

# Who should undergo intracranial pressure monitoring in acute liver failure?

A Concise Clinical Review

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## Abstract

The hallmark of acute liver failure is hepatic encephalopathy, which often presents with the devastating complication of cerebral edema. Given the extremely high mortality rate associated with the development of cerebral edema, it is prudent to aggressively manage this pathology. One tool that is used to guide treatment of cerebral edema is an intracranial pressure monitor. This article will review the literature regarding the use of intracranial pressure monitors in acute liver failure in an effort to elucidate their utility in this setting.

## What is acute liver failure?

Acute liver failure (ALF) is defined as the presence of synthetic hepatic dysfunction and encephalopathy of less than 26 weeks duration.<sup>1,2</sup> While there have been a myriad of modern classifications of acute liver failure that contribute to the difficulty in defining the clinical syndrome,<sup>3,4,5,6,7</sup> the King's College Criteria are the most widely accepted that define laboratory values for acetaminophen and non-acetaminophen-based acute liver failure for liver transplantation consideration.

**Table 1.** Kings College criteria for liver transplantation.



Fulminant hepatic failure, that defined the syndrome prior to the broadened classification of ALF, initially was defined as a “potentially reversible severe liver injury, with the onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease.”<sup>8</sup> More recently, fulminant hepatic failure has become a subset of ALF, defined as the onset of encephalopathy anywhere from 2-8 weeks from the onset of jaundice, depending on the classification system.<sup>4</sup> Up to 60% of patients with ALF will require liver transplantation and 80% will survive.

## Why do patients develop acute liver failure?

In the United States, approximately half of all causes of acute liver failure are due to drug ingestion, most notably acetaminophen overdose.<sup>9,10</sup> This overdose may be intentional (as a suicide attempt) or “accidental” in the context of ingestion of narcotic/acetaminophen combination. This distinction may be important in assessing the psychological suitability of a candidate for liver transplantation.

Worldwide, however, viral organisms are the most common cause of ALF with a greater than 50% mortality rate in the developing world.<sup>4,11</sup> Recreational drug use (specifically 3,4-methylenedioxy-methamphetamine, or “ecstasy”), acute ischemic injury, neoplasm, Budd-Chiari syndrome, heatstroke, mushroom ingestion, and Wilson’s disease are less common causes of acute liver failure.<sup>4,11,12</sup> Lastly, a large number of cases of ALF do not have an identifiable etiology and therefore classified as idiopathic.

As progression to encephalopathy is part of the very definition of ALF, there has been significant interest in its prognosis and treatment. Encephalopathy frequently presents with cerebral edema, which portends an extremely poor prognosis and is the leading cause of death in these patients.<sup>4</sup> Although dramatically improved with the advent of critical care, rates of intracranial hypertension (ICH, intracranial pressure >25 mm Hg)<sup>3</sup> in ALF for grade 3-4 encephalopathy remain 20-29%, with a mortality rate of 55% among those who develop ICH.<sup>13</sup>

**Table 1.** West Haven hepatic encephalopathy grades with Amodio modifications.

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<http://journal.pulmccm.org/wp-content/uploads/2015/06/Table-2-ICP-monitoring-during-liver-failure-11-19-2-SM.docx-2015-06-23-07-44-31.jpg>

## Why do patients with acute liver failure develop intracranial hypertension?

Given the liver’s extensive role as both a synthetic and metabolic organ, acute liver failure can affect every organ system. In all causes of ALF, the end result is hepatocyte death. Hepatocyte death signals damage-associated molecular pathways, which in turn lead to the activation of macrophages. The macrophages aim to protect the liver from worsening injury, but in fact release cytokines that contribute to a prolonged and destructive immunological response.<sup>14</sup> In addition, depletion of glutathione reserves and other natural antioxidants result in a buildup of toxic metabolites, which further hepatocyte destruction and acute liver failure. The disease process is manifested by systemic vasodilation, immunologic incompetency, electrolyte abnormalities, coagulopathy, and hepatic encephalopathy.

