Management of Cerebral Edema in Acute Liver Failure

Beverley Kok, MBBS1  Constantine J. Karvellas, MD, SM1

1 Division of Gastroenterology (Liver Unit), Department of Critical Care Medicine, University of Alberta, Edmonton, Canada

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Address for correspondence  Constantine J. Karvellas, MD, SM, FRCPC, Division of Gastroenterology (Liver Unit), Department of Critical Care Medicine, University of Alberta, 1-40 Zeidler Leducor Building, Edmonton, Alberta T6G-2B8, Canada (e-mail: dean.karvellas@ualberta.ca).

Acute liver failure (ALF) is a condition wherein a patient with a previously healthy liver rapidly deteriorates, resulting in jaundice, coagulopathy, and encephalopathy. This is usually accompanied by peripheral vasodilatation, features of the systemic inflammatory response syndrome, and ultimately multigorgan failure.1 The development of hepatic encephalopathy (HE) marks the transition from acute liver injury to ALF, and the timing of HE relative to the onset of jaundice plays a key role in defining prognosis.2 In the context of ALF, high-grade encephalopathy is commonly a manifestation of cerebral edema that may progress to cause death from cerebral herniation.3,4

There are approximately 2,000 cases per year of ALF in the United States, and approximately 1 in 6 cases per million annually throughout the world.5–7 Acetaminophen-induced ALF is the most common in developed nations, though viral infections are the predominant cause in developing countries.8

Previously, cerebral edema occurred in up to 80% of patients with ALF, contributing to the most common cause of death in ALF from herniation.3 Incidence of cerebral edema in ALF has, however, markedly declined over the past three decades.9 A review of more than 3,300 patients presenting to Kings College Hospital (the largest liver transplantation [LT] program in Europe) over a 35-year period showed the proportion of ALF patients who developed intracranial hypertension had fallen from 76% during 1984–1988 to 20% during 2004–2008 (p < 0.0001).5 Mortality from intracranial hypertension had also fallen from 95 to 55% (p < 0.0001), likely a consequence of earlier illness recognition, improved intensive care, and use of emergency LT.9

Despite these improvements, brain herniation from cerebral edema remains one of the leading causes of mortality in ALF, following sepsis or sepsis-induced multigorgan failure.10 Once cerebral edema is present, it is associated with poor outcomes and complex management is required.9,11 This review will focus on the management of cerebral edema and intracranial hypertension in ALF.

Pathophysiology

Cerebral edema is a net increase in total brain water content. The rigid cranium protecting the brain limits its compliance, and small increases in fluid can cause significant rise in intracranial pressure (ICP), leading to decreased cerebral perfusion pressure (CPP) and capillary blood flow, causing ischemia.11 If sufficiently severe, cerebral edema culminates in tentorial brain herniation and death.11
The mechanisms behind the development of cerebral edema in ALF are complex and multifactorial, though cytotoxic edema (predominantly related to ammonia) is recognized to play a central role. Other mechanisms involved include vasogenic edema and impaired cerebral autoregulation. Ammonia predominantly originates from small bowel and is metabolized to urea by the liver through the urea cycle. In ALF, failure of the liver to detoxify ammonia leads to increases in serum ammonia. Ammonia diffuses across the blood–brain barrier easily. It is exclusively detoxified by glutamine synthetase contained within astrocytes into glutamine. Glutamine accumulation within astrocytes acts as an organic osmolyte drawing water and resulting in astrocytic swelling. In addition, glutamine may transport ammonia into mitochondria (“Trojan Horse hypothesis”) inducing oxidative and nitrosative stresses that impair mitochondrial function and further potentiate astrocyte swelling. Mediators of systemic inflammatory response and proinflammatory cytokines may also act synergistically with ammonia to induce cerebral edema, though these pathways are less well characterized.

To a much smaller extent, altered blood–brain barrier permeability may exacerbate cerebral edema through a vasogenic mechanism. Magnetic resonance imaging of patients with ALF demonstrating interstitial brain edema lends support to this theory.

