Neurological Monitoring in Acute Liver Failure

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Cerebral oedema and Intracranial Hypertension (ICH) are serious complications of acute liver failure affecting approximately 30% of patients, resulting in neurological injury or death. Multiple pathogenetic mechanisms contribute to the pathogenesis of HE including circulating neurotoxins such as ammonia, systemic and neuro-inflammation, infection and cerebral hyperaemia due to loss of cerebral vascular autoregulation. Early recognition and diagnosis is often difficult as clinical signs of elevated Intracranial Pressure (ICP) are not uniformly present and maybe masked by other organ support. ICP monitoring provides early diagnosis and monitoring of ICH, allowing targeted therapeutic interventions for prevention and treatment. ICP monitoring is the subject of much debate and there exists significant heterogeneity of clinical practice regarding its use. The procedure is associated with risks of haemorrhage but may be considered in highly selected patients such as those with highest risk for ICH awaiting transplant to allow for patient selection and optimisation. There is limited evidence that ICP monitoring confers a survival benefit which may explain why in the context of risk benefit analysis there is reduced utilisation in clinical practice. Less or non-invasive techniques of neurological monitoring such as measurement of jugular venous oxygen saturation to assess cerebral oxygen utilisation, and transcranial Doppler CNS to measure cerebral blood flow can provide important clinical information. They should be considered in combination as part of a multi-modal platform utilising specific roles of each system and incorporated within locally agreed algorithms. Other tools such as near-infrared spectrophotometry, optic nerve ultrasound and serum biomarkers of brain injury are being evaluated but are not used routinely in current practice. (J CLIN EXP HEPATOL 2018;8:441–447)

Acute Liver Failure (ALF) can be defined as loss of hepatic function in a patient without pre-existing liver disease occurring in less than 24 weeks, as determined by coagulopathy (international normalised ratio [INR] ≥ 1.5) and any degree of hepatic encephalopathy (HE).¹ ALF is relatively uncommon, with an incidence of less than ten cases per million persons in the developed world but with a higher incidence in the developing world due to a significantly greater incidence of acute viral hepatitis.² ALF develops after a catastrophic insult to the liver resulting in massive hepatocellular necrosis leading to the development of a life-threatening multi-system illness. The pathogenesis of HE in ALF is multifactorial and can rapidly progress to cerebral oedema and raised Intracranial Pressure (ICP), with Intracranial Hypertension (ICH) (ICP > 25 mmHg) predisposing to cerebral herniation and death. Clinical manifestations of HE may include irritability, confusion, agitation, reduced

consciousness and coma. Whilst generally in decline ICH remains a frequent complication of ALF and associated with significant morbidity and mortality. Neurological monitoring is critical allow the early detection and targeted management of raised ICP in order to prevent neurological injury and death.

HE AND BRAIN OEDEMA IN ALF

Hyperammonaemia

The pathogenesis of HE in ALF is complex and multifaceted but neurotoxins, ammonia in particular has been shown to play a critical role. Reduction in ammonia detoxification due to hepatic insufficiency results in an increased cerebral burden of ammonia clearance triggering osmotic and cellular dysregulation, leading to cerebral oedema. Astrocytes are uniquely responsible for conversion of ammonia to glutamine by glutamine synthetase. Glutamine accumulation exerts an osmotic stress causing astrocytic swelling resulting in cytotoxic brain oedema. Hyperammonaemia in addition can impair brain energy metabolism,³ alter neurotransmission⁴ and induce mitochondrial dysfunction leading to oxidative stress and cerebral oedema.⁵ Although the mechanism of cerebral oedema is primarily cytotoxic, with the blood brain barrier remaining largely structurally intact,⁶ alterations in its permeability⁷ can result in presence of vasogenic oedema.⁸ Hyponatraemia can potentiate and exacerbate cytotoxic

Keywords: acute liver failure, intracranial hypertension, intracranial pressure, neurological monitoring

Received: 16 January 2018; **Accepted:** 25 April 2018; **Available online:** 5 May 2018

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Abbreviations: ALF: Acute Liver Failure; ICP: Intracranial Pressure; IHP: Intracranial Hypertension

<https://doi.org/10.1016/j.jceh.2018.04.013>

oedema and ICP in ALF patients with weak but significant inverse correlation demonstrated between serum sodium and first ICP measurement.⁹

An elevated plasma ammonia correlates not only with the severity of HE, levels $> 146 \mu\text{mol/L}$ predict cerebral herniation,¹⁰ and in those with an ammonia $> 200 \mu\text{mol/L}$, 55% of patients develop ICH,¹¹ but also mortality, an arterial ammonia of $> 124 \mu\text{mol/L}$ is predictive of mortality with 77.5% diagnostic accuracy.¹² Persistent arterial hyperammonaemia increases the concentration of glutamine in the brain correlating with raised ICP, however a reduction in ammonia leads to a reduction in ICP.¹³ Monitoring plasma ammonia levels and treatment of hyperammonaemia constitutes an important aspect in neurological management of ALF patients.