The pathophysiology between the progression from hepatic encephalopathy to intracranial hypertension (ICH) is not completely understood, although ammonia appears to play a role that is accentuated by inflammatory cytokines.<sup>15,16,17,18,19,20</sup> In ALF, ammonia levels increase due to the liver’s inability to convert ammonia into urea.<sup>17</sup> Cerebral conversion of ammonia to glutamine results in increased intracellular osmolarity with corresponding fluid shifts into cells, cerebral edema, and in turn, decreased cellular function.<sup>15,16,17,18</sup> The drug l-ornithine-l-aspartate (LOLA) is known to assist detoxification of ammonia to glutamine in muscle cells. However, clinical use of this drug in a large randomized study was unable to show a reduction in ammonia levels, encephalopathy, or mortality in patients with acute liver failure.<sup>21</sup> Specifically, 201 patients with ALF were randomized to receive placebo or LOLA infusion for 3 days. Ammonia levels were measured for the

following 6 days. Both groups saw a significant decrease in ammonia level over time, but there was no significant difference in the decrease between the two groups. There was no difference in mortality, encephalopathy, or other complications such as seizures and renal failure.

Additionally, there are patient specific factors that influence the likelihood of developing ICH. Infection, systemic hypotension, and other inflammatory mediators may trigger the syndrome.<sup>4</sup> Normal osmotic compensatory mechanisms often fail when the onset of ALF is rapid so patients with the most acute presentation of ALF (such as acetaminophen overdose) are at the highest risk of developing cerebral edema.<sup>4,13</sup>

## **Which patients should receive an ICP monitor, and where should it be placed?**

Intracranial pressure (ICP) monitoring is a commonly used diagnostic and/or therapeutic intervention in traumatic brain injury (TBI). The Brain Trauma Foundation Guidelines recommend the use of ICP monitoring for TBI patients in a coma with an abnormal CT scan or a normal CT with a combination of hypotension, age >40 years, severely depressed neurologic status (GCS motor <3 or pupillary abnormalities), or inability to follow patient's neurologic exam.<sup>22</sup> The benefits of ICP monitoring in patients with TBI are controversial, as a recent multicenter randomized controlled trial failed to show any difference in functional or cognitive status, mortality, or adverse event when comparing outcomes in TBI patients treated with and without an ICP monitor.<sup>23</sup>

In non-TBI patients, the indications are less clearly defined. Indications include reduced (?8) Glasgow coma score, cerebral edema on imaging, neurological worsening, and mass effect.<sup>24</sup> ICP monitoring may be considered in reversible/treatable pathologic processes that result in cerebral edema, such as meningitis/encephalitis, hypoxic ischemic injury, ischemic stroke, and hepatic encephalopathy.<sup>24</sup> ICP monitors can be placed in several different locations within the cranium including the brain parenchyma, ventricles, subdural or epidural spaces. Intraventricular catheters (IVCs) have the additional advantage of being able to drain cerebral spinal fluid (CSF) in an effort to lower ICP. Conversely, there also is an increased risk of infection as well as fatal hemorrhage given their location. Epidural placement has the lowest complication rate (3.8%), followed by subdural bolts (20%), and intraparenchymal monitors (22%).<sup>25,26,27</sup> Complications of ICP placement include brain hemorrhage, infection, and dislodgement.<sup>22</sup> Infection rates are as low as 0-1.8% in those with epidural placement, whereas a higher rate of 7.9% is reported in patients who have an IVC. Hemorrhage rates recently have been reported ranging from 2.5-10%,<sup>2,28</sup> with studies directly comparing catheter locations consistently revealing a higher rate for IVCs.<sup>29,30</sup>

## **What are the risks and theoretical benefits of ICP monitoring in acute liver failure?**

ICP monitoring is a potentially useful adjunct in the management of liver failure as it allows the physician to determine the severity of cerebral edema and to guide therapy, although there is always the risk of mistreating due to inaccurate readings. There are no universally accepted guidelines for ICP monitoring in ALF patients. Many centers utilize ICP monitoring in patients with grade III and IV hepatic encephalopathy.<sup>25,31</sup> High arterial ammonia levels have been shown to be associated with cerebral herniation,<sup>32,33</sup> and thus may be a useful adjunct for consideration of ICP monitoring, particularly for patients who are liver transplant candidates.<sup>34,35</sup>