Impaired cerebral autoregulation and cerebral hyperemia have been reported in clinical and animal models, exacerbating raised ICP with ALF. Cerebral autoregulation usually serves to maintain a stable cerebral blood flow (CBF) to the brain commensurate with metabolic demands despite variations in mean arterial pressure (MAP). This mechanism is disrupted in ALF allowing inappropriate rises in CBF with increased MAP, or vice versa with hypotension.

### Clinical Diagnosis of Cerebral Edema in ALF

Early recognition of cerebral edema is important, as prolonged exposure may result in cerebral ischemia with permanent neurological disability and significant morbidity and mortality. The goals of treating cerebral edema are hence not only to prevent herniation but also to optimize neurological recovery.

ALF patients who are particularly at risk for developing substantial cerebral edema include those with a more rapid progression of liver injury to HE, such as those with hyperacute or acute presentations (i.e., acetaminophen), those with high-grade HE (grade III/IV), high serum ammonia (>150–200 µmol/L), younger individuals (age < 35 years), those with infection and/or systemic inflammatory response syndrome, those with high Sequential Organ Failure Assessment (SOFA) scores, and those requiring vasopressors or renal replacement therapy (RRT).

The risk of cerebral edema increases to 25 to 35% with grade III HE and 65 to 75% or more in patients reaching grade IV HE.

ALF patients should have frequent examinations (at least every 2 hours) concentrating on pupil size, coma grade, evidence of delirium, and deep tendon reflexes. The development of grade II or higher HE should result in transfer to a critical care area, with development of grade III HE usually necessitating intubation and ventilation. As cerebral edema may not always be associated with clinical signs, ammonia may also be useful in guiding preemptive management in this respect. Arterial ammonia >150 to 200 µmol/L predicts a greater likelihood of developing or dying from brain herniation.

Development of raised ICP should be suspected with sudden-onset systemic hypertension, changes in pupillary reactivity (usually dilatation), and abnormal oculovestibular reflexes or decerebrate posturing, though these signs are neither specific nor sensitive for elevated ICP. Seizures and agitation are frequently present. While computed tomography is insensitive in detecting cerebral edema, its usage is worthwhile to rule out other intracranial pathology such as hemorrhage.

### Monitoring: To Bolt or Not to Bolt?

Invasive ICP monitoring remains the most accurate tool for diagnosis and management of cerebral edema, though its use is limited by a 1 to 10% risk of significant intracranial hemorrhage and the limited evidence proving clinical benefit. ICP in ALF may suddenly rise from normal to life-threatening levels within minutes, and in this situation continuous ICP monitoring allows rapid and specific management.

The United States ALF Study Group (ALFSG) as well as several other groups recommend the placement of ICP monitors in patients with high-grade HE (grade III/IV). An approach by Kings College Hospital is to monitor ICP in patients with clinical signs or evidence of evolving cerebral edema.

Other indications for increased risk and hence invasive ICP monitoring may include ammonia >150 to 200 µmol/L; listing for LT; meeting Kings College criteria for poor prognosis; the presence of multisystem organ failure, HE and hyponatremia, HE and seizures, and the presence of abnormal jugular venous oxygen saturations, and transcranial Doppler ultrasonography (TCD) indicating very high or very low CBF. Clinical endpoints for...
ICP monitoring are not standardized, but most centers aim to achieve an ICP < 20 to 25 mm Hg and CPP > 50 to 60 mm Hg.\textsuperscript{55,62,63}

In a recent survey of 22 high-volume transplantation centers in 11 countries, ICP monitoring in ALF was employed in 12 centers, with the most common indications being papilledema and acute kidney injury.\textsuperscript{62} The overall proportion of patients with grade III HE and above who underwent ICP monitoring was low, even in centers that performed this procedure often. Among the centers that did utilize ICP monitoring, six centers reported using it in <25% of the patients with high-grade HE and four centers performed monitoring in >75% of patients with high-grade HE. Earlier surveys from the United States have similarly showed decreasing use of ICP monitoring.\textsuperscript{50} Use of fresh-frozen plasma, cryoprecipitate, and platelets prior to ICP monitor insertion may be required,\textsuperscript{63,66} though additional dynamic assessments of coagulation such as with thromboelastography may aid in the decision making in the correction of coagulopathy.