Systemic and Neuroinflammation

HE is critically modulated by inflammation, which may be “sterile inflammation” in response to the inflammatory mediators and damage associated proteins from necrotic hepatic cells, or secondary to infection and sepsis, which occur frequently in ALF. The systemic inflammatory response whether related to infection or not is associated with a worsening of HE and poorer prognosis.^{14,15} Neuroinflammation as evidenced by microglial activation¹⁶ and brain cytokine production contribute to the pathogenesis of HE, with cerebral cytokine flux positively correlating with uncontrolled ICP.¹⁷ Uncontrolled raised ICH, when treated with moderate hypothermia can decrease cytokine production (TNF- α , IL-1, IL-6) with a consequent reduction in ICP.¹⁸ However, no survival benefit has been found with use of moderate hypothermia in ALF patients with high grade HE in either a randomised control trial,¹⁹ or large retrospective case controlled series.²⁰

Cerebral Blood Flow (CBF)

Under normal circumstances CBF is tightly autoregulated to match metabolic demands. Although in ALF a wide spectrum of CBF has been noted,²¹ an uncoupling of this demand occurs²² with a increased blood flow relative to demand.²³ Loss of cerebral autoregulation to pressure is seen in ALF²⁴ such that an increased CBF can lead to raised ICP given the fixed volume of the skull. Cerebral hyperaemia is associated with increased rates of brain oedema and increased mortality.^{22,25} However, the cerebral vascular response to carbon dioxide remains intact,²³ thus hyperventilation to induce hypocapnic vasoconstriction to decrease CBF can be utilised as a short term strategy with those with raised ICP.

INCIDENCE OF ICH IN ALF

The incidence of ICH in ALF is becoming less frequent. In a study of over 3000 patients with ALF at King's College

Hospital, ICH occurred in 76% of patients in 1984–88 compared to in 20% of patients in 2004–08, associated was a corresponding drop in mortality in those with ICH from 95% to 55%.²⁶ In 165 patients with ALF and severe HE (grade 3 or 4), only 29% showed clinical signs of ICH, however of those with ICP monitoring, ICH was evident in 64%.¹¹ In a smaller study of 22 ALF patients with grade 3/4 HE almost all ($n = 21$) had at least one episode of ICH,²⁷ suggesting ICP spikes may occur without apparent clinical manifestations. The estimated risk of ICH in grade 3 HE is approximately 25–35% increasing to 65–75% in grade 4 HE.²⁸ ICH and cerebral herniation account for 30% of deaths in ALF patients managed without transplantation.¹¹ Risk factors for ICH include hyperacute or acute presentations,²⁹ younger age,¹¹ requirement of vasopressors or renal replacement therapy¹¹ and those with those with high Sequential Organ Failure Assessment (SOFA) scores.³⁰

The reducing incidence and mortality of ALF associated ICH is likely due to enhanced recognition coupled with overall improvement in the intensive care management of ALF patients.²⁶ Proactive targeted correction and monitoring of parameters such as infection, haemodynamics, electrolytes, temperature and carbon dioxide, which all influence the severity of HE and progression of ICP, with earlier institution of ammonia lowering therapy have been central. In addition, the advancement in neurocritical care of those with ICH has been positively influenced by translation of care from neurocritical patients, especially from those with traumatic brain injuries.

NEUROLOGICAL MONITORING IN ALF

Clinical and Radiological Monitoring

Regular clinical and neurological examination is mandatory in to monitor progression of HE and in early detection of raised ICP. The West Haven Criteria is a bedside tool that categorises HE into 4 stages based solely clinical criteria.³¹ Patients with grade 3 HE or above should be intubated and ventilated and neurological examination focus on assessing tone, reflexes especially hyperreflexia and clonus and pupillary responses.³² Clinical signs however are of limited reliability with regards to sensitivity and specificity of detecting early changes in raised ICP and may be masked by medication and cardio-respiratory support used to manage such patients. Abnormal pupillary responses and vasomotor signs such as spasticity and extensor posturing are often late signs as is Cushing's reflex (bradycardia and hypertension secondary to ICH). These may only occur in the context of severe ICP and neurological injury, thus their absence should not be relied upon to exclude raised ICP. Close attention to look for clinical signs of seizure activity is important as this occurs in 25% of ALF patients,³³ with the incidence of sub clinical seizures even higher.³⁴

Cerebral imaging with CT may be useful to exclude other aetiologies but is insensitive in detecting elevated ICP³⁵ and thus not routinely recommended, as a negative scan does not rule out ICH. MRI scanning is more sensitive for cerebral oedema but use is limited by the risks and logistics involved in performing for a critically ill ventilated patient. Given the challenges and inherent limitations in using standard clinical, biochemical and radiological parameters to diagnose and monitor raised ICP there is a need for real-time assessment of cerebral haemodynamic, biochemical and metabolic changes as markers of raised ICP.