The major concern regarding placement of an ICP monitor is intracranial hemorrhage, which is especially

problematic in patients with ALF. Initial data indicated a hemorrhage rate as high as 20% with ICP monitor placement in this patient population, but more recent reviews have shown a lower rate of bleeding in the range of 2.5-10%.<sup>2,28</sup> Prospectively collected data by Vaquero and colleagues of 332 patients with ALF and grade 3-4 hepatic encephalopathy found an intracranial hemorrhage rate of 10.3% (among the cohort of 92 patients who received an ICP monitor), with half being incidental radiology findings.<sup>28</sup> More recently, Karvellas evaluated 629 patients with ALF and grade 3-4 encephalopathy (140 who had ICP monitors placed) and found an intracranial hemorrhage rate of 7%.<sup>2</sup> Theoretically, ALF patients may be expected to have a higher risk of ICP infection due to their immunocompromised state, although no data support this contention.

Recombinant Factor VIIa, given prior to catheter placement, can minimize bleeding complications as secondary hemostasis is restored, although recombinant Factor VIIa is ineffectual in the setting of acidosis.<sup>36,37,38</sup> One small study evaluated 15 patients with ALF meeting King's College criteria for transportation, with 8 patients receiving fresh frozen plasma (FFP) alone and 7 receiving FFP and Factor VIIa. All patients receiving Factor VIIa had temporary (2-6 hour) correction of coagulopathy whereas none of the patients receiving FFP alone experienced this normalization. Due to this, all the patients in the Factor VIIa cohort underwent ICP placement, but only 38% of the FFP cohort. Lastly, 2 patients in the FFP group experienced bleeding complications, and there were no hemorrhagic complications in the Factor VIIa group.<sup>36</sup> In another study, 11 consecutive patients with ALF who received Factor VIIa for ICP monitor placement were evaluated following the procedure with a computed tomographic (CT) scan of the brain. There were no hemorrhagic complications noted in any of the patients in this study.<sup>38</sup>

## **How should ICP elevations be treated in acute liver failure?**

Simple bedside maneuvers should be attempted first to address an elevated ICP. The patient should be kept in a quiet environment in an effort to minimize tactile stimulation. Maneuvers causing a surge in ICP, such as coughing, gagging, agitation, seizures, fevers, hypertension, frequent turning, and suctioning should be avoided as much as possible.<sup>25</sup> The head of the patient's bed should be maintained upright greater than 30 degrees at all times to improve venous drainage. Administration of lactulose or a similar nonabsorbable antibiotic (such as rifaximin or neomycin) should be considered given the presumed involvement of ammonia in the pathophysiology of cerebral edema, although this is controversial as there is a lack of randomized controlled trials evaluating effect on ICP.<sup>19,25</sup> Some believe lactulose to be potentially deleterious in the setting of ALF, and should be avoided because there are no clinical trials to suggest a survival benefit and there is concern that ileus may be worsened in these patients.<sup>4</sup> For these reasons we agree with most authors that lactulose is not recommended for patients with ALF. A recent investigation has shown promise for the use of polyethylene glycol 3350-electrolyte solution (PEG) instead of lactulose in limiting hepatic encephalopathy in cirrhotics presenting with acute hepatic encephalopathy.<sup>39</sup> PEG has not been thoroughly investigated in patients with ALF, and cannot be recommended at this time.

The role of hyperventilation is limited to the short term. Hyperventilation to a pCO<sub>2</sub> level of 30-35 mm Hg causes cerebral venous and arterial vasoconstriction, thus decreasing the amount of extracellular blood in the cranium thereby decreasing ICP. Hyperventilation has been shown to restore cerebral blood flow autoregulation in patients with acute liver failure.<sup>40</sup> The concern remains, however, that prolonged hyperventilation will result in decreased cerebral perfusion and secondary brain injury.