Such trends of decreased use of ICP monitoring may be a reflection of evidence to date failing to demonstrate a survival benefit.\textsuperscript{62} In a large multicenter retrospective cohort study, Karvellas et al\textsuperscript{52} showed that raised ICP was present in 51% of those with ICP monitors, and patients with ICP monitoring received significantly more cerebral edema–directed therapies. Hemorrhagic complications leading to death were low (5%), but there was no 21-day mortality benefit in acetaminophen–related ALF patients who received monitoring, and a worse prognosis in the non-acetaminophen group. These results are similar to earlier retrospective studies that did not demonstrate improved survival with ICP monitoring, although complication rates were low.\textsuperscript{50,54,57,64} Jugular venous oxygen saturation monitoring in addition to ICP monitoring is recommended by some groups; this provides an indication of cerebral metabolism and oxygenation, which become abnormal with the loss of CBF autoregulation.\textsuperscript{60,65}

TCD offers a noninvasive alternative to obtaining indirect evidence regarding ICP and CBF;\textsuperscript{66} though there are limited data to guide clinical use specifically in ALF.\textsuperscript{67,68} It may be useful in patients with severe coagulopathy at high risk for bleeding complications, and has an added advantage over standard invasive monitoring in its ability to estimate CBF.\textsuperscript{69} Reduced blood flow on TCD can indicate cerebral edema, although it may be inaccurate for mild–to–moderate ICP elevations.\textsuperscript{69} Alternative noninvasive monitoring techniques such as continuous neurophysiological monitoring, near-infrared spectroscopy, optic nerve sonography, and pupillometry are not validated in ALF.\textsuperscript{70}

**General Measures: Prophylaxis**

It is recommended that patients with ALF and impending cerebral edema be managed in an intensive care unit (ICU); the U.S. Acute Liver Failure Study Group (ALFSG) guidelines propose that an ICU setting is indicated with progression to grade II HE.\textsuperscript{55} Management in the ICU aims to provide organ support with continuous monitoring of central hemodynamic parameters, but, in addition, should encompass neuroprotective measures designed to prevent the development or ameliorate the severity of raised ICP (Table 2).\textsuperscript{1,59}

Progression to grade III/IV HE should prompt sedation with propofol, intubation, and ventilation.\textsuperscript{55,71} In a recent multicenter survey, grade II HE was the most common grade of HE prompting transfer to an ICU or high dependency bed, and most centers intubated patients at grade III HE.\textsuperscript{62}

Propofol has anticonvulsant properties and may reduce ICP by reducing CBF.\textsuperscript{49,60,72,73} Seizures should be treated, but prophylactic phenytoin has not been shown to reduce the incidence of seizures nor mortality in ALF.\textsuperscript{74,75} Positive end-expiratory pressure (PEEP) may also increase ICP when mean airway pressures are increased and should be used carefully.\textsuperscript{76} though PEEP < 15 has not been shown to affect ICP significantly.\textsuperscript{70} Procedures provoking high intrathoracic pressures (such as endotracheal suctioning) may also result in venous outflow obstruction and should be minimized.\textsuperscript{55,77} Environmental stimulation should be minimized.\textsuperscript{44,55}

Due to impaired cerebral autoregulation, systemic hypotension may reduce CPP and induce brain ischemia, though hypotension may also increase ICP.\textsuperscript{78} A reasonable goal is to aim for a MAP of > 75 mm Hg.\textsuperscript{79} Central venous pressure should be maintained at < 20 mm Hg to avoid impeding cerebral venous return.\textsuperscript{80} In patients with persistent hypotension despite volume repletion, norepinephrine is the preferred vasoressor, with or without adjunctive vasopressin or vasopressin analogs.\textsuperscript{81}

If cerebral edema is confirmed, the head should be in neutral position and the head of the bed elevated to 30 degrees\textsuperscript{82} to maximize cerebrospinal fluid and venous drainage.\textsuperscript{76,83} Some with markedly compromised CPP may not tolerate elevation of the bed, and so it is always necessary to make individual assessments.\textsuperscript{45}

Use of lactulose may cause bowel distention and ileus and should be limited.\textsuperscript{70} Hypoglycemia should be treated, but large-volume infusions of hypotonic fluids which may result in hyponatremia and worsen cerebral swelling should be avoided.\textsuperscript{1}