Invasive ICP Monitoring (ICPM)

ICPM allows direct real time continuous measurements of ICP by placement of a catheter into the cranial cavity, either into the epidural, subdural or ventricular spaces or directly into the brain parenchyma. Although considered gold standard there is considerable debate surrounding its use. ICPM allows early detection of spikes in ICP, which can be clinically non-apparent.^{27,36} As cerebral perfusion pressure (CPP) is a function of MAP and ICP [$CPP = MAP - ICP$], any sustained spikes in ICP will compromise cerebral perfusion and may result in cerebral hypoxia. Specific targeted therapy can be delivered to normalise ICP in real time to maintain adequate cerebral perfusion pressures, with the aim of improving outcomes and allow optimisation for those undergoing transplantation. Patients with refractory ICH are likely to suffer from irreversible brain injury which may preclude them from undergoing liver transplantation.³⁷

Despite the putative advantages of ICPM there is significant heterogeneity in the clinical uptake and utilisation of this technique. In a prospective survey of 24 centres comprising the United States Acute Liver Failure Study Group (ALSG), ICPM was used only in 28% of patients with Grade 3 and Grade 4 HE, which comprised those in whom the risk of ICH was highest.³⁸ Certain centres used it more than others, with some centres not using it altogether. Similarly in a survey of members of the European Acute Liver Failure Consortium including 22 transplant centres in 11 countries, only 55% used ICPM, with only a small percentage of all patients with grade 3 HE or above having ICPM.³⁹ There also exists variability in the types of transducers used, with subdural catheters most common (63.8%) followed by intraparenchymal (20.7%) and epidural (15.5%).³⁸ The trend is indicative of reducing rates of ICPM utilisation; this is manifest in the UK with no patients at our centre having ICPM in the past 5 years. In those centres that use ICPM, the commonest indicators were pupillary abnormalities and renal dysfunction,³⁹ with more frequent use in those listed for urgent liver transplant.³⁸ The recent European association for the study of the Liver (EASL) guidelines only suggest consideration of ICPM in a select group of patients at high risk of

ICH.⁴⁰ The American association for the study of liver diseases (AASLD) recommends ICPM use in only those awaiting liver transplant and in centres with relevant expertise.⁴¹ Not only is there variable ICPM use, targets for ICP and CPP vary by centre and clinical endpoints lack standardisation. Most centres aim for ICP between 20–25 mmHg and a CPP of 50–60 mmHg.³⁹

The main risk associated with the use of ICPM is haemorrhage compounded in ALF patients by coagulopathy. The incidence of haemorrhagic complications is approximately 10%,^{38,42} with bleeding as a cause of death in approximately 1%. More recent data suggests that the incidence has further dropped both in the USA (7%)⁴³ and UK (3%).⁴⁴ Bleeding complications is lowest with epidural catheters but higher for subdural and parenchymal devices.⁴² The overall risk of central nervous system infections associated with the use of ICPM is low at 1.5%.⁴² Risk of haemorrhagic complications were shown to be further minimised to 4% by using protocol guided correction of coagulopathy with recombinant Factor VIIa,⁴⁵ but equivalent results have been seen without recombinant Factor VIIa.⁴⁴

Despite the theoretical benefits of ICPM, there is little evidence its use impacts on long term survival in ALF.^{38,42} In a study of 63 patients with grade 4 encephalopathy, ICPM has been shown to only prolong survival by hours when compared to the non-monitored group (median 60 h vs. 10 h non-monitored), with no difference in overall survival or mode of death.³⁶ A recent multicentre retrospective cohort study of 140 patients with ICPM vs. 489 controls revealed no difference in 21 day mortality (33% vs 38% controls, $P = 0.24$).⁴³ Moreover, when the ICPM group was stratified by aetiology with regards to acetaminophen use, those in the non-acetaminophen group had an increased 21 day mortality (OR ~ 3.04 , $P = 0.014$). The quality of evidence supporting ICPM use is limited by its retrospective nature. There are no prospective randomised trials, and although these are urgently required to answer the controversies surrounding its use, difficulty arises due to small numbers of ALF patients.⁴⁶

Jugular Venous Oxygen Saturation (SjvO₂)

