pressure are advanced, but is indicated if focal deficits are evident clinically, especially to exclude the rare complication of spontaneous intracranial haemorrhage secondary to coagulopathy.

**Management of cerebral oedema and intracranial hypertension**

Given the relatively small number of patients presenting with severe ALF at risk of cerebral oedema, conducting adequately sized trials to determine the impact of specific single interventions on outcome is difficult. Nonetheless, a suite of supportive therapies with biologically plausible mechanisms that target key pathophysiological processes may provide protection. These are additional to conventional neurological nursing care such as head elevation, a low stimulus environment and avoidance of upper body venous congestion. Delayed attempts to address severe hyperammonaemia and associated severe cerebral oedema may result in treatment failure if neurological injury has progressed to the point where a harmful positive feedback cycle of progressive damage is established.

A range of physical and pharmacological interventions have been proposed for treating cerebral oedema and many have been subjected to small studies to assess efficacy. While several provide benefit, the clinical significance of their impact has been questioned. This may be because strategies based upon a single approach address only some aspects of the complex pathophysiological pathways involved. It is logical that a more comprehensive approach which combines hyperventilation, induced hypothermia, therapeutic hypernatraemia and haemodiafiltration to target several aspects of the underlying problems would be more effective.

**Hyperventilation**

Patients with severe ALF routinely hyperventilate spontaneously, even when in advanced states of encephalopathy. It is crucial that this phenomenon is appreciated at the time of intubation and initiation of mechanical ventilation in order to avoid inadvertent relative or absolute hypercapnia. Minute ventilation volumes should be set which target a PaCO2 equal to that present prior to intubation. At the very least, PaCO2 should be maintained at the lower end of the normal range (35 mmHg). More extreme hyperventilation is not recommended as a routine management strategy. Hyperventilation reduces intracranial hypertension via changes in pH of the cerebral interstitial fluid, which induces cerebral vasoconstriction. Given that cerebral hyperaemia is a hallmark of ALF, some reduction in CBF from mild hyperventilation is theoretically beneficial and appears to be safe. The reduction of intracranial pressure (ICP) resulting from more extreme hyperventilation is transient and subsequent normalisation of PaCO2 may result in rebound increases of ICP to disastrous levels. Aggressive hyperventilation should therefore be reserved only for otherwise refractory major elevations of ICP. The reactivity of cerebral blood vessels to manipulation in PaCO2 is preserved in ALF encephalopathy, and some degree of autoregulation may be restored through increased minute volume without adversely impacting cerebral oxidative metabolism.

**Haemodiafiltration**

Continuous renal replacement therapy (CRRT) provides a range of benefits for patients with ALF-associated cerebral oedema. Renal failure is very common in ALF, from either the initiating insult (e.g. severe paracetamol toxicity is directly injurious to the renal tubule), or from the associated systemic
inflammatory response and vasodilatory shock. CRRT has, therefore, been primarily considered as a means of addressing the direct consequences of renal failure itself, but its benefits might be broader. Haemodiafiltration may actually be a crucial part of a comprehensive neuroprotective strategy and should be commenced early, rather than waiting for manifest evidence of renal failure (e.g. refractory oliguria). In this regard, CRRT probably has its greatest impact through clearance of ammonia, and its intensity should be modulated to achieve adequate control of hyperammonaemia.

Ammonia has similar electrochemical kinetics to urea in terms of diffusive and convective clearance techniques, with both modalities being effective. Dialytic therapies appear modestly more effective than convective techniques and for patients with extreme levels of hyperammonaemia. Prolonged dialysis, using modalities such as Slow Low Efficiency Dialysis or hybrid modes (such as diafiltration), may be useful. However, temporary cessation of therapy is not logical in these patients, making intensive CRRT a more rational approach. The intensity of therapy is important and the ‘dose’ of therapy should be directed to achieve effective reductions of blood ammonia to as close as possible to normal levels (less than 60 to 70 μmol/l). For convective clearance, this generally equates to 40 to 50 ml/kg/hour of CRRT intensity. In addition to early application and intensity of therapy, it is important to minimise interruptions of CRRT in order to ensure continuity of ammonia clearance and exposure to the other benefits provided by the treatment. Many patients do not require anticoagulation, as severe liver failure is usually associated with a coagulopathic state. Heparin administration does not improve filter life, and bleeding complications associated with CRRT are relatively frequent. Ensuring high rates of blood-flow (200 to 300 ml/minute) and introducing some replacement fluid as a diluent pre-filter during haemofiltration are effective means of reducing the likelihood of clot forming within the CRRT circuit.