Currently, the use of prophylactic antibiotics and antifungals in patients with ALF is not generally recommended, though periodic surveillance is advocated.\textsuperscript{84}

**Intracranial Pressure–Lowering Measures**

Once cerebral edema has developed, the main strategies for improving it can be classified into those aimed at reducing brain volume and those reducing CBF (Table 3).\textsuperscript{60}

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**Table 2** General measures in patients with cerebral edema

<table>
<thead>
<tr>
<th>Measure</th>
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<tbody>
<tr>
<td>Intubation and ventilation in high-grade hepatic encephalopathy</td>
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<tr>
<td>Sedation with propofol</td>
</tr>
<tr>
<td>Minimal environmental stimulation</td>
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<tr>
<td>Head in neutral position; head of bed elevated to 30 degrees</td>
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**Table 3** Intracranial pressure–lowering measures

<table>
<thead>
<tr>
<th>Measure</th>
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<tbody>
<tr>
<td>Positive end-expiratory pressure (PEEP)</td>
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<tr>
<td>Positive inotropes</td>
</tr>
<tr>
<td>Attenuate dopamine</td>
</tr>
<tr>
<td>Mannitol (5% or 20%)</td>
</tr>
<tr>
<td>Hypertonic saline</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>Fresh-frozen plasma</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
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<tr>
<td>Platelets</td>
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<tr>
<td>Thromboelastography</td>
</tr>
<tr>
<td>Optic nerve sonography</td>
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<tr>
<td>Near-infrared spectroscopy</td>
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<tr>
<td>Sedation</td>
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<tr>
<td>ventilation</td>
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<tr>
<td>Inotropes</td>
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<td>Near-infrared spectroscopy</td>
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Table 3 Intracranial pressure–lowering measures

<table>
<thead>
<tr>
<th>Reducing brain volume</th>
<th>Reducing cerebral blood flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous renal replacement therapy</td>
<td>Propofol sedation</td>
</tr>
<tr>
<td>Hypertonic saline53</td>
<td>Forced</td>
</tr>
<tr>
<td>Mannitol52</td>
<td>Hyperventilation108, a</td>
</tr>
<tr>
<td></td>
<td>Moderate hypothermiaa</td>
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</tbody>
</table>

*Only in refractory situations.

Reducing Brain Volume

Recently published clinical practice guidelines from the European Association of the Study of Liver (EASL) for the management of ALF have recommended the use of either hypertonic saline (HTS) or mannitol as the first-line therapy in established cerebral edema, in addition to optimal sedation.43

HTS and mannitol both ameliorate cerebral edema predominantly via an osmotic dehydration effect, promoting a fluid shift from the brain to the intravascular compartment, reversing cerebral edema and ICP.85,86

Hypertonic Saline

The efficacy of HTS in lowering ICP is similar to mannitol87,88 and may result in a more prolonged reduction to ICP, though this difference may be restricted to the first bolus.88 In the only prospective randomized controlled clinical trial involving HTS in the management of ALF, HTS was shown to be beneficial in reducing the incidence of intracranial hypertension, and decreased ICP relative to controls.53 Some guidelines hence advocate the prophylactic use of HTS in those at highest risk of developing HE,108, a

Reducing Cerebral Blood Flow

In the context of ALF, disrupted cerebral autoregulation to ICP leads to cerebral hyperemia.100 Reduction of CBF may be mitigated by processes that either reduce brain metabolism or result in cerebral vasoconstriction.

Pharmacologic Coma

Propofol

Propofol decreases the cerebral metabolic rate and oxygen demands and hence reduces CBF.101 It has been shown to control ICP in ALF patients.102 Propofol has beneficial anticonvulsant properties and permits a faster return to wakefulness, as its pharmacokinetics are not influenced by liver failure;103 hence, its use has largely replaced barbiturate-induced coma. Propofol sedation is usually utilized early in

those with intracranial hypertension significantly reduced ICP, though there was a lack of effect in those with renal failure82 or severe intracranial hypertension (>60 mm Hg).94 Though a range of doses have been used in patients with ALF (0.25–1.0 g/kg),36,92 the EASL 2017 guidelines recommend a bolus of 50 mL, 20% to be administered over 20 minutes.43 The U.S. ALFSG guidelines recommend that mannitol therapy may be repeated once or twice, so long as serum osmolality remains <320 mOsm/L.55