The use of hypertonic saline for increased ICP in acute liver failure is extrapolated from its use in head trauma. Specifically, elevating plasma osmolality by administration of hypertonic saline or osmotic agents, such as mannitol, enables a reduction in cerebral water content and endothelial swelling, thus simultaneously reducing edema and improving perfusion.<sup>41,42,43</sup> In a small study of 45 patients, Murphy and colleagues found a

statistically significant reduction of ICP when hypertonic saline was used in patients with grade III and IV hepatic encephalopathy. The study did not find a difference in mortality between the groups.<sup>44</sup> One study in 34 patients found a reduction in cerebral edema when mannitol was administered to patients with fulminant hepatic failure. Furthermore, among the patients who developed cerebral edema, those who received mannitol had a statistically significant increase in survival.<sup>45</sup> Mannitol should be used judiciously in this patient population, as it is a diuretic and affects plasma osmolality. Thus its use is of limited value in patients with decreased end organ perfusion as is commonly the case in ALF.

Clinical observations have shown therapeutic hypothermia can reduce ICP<sup>46,47</sup> but further investigation is warranted before adoption into clinical practice. This effect is likely due to the fact that hypothermia slows the body's metabolism, shutting down many bodily functions and thereby lowering systemic production of ammonia as well as the cerebral uptake and metabolism.<sup>4,18</sup> However, a randomized control trial of patients with high grade encephalopathy failed to show a reduction of ICH in the experimental group. 33 patients with ALF and imminent cerebral edema receiving an ICP monitor were evaluated in a randomized controlled trial where the subjects were randomized to receive standard medical therapy or standard medical therapy plus hypothermia. This study demonstrated no reduction in the incidence of ICH or mortality.<sup>48</sup>

Indomethacin has been shown to induce cerebral vasoconstriction and increase cerebral perfusion pressure.<sup>49</sup> A small retrospective study of 12 patients with ALF and cerebral edema reviewed the effect of indomethacin on ICP measured by transcranial doppler ultrasonography (TCD). The measurements obtained from these 12 patients revealed that ICP significantly decreased and cerebral perfusion pressure (CPP) significantly increased following indomethacin injection, however, there was no control group for comparison.<sup>49</sup> Indomethacin is not routinely used in the treatment of intracranial hypertension in acute liver failure given the side effects of nephrotoxicity, platelet dysfunction, and gastrointestinal bleeding. Further investigation is warranted to evaluate the role of indomethacin as a rescue therapy for increased ICP.

In general, although sedation is to be avoided, propofol can be used to reduce ICP.<sup>50</sup> Although not involving ALF patients, a prospective multicenter randomized trial involving 42 patients with moderate to severe head injury showed a decrease in ICP in on day 3 in patients receiving propofol therapy as opposed to morphine. There was no significant difference between the groups in mortality or adverse events.<sup>51</sup> The mechanism of ICP reduction is thought to be related to metabolic suppression and decreased CPP.<sup>19</sup> Minimizing agitation can also contribute to avoiding ICP surges. Lastly, an additional benefit is that clearance of propofol is not affected by acute liver failure, and thus neurologic assessments off of propofol can be done expeditiously.

Historically, induction of barbiturate coma has been used to decrease ICP and decrease cerebral metabolism.<sup>19</sup> However, liver failure results in prolonged clearance of pentobarbital, and it has largely been replaced by propofol for induction of pharmacologic coma.<sup>19</sup>

Seizures increase cerebral oxygen requirements substantially and worsen cerebral edema.<sup>52</sup> A randomized trial of 42 patients showed that the experimental group receiving phenytoin prophylaxis had an equivalent rate of development of cerebral edema as well as seizures.<sup>52</sup> Given these findings, phenytoin prophylaxis is no longer used routinely.

Extracorporeal albumin dialysis (EAD) uses a combination of conventional hemodialysis to remove water-bound substances as well as albumin dialysis to remove albumin-bound substances.<sup>19</sup> Two porcine studies on pigs with ALF have shown that EAD decreases serum ammonia levels and improves cerebral hemodynamics.<sup>53, 54</sup> A meta analysis looking at 10 studies (9 randomized, 1 nonrandomized) showed that EAD improved hepatic encephalopathy but did not have a statistically significant effect on mortality.<sup>55</sup> One study found a higher risk of bleeding complications in patients using EAD, though these results are potentially confounded by the fact that the bleeding patients had worse coagulation profiles at baseline.<sup>56</sup> Thus EAD may have a role for decreasing