CRRT is also an extremely effective way of inducing hypothermia and controlling core temperature within a tight therapeutic range. Ensuring that the CRRT machine’s heater unit is turned off is a necessary step in this strategy, and clinicians must monitor true core temperature carefully during periods where CRRT is interrupted. CRRT also allows a degree of additional control of serum electrolytes, fluid balance and acid-base physiology. In particular, CRRT allows complete and continuous control of fluid balance. This is important because the administration of blood and/or blood products is common in ALF and can easily lead to fluid overload that, in turn, can contribute to pulmonary and cerebral oedema. The maintenance of a near-neutral fluid balance is another important step aimed at minimising the risk of cerebral oedema. Clinically important uraemia is rare in severe ALF. Extreme degrees of liver failure inevitably lead to major reductions in urea production through loss of the hepatic contribution to the urea cycle. The early initiation of high-intensity CRRT ensures that urea levels rarely rise far above the normal range. A requirement for phosphate administration is common to avoid serious hypophosphataemia, especially if higher intensity CRRT is applied and if liver regeneration occurs. Phosphate levels should be monitored at least twice daily, and supplemental phosphate (approximately 60 to 80 mmol/day) is typically needed.

Intermittent haemodialysis should not be used in ALF as, in the setting of cerebral oedema, the resultant loss of continuous control over hyperammonaemia, sodium concentration, core temperature and fluid balance could be highly detrimental. In addition, most patients with ALF are in an advanced state of shock and do not tolerate the circulatory effects of intermittent dialysis.

**Hypernatraemia**

Osmotherapies for cerebral oedema rely on some degree of integrity within the BBB in order to exert a beneficial effect. By increasing serum tonicity, the administration of concentrated saline induces the egress of water from brain tissue into the bloodstream. Sodium has a slightly higher reflection coefficient than mannitol (1.0 versus 0.9) and is effective in inducing cerebral dehydration. Hypertonic saline may also expand the circulating volume without contributing to an overall positive fluid balance. Microcirculatory benefits as well as modification of the inflammatory response within the CNS may also be important mechanisms of cerebral protection with hypertonic saline. By stabilising cell membranes, maintenance of the BBB integrity is also improved, therefore also reducing the propensity of plasma water to move into the brain interstitium during hyperaemic states. Osmotherapy using concentrated saline may improve cerebral vasoregulation by reducing blood viscosity and decreasing endothelial oedema, thus lowering capillary resistance. These rheological effects may secondarily lead to cerebral vasoconstriction. Such a mechanism would be advantageous in the context of the pathologically elevated cerebral blood-flow seen in severe hepatic encephalopathy.
Therapeutic hypernatraemia may be readily achieved by a continuous infusion of hypertonic saline. Continuous infusion of 20% sodium chloride via a dedicated central line lumen allows a low volume to be given, is easily titratable and can be dosed according to serum sodium measurements obtained via point-of-care arterial blood gas analysis. Serum sodium concentrations maintained between 145 to 155 mmol/l via the administration of concentrated saline appear to be beneficial and safe, with little risk of deleterious metabolic or circulatory adverse consequences.

Mannitol has similar initial benefits on elevations on ICP in ALF and has been used for over 30 years. In the setting of clinical findings consistent with severely elevated intracranial pressure or ICP measurements >25 mmHg, the commonly recommended bolus dose is 0.5 to 1.0 g/kg. However, it is potentially problematic due to the risk of delayed worsening of cerebral oedema if it enters into brain tissue through a damaged BBB after repeated dosing and induces a ‘reverse’ osmotic gradient. For patients with persisting urine output, there is also the theoretical risk of an uncontrolled osmotic diuresis and resultant hypovolaemia, which could worsen any existing shocked state. The use of mannitol in a prophylactic manner has not been studied.

Hypotonic fluids should always be avoided in patients with cerebral oedema. If a patient with ALF requires administration of intravenous glucose to prevent hypoglycaemia, concentrated solutions given via a dedicated central line lumen are preferred.