Mannitol will transiently expand circulating blood volume, and concurrent ultrafiltration may be required to prevent rise in central venous pressure and to maintain euvolemia.55 Once administered, serum osmolality should be assessed regularly, though it has been shown that serum osmolality correlates poorly with mannitol concentrations, and a normal osmolar gap may be a more accurate measure of adequate mannitol clearance prior to administration of subsequent doses.94 A maximal serum osmolality of <320 mOsm/L is generally quoted, though this was derived from limited evidence to prevent renal tubular damage, and breaching this target may not be harmful provided the patient is not volume depleted.55,96 Repeated use of mannitol may be especially associated with serious adverse effects such as intravascular volume depletion, rebound ICP elevation, and renal failure from mannitol accumulation.95,97

Renal Replacement Therapy

Slack et al demonstrated that early initiation of RRT with continuous veno-venous hemofiltration is an effective method of decreasing the level of circulating ammonia, with a clear correlation between creatinine clearance and ammonia clearance.98 Continuous rather than intermittent dialysis is generally used to achieve greater metabolic and hemodynamic stability.99 Though initiation of RRT primarily for hyperammonemia rather than acute kidney injury has not been studied in a randomized controlled fashion, the latest EASL guidelines recommend the early consideration of continuous RRT for those in ALF with persistent hyperammonemia and/or progressive HE, control of hyponatremia and metabolic abnormalities, fluid balance, and potentially temperature control.43

Propofol sedation is usually utilized early in
the course of ALF to facilitate intubation and ventilation once a patient develops high-grade HE, and hence offers potential protection from the development of intracranial hypertension.

**Barbiturates**

Barbiturates such as thiopental or pentobarbital reduce the cerebral metabolic rate and may be utilized to decrease ICP. Due to their side-effect profile, however, they are generally considered a short-term salvage therapy. Although previously recommended in refractory cases, rescue therapy with barbiturates has now been replaced by alternative strategies in many liver units. Potential adverse effects with barbiturate coma include loss of neurological exam, risk of infection, cardiac depression, and significant systemic hypotension.

**Hyperventilation**

Forced hyperventilation induces hypocapnia and precapillary vasoconstriction and decreases CBF and ICP. Hyperventilation has also been shown to restore impaired cerebral autoregulation in ALF, though this effect may be short-lived. Hyperventilation carries a serious risk of provoking cerebral ischemia, and hence it should only be used in situations of cerebral hyperemia (which may be monitored by measuring jugular bulb saturations). The U.S. ALFSG recommends that spontaneous hyperventilation need not be treated, and targeting a low-normal PaCO₂ (4–4.5 kPa) may be adopted instead. The utility of forced hyperventilation is in emergency rescue therapy of patients with evidence of diencephalic herniation. If employed, it should not be used for sustained periods. Some recommend that hyperventilation be stopped as soon as cerebral edema is controlled by other means. EASL 2017 guidelines recommend a short period of hyperventilation in resistant scenarios to reduce arterial PaCO₂ to 25 to 30 mm Hg.

**Moderate/Therapeutic Hypothermia**

The protective effect of hypothermia has been attributed to a reduction in the cerebral metabolic rate and brain energy demands. Hypothermia also protects neurons by maintaining the integrity of the lipoprotein membrane and decreasing enzymatic reactions that lead to cell damage or death. In ALF, further protective mechanisms of moderate hypothermia (MH) include: (1) normalization of CBF; (2) reduction of arterial ammonia concentrations by slowing down protein catabolism; which together decrease delivery of ammonia to the brain; (3) reduced uptake of ammonia by the brain; (4) attenuating pathways that occur downstream of ammonia exposure within the brain, resulting in decreased lactate and glutamate accumulation and decreased cytokine production. In practice, clinical studies in ALF have achieved MH through the use of cooling blankets with targeted temperature measurements based on either superficial or core body temperatures.