ICP in acute liver failure but its clinical indications have yet to be defined and is not currently recommended for routine use.[19](#)

## **Alternatives to conventional ICP monitoring in acute liver failure**

Given the complications associated with ICP monitor insertion, there has been interest in noninvasive ICP monitoring. Transcranial doppler ultrasonography (TCD) measures middle cerebral artery blood flow velocity, creating a velocity-time waveform that can be tracked to monitor changes in cerebral hemodynamics.[13](#) A retrospective study of 16 patients with ALF who underwent both TCD and ICP monitoring showed that TCD changes correlated with the ICP monitoring, lending credence to the use of TCD to monitor for dynamic changes in ICP in this patient population. Further studies are still needed, however, to define the clinical indications for TCD.[57](#)

## **Outcome difference of ICP monitoring in acute liver failure patients**

To date there have been no randomized controlled trials examining the utility of ICP monitoring in acute liver failure. Thus, it is difficult to speculate on the appropriate indications for its use in this population. Retrospective studies have been unable to show that monitoring confers a mortality benefit or improved neurologic outcomes.[2:28](#)

Karvellas and colleagues retrospectively reviewed 629 patients with grade III or IV hepatic encephalopathy (n=140 ICP-monitored patients and n=489 control non-monitored patients). Of the 75 ICP monitors with reported location, 17 were epidural, 20 subdural, 18 intraparenchymal, seven intraventricular, and 13 lumbar monitors. Of the 56 ICP monitors who had complication data available, four (7%) reported hemorrhagic complications. Three were intracranial in location and one spinal. In the first seven study days, patients with ICP monitors were significantly more likely to be on renal replacement therapy (52% vs. 38%), mechanical ventilation (98% vs. 82%), and vasopressors (55 vs. 39%). These patients were more likely to receive ICH therapies such as mannitol (56% vs. 21%), hypertonic saline (14% vs. 7%), barbiturates (25% vs. 5%), and hypothermia (24% vs. 10%). Patients with ICP monitors were more likely to receive fresh frozen plasma (84% vs. 61%) and platelets (43% vs. 25%). There was no significant difference in any complication measured (gastrointestinal bleeding, bacteremia, tracheal aspirate infection, abnormal chest radiograph or CT scan). The use of ICP monitoring, however, was associated with listing for liver transplant as well as receipt of liver transplant. There was no mortality benefit associated with ICP monitoring, and the authors performed a multivariable analysis that suggested worse outcomes with its use in the setting of non-acetaminophen induced ALF, though this was not seen in acetaminophen induced ALF.[2](#)

Vaquero and associated retrospectively reviewed 332 patients with acute liver failure and severe hepatic encephalopathy (n=58 ICP-monitored patients). Amongst the centers reviewed, there was wide range of use of ICP monitors, from 0 to greater than 75% of patients. Of the 58 ICP monitors whose location was reported, 63.8% were subdural, 20.7% were intraparenchymal, and 15.5% were epidural. Intraventricular catheters were not used at any center. Complications were noted in 6 of these 58 patients (10%), all of which were bleeding episodes. Three of these patients had clinical symptoms associated with the bleed. The patients with ICP monitors had a statistically significant higher use of mannitol, barbiturates, and vasopressors. Both groups of patients had similar 30-day mortality and there was no difference in other outcome measures.[28](#)

With a concurrent encephalopathy, the development of cerebral edema is often clinically silent and difficult to recognize. Proponents of ICP monitoring argue that changes made based on pressure readings can assist in

bridging patients during the critical time in which they wait for their liver transplant. Opponents cite the complication rates of ICP monitors and argue that if there is a suspicion of cerebral edema, it is reasonable to initiate treatment without utilizing an ICP monitor for guidance. At this time, routine use of ICP monitors cannot be recommended as any benefit remains unproven. Long term studies on neurologic outcomes as well as a prospective, randomized controlled trial are needed to determine the utility of ICP monitors in acute liver failure. Large transplant centers with experience utilizing these devices are best equipped to use ICP monitors in this patient population as well as design the randomized studies to evaluate their outcomes. Until these studies are available, ICP monitors should be used selectively in ALF.

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