SjvO₂ can be used as a surrogate marker for cerebral metabolism and brain oxygen consumption. Measuring the oxygen saturation of the jugular vein allows the Arteriovenous Oxygen Difference (AVDO₂) to be assessed, which is indicative of metabolic demand compared to oxygenation. Measurement involves placement of a retrograde catheter in the internal jugular vein with the tip at the jugular venous bulb. Complications related to this modality of neuro-monitoring are uncommon and are similar to the risk of a central line insertion.⁴⁷ AVDO₂ is a function of the cerebral metabolic rate of oxygen consumption (CMRO₂) divided by CBF. Thus SjvO₂ can be utilised to optimise brain oxygenation and detect situations where demand may be increased, such as in

seizures. The $SjvO_2$ decreases when cerebral oxygen demand exceeds supply as a greater amount of oxygen is extracted by the brain. Conversely, when supply exceeds demand, the $SjvO_2$ is increased. In normal physiological conditions the $SjvO_2$ ranges from approximately 55–75%.⁴⁷ In those with ALF a $SjvO_2$ persistently <60% or >80% is associated with a high degree of sensitivity and specificity of elevated ICP.²⁸

A drop in $SjvO_2$ indicates excessive cerebral oxygen utilisation such as during fevers or seizures or due to reduction in CPP caused by a spike in ICP caused by osmotic swelling.²⁸ An elevated $SjvO_2$ can indicate cerebral hyperemia or under utilisation of oxygen. In cases where the $SjvO_2$ and ICP are both high, treatment should be directed at reducing CBF with measures such as or short term hyperventilation.⁴⁸ Changes in the $SjvO_2$ can be used in an algorithmic fashion to guide clinical decision making in those with severe HE, as the one developed at our institution (Figure 1).⁴⁸

Limitations of $SjvO_2$ monitoring include inappropriate catheter placement resulting in sampling of blood from outside the brain such as scalp, reducing accuracy. A falsely high $SjvO_2$ may also occur from leftward shift of the oxyhaemoglobin dissociation curve during alkaline conditions.⁴⁷

Measuring Cerebral Blood Flow

The gold standard methodology for assessing CBF is the Kety-Schmidt technique.⁴⁹ This method assesses absorption rate of a freely diffusible indicator in the brain tissue by calculating the difference between at the arterial and venous washout curves. CBF may also be assessed by use of radioisotopes such as Xenon-133,⁵⁰ however these

methods are impractical for bedside patient use and surrogates for CBF have been sought.

Transcranial Doppler (TCD)

TCD ultrasonography is a non-invasive bedside method that allows estimation of CBF, and has been used in a variety of clinical scenarios.⁵¹ TCD utilises pulsed wave Doppler to image vessels through an acoustic window, of which the transtemporal window is the most commonly used, allowing flow assessment of the anterior, middle and posterior cerebral arteries. TCD can be used to calculate CBF mean flow velocity, which was found in a series of 5 ALF patients to be reduced in 80% of cases, consistent with a hypoperfusion pattern.⁵² The pulsatility Index (PI) [(systolic velocity – diastolic velocity)/mean velocity] demonstrates good correlation with ICP, with a correlation coefficient of 0.938 ($P < 0.0001$) in a study of 81 patients who had intraventricular catheters for a range of neurosurgical conditions.⁵³ In 4 ALF patients a PI > 1.0 was predictive of a poor outcome.⁵⁴ Given the complex interplay of physiological parameters influencing cerebral regulation in ALF, attempts have been made at more sophisticated interpretations of ICP. Aggarwal et al. in a retrospective study of 16 ALF patients with simultaneous TCD and ICP measurements identified four TCD waveform features which correctly classified subjects into the proper ICP/CPP groups 43–76% of the time.⁵⁵ TCD has significant potential but limitations include inadequacy of transtemporal windows in 10–20% of patients,⁵¹ it is also highly operator dependent requiring a long learning curve to acquire competency. Widespread use is contingent on further delineation of quantitative data with larger number of patients.

Figure 1 Algorithm of $SjvO_2$ use in the management of ALF patients with grade 3 or 4 HE based on practice guidelines at our institution (Royal Free Hospital, London).⁴⁸

Non-Invasive Methods

Optic sheath nerve diameter (OSND) as measured by ultrasound allows a non-invasive measure of ICP as the optic nerve sheath communicates directly with the sub-arachnoid space and can reflect changes in ICP. There is linear correlation between OSND and ICP,⁵⁶ a cutoff > 0.48 cm has been associated with ICP values > 20 mmHg based on neuro-critical care patients.⁵⁷ OSND has only been used in few ALF cases^{58,59} during the peri-operative liver transplantation period where patients are at high risk of ICP surges. In a prospective pilot study of 24 children with ALF, OSND correlated with