**Hypothermia**

The deliberate lowering of core body temperature has been utilised for a range of neurological conditions and is now a well-established means for preventing secondary brain injury in survivors of cardiac arrest. As such, it is readily and safely applied to critically ill patients worldwide. Several explanations have been proposed regarding the beneficial effects observed in the cerebral oedema of ALF. Hypothermia slows basal metabolic rate, attenuates proteolysis, reduces ammonia production by intestinal flora and hence, reduces splanchnic ammonia production. Cerebral ammonia levels are reduced through decreased cerebral ammonia uptake and production within the CNS. Astrocyte glutamate transporter function is also improved after reductions in brain ammonia levels, resulting in reduced neuro-excitation through normalisation of glutamate neurotransmitter inactivation. Cerebral cytokine production and oxidative stress are also diminished with hypothermia, reflecting reduced inflammation and maintenance of aerobic metabolism. Hypothermia also ameliorates cerebral hyperaemia so that the vasogenic contribution to cerebral oedema is significantly attenuated.

Most studies in severe ALF-associated cerebral oedema have targeted a core temperature range of 32°C to 33°C, but higher targets of up to 35°C are also effective and may be safer. Lower temperatures may provide further cerebral protection, but with an increased theoretical risk of complications such as immunosuppression and sepsis. External cooling is usually effective, possibly in part due to the generalised vasodilatation present in most patients with ALF. At the initiation of therapy, muscle relaxants may be required to prevent shivering. Sedation requirements are variable and may be reduced due to the existing encephalopathic state. Servo-controlled cooling blankets are very effective, as is the application of continuous renal replacement therapy, during which the blood warmer module can be turned off. Fever must be carefully avoided to prevent exacerbating cerebral complications.

The necessary duration of therapy can be difficult to know and depends on the need and timing for transplantation or recovery in some cases (e.g. paracetamol-induced ALF). Periods of up to five days of therapeutic hypothermia have been suggested as safe. Carefully controlled re-warming can be guided by evidence of general recovery in the context of normal (or near normal) blood ammonia levels and should occur over 48 to 72 hours to prevent rebound increases in ICP. Continuous monitoring of core temperature using a thermistor-tipped bladder catheter or similar device is necessary to achieve the required precision of thermal measurement.

**RESCUE THERAPIES FOR REFRACTORY CEREBRAL OEDEMA**

**Deep sedation and muscle relaxants**

Most patients with high-grade hepatic encephalopathy do not require deep sedation, but occasionally agitation and neuromuscular irritability can interfere with some components of treatment and contribute to worsening intracranial pressure. Transient improvement may be obtained through deepening of sedation and the administration of a muscle relaxant if required. Difficulties with this approach include the masking of neurological signs, hypotension and risk of hypoventilation if sufficient mandatory breaths are not provided. Small doses of short-acting agents that impact minimally on the circulation are preferred. Propofol is an eff-
ective means of safely providing additional sedation in this context, although hypotension associated with its use may require the co-administration of vasopressor therapy. While aiming to achieve a predefined cerebral perfusion pressure may be undesirable in the setting of ALF cerebral hyperaemia, it is reasonable to target a mean arterial blood pressure of more than 60 mmHg in order to maintain adequate end-organ perfusion.

Severe ALF does not substantially impact on the pharmacokinetics of propofol, and the relatively short duration of effect avoids clouding the neurological assessment after infusion has ceased. Propofol slows CMR, reduces neuronal excitation and may impart anti-inflammatory as well as antioxidant effects. However, hypothermia may decrease propofol clearance and, in such patients, lower doses may be desirable. Thiopentone is another anaesthetic agent that has been used to manage severe intracranial hypertension. While it reduces CMR and blood-flow, prolonged infusion results in a lengthy duration of CNS depression, which may interfere with clinical assessment. Additionally, thiopentone can cause immune dysfunction and metabolic abnormalities that are undesirable in the critically ill. As such, thiopentone should be reserved only for circumstances where all other measures have failed.

Further hypothermia

Lowering core temperature to less than 33°C may provide additional reductions in cerebral oedema and intracranial pressure as a rescue therapy via the mechanisms outlined above. Complications might include worsening coagulopathy, vulnerability to infections and impaired hepatic regeneration.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs cause cerebral vasoconstriction via a range of mechanisms involving inhibition of endothelial cyclooxygenase. Indomethacin is a potent cyclooxygenase inhibitor and may be effective in temporarily improving the hyperaemic cerebral circulation of ALF when other measures have failed. The transient nature of the effect, as well as potential side-effects, mean that indomethacin should be reserved for situations where a life-saving transplant is imminent and it is necessary to treat very high ICP during the perioperative period.