Jalan et al demonstrated that in patients with ALF who fulfilled poor prognosis criteria with raised ICP refractory to mannitol and ultrafiltration, MH to 32 to 33°C core temperature resulted in rapid control of ICP, reduction in CBF, increase in CPP, and reduction in arterial ammonia and cerebral uptake of ammonia. Subsequent studies by the same group demonstrated good outcomes and safety of using MH as a bridge to and during LT in ALF patients with refractory intracranial hypertension who would not otherwise have been considered suitable candidates.

Clinical studies to date have, however, not demonstrated a beneficial impact on the prevention of intracranial hypertension with MH. Karvellas et al in a retrospective cohort study investigated the impact of MH on the prevention of elevated ICP and transplant-free survival in ALF patients with grade III–IV HE deemed high risk for developing intracranial hypertension. No differences in 21-day overall or transplant-free survival were found, though MH appeared to be associated with improved survival in young patients (< 25 years) with acetaminophen-ALF. The authors concluded that the results of their study could not conclusively confirm or refute the utility of MH for the prevention of intracranial hypertension in ALF patients. In the only multicenter randomized controlled trial regarding MH in ALF, Bernal et al investigated the prophylactic role of MH in ALF patients at high risk of cerebral edema. In their cohort of 43 patients, hypothermia at 34°C was administered for 72 hours and did not confer a benefit above 36°C in prevention. The trial was terminated early due to futility and an observed trend toward worsened ICP in those who received MH.

Adverse event rates appear to relate closely to the minimum temperatures induced. Increased occurrence of sepsis has been observed in those cooled below 33°C, though arrhythmias have also been reported. Other reported concerns with MH, such as worsening of coagulopathy or reduced hepatic regeneration, have not been observed in the ALF clinical trials so far. Risks associated with rewarming have, however, not been specifically addressed in the published literature so far. Although rewarming after LT appeared to be safe, a high death rate was observed to occur during or immediately following rewarming due to rapid rebound of ICP. Due to the possibility of rebound ICP, invasive ICP monitoring should probably form a necessary requirement as part of MH therapy, though there is currently a lack of evidence to support this.

Presently, MH remains a recommended treatment option, but only in those with refractory ICP elevation. There is no evidence to support an optimal temperature or duration of MH. In the absence of refractory ICP elevation, a pragmatic approach to temperature management is to avoid fever and maintain a core body temperature of 35 to 36°C.

**Indomethacin**

Indomethacin acts by inducing cerebral vasoconstriction through multiple mechanisms. Though shown to be effective in reducing ICP in refractory intracranial hypertension, its use should only be in the context of hyperemic CBF to be accompanied by concurrent jugular venous bulb saturations monitoring due to risk of compromising
CBF. It is currently indicated only if ICP remains elevated despite mannitol or HTS.43

Others

Plasmapheresis/Artificial Liver Support
Larsen et al investigated the effects of high-volume plasmapheresis in 12 patients with ALF (11 of who had grade IV HE) and reported a significant improvement in grade of HE and median CPP, although CBF was increased and ICP remained unchanged.129 These results showing improvement in cerebral hemodynamics were not replicated in a subsequent prospective randomized controlled trial looking at ALF patients (with minimum of grade II HE), although the authors report that the latter study was not sufficiently powered to observe any potential benefit.130 Use of albumin dialysis with the Molecular Adsorbent Recirculating System (MARS) in a randomized controlled trial of ALF patients did not demonstrate any significant improvement to ammonia levels or HE, though its effect on modulating cerebral edema is uncertain as none of the patients in the study had received ICP monitoring.131

Total Hepatectomy
Therapeutic hepatectomy in patients awaiting LT may be of value in desperate situations.39,132 The proposed hypothesis for this measure is that removing “necrotic liver” may reduce liver-derived proinflammatory cytokines, reducing nitric oxide and CBF as well as improving mediator-induced cytotoxic injury.133,134

Conclusion
Several options exist for the treatment of established intracranial hypertension in ALF and may successfully bridge patients to definitive treatment of transplantation. The utility of invasive ICP monitoring remains controversial, but is indicated in high-risk cases and could be supported by additional noninvasive monitoring (such as reverse jugular saturations and TCD). Further work is needed in delineating futility of treatment in patients with cerebral edema who are not suitable for LT.

Conflict of Interest
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