Seizure management

Seizures are not a prominent feature of ALF-associated neurological impairment, but should be considered in the event of deterioration or new evidence of elevations in ICP. Clinical manifestations may be subtle and an electroencephalogram is necessary under such circumstances to diagnose or exclude the possibility with certainty. In the event of focal neurological deficits or evidence of fitting, consideration for neuro-imaging via computed tomography is appropriate to exclude the rare possibility of a spontaneous intracranial haemorrhage associated with coagulopathy.
In the event of fitting, anticonvulsant therapy (such as benzodiazepines, propofol or levetiracetam) should be administered. Sodium valproate should be avoided due to the risk of further elevating ammonia levels. No role has been established for prophylactic anticonvulsant therapy.

**Advanced blood purification and other therapies**

A number of technologies have been developed for the purpose of cleansing the blood of toxic substances, which accumulate in severe liver failure with multiple organ dysfunction. These therapies utilise veno-venous extracorporeal circuits to apply various combinations of dialysis, haemofiltration and adsorption to the bloodstream in order to remove toxic metabolites and inflammatory mediators.

Coupled Plasma Filtration Adsorption diverts a modest proportion of plasma from the main blood circuit and passes it across a resin adsorbent before directing it back to rejoin the whole blood and directing it through a conventional haemofilter

The Molecular Adsorbent Recirculation System uses diffusive techniques in two stages—first, dialysing blood against an albumin-rich intermediate fluid, which is then secondarily diafiltered and run through a charcoal haemoperfusion and resin adsorbent cartridge

Case series and small studies have demonstrated effective clearance of several purported metabolic toxins from the blood. Haemodynamic and metabolic benefits have also been described, although evidence of compelling clinical benefits is less clear.

Given that neuroprotection may be achievable via conventional CRRT, advanced blood purification therapies such as Coupled Plasma Filtration Adsorption and the Molecular Adsorbent Recirculation System are perhaps best reserved as rescue therapies for refractory intracranial hypertension, or for advanced states of shock. Vasodilatory shock associated with the severe systemic inflammatory response of ALF may improve through clearance of toxins and various mediators from the circulation. Further research in the form of randomised controlled trials is required to clarify the role of such strategies.

Plasma exchange has also been shown to provide some benefit in preliminary studies, but remains an experimental therapy in the context of acute liver failure.

L-ornithine-L-aspartate and L-ornithine phenylacetate administration have been studied as an alternate means of reducing blood ammonia concentrations on the basis of promising preliminary animal and clinical studies. By providing crucial urea cycle substrate, ammonia metabolism is accelerated. Further evaluation is required to ascertain their therapeutic potential and safety profile.

**Other important aspects of care**

As with any critical illness, the clinical problems of severe ALF result from the complex interplay of parallel pathophysiological processes affecting a range of organ systems. With advanced and inter-dependent multiple organ failure, a co-ordinated approach to management ensures that all the important issues are addressed in an appropriately prioritised manner. In addition to the approaches already detailed, close attention must be paid to ensuring that metabolic, haematological, cardiovascular and respiratory aspects of care are addressed.

Close monitoring of clotting parameters is necessary; however, serious bleeding is rare and measurements of the International Normalized Ratio, while often abnormal, do not necessarily reliably predict bleeding tendency. It may be that many patients with acute liver failure are actually hypercoagulable, despite routine test results suggesting otherwise, and a balanced approach to clotting factor administration is advisable in order to avoid thrombotic complications.

Serious infection is a common cause of death and complications, so the early empirical initiation of appropriately broad-spectrum antimicrobials (antifungal agents as well as antibiotics) is recommended along with a comprehensive microbiological evaluation.

**CONCLUSIONS**

Severe cerebral oedema with resultant intracranial hypertension is a common cause of death in ALF. The combination of hyperventilation, haemodiafiltration, hypernatraemia and hypothermia (quadruple-H therapy) addresses a range of pathophysiological processes which underlie the development of cerebral oedema (Table 1), and it is likely that maximal benefit will be obtained when initiated at the time high-grade encephalopathy first develops. Whereas the use of single therapies may have some effect, the use of all four treatments simultaneously may be required to achieve a clinically significant impact on the attenuation of cerebral oedema. All are within the scope of experienced intensive care units to provide, as they are relatively simple to administer and involve minimal additional expense beyond that incurred through routine care. Prospective studies to evaluate the impact of quadruple-H therapy on outcome are warranted.
REFERENCES


Anaesthesia and Intensive Care, Vol. 42, No. 1, January 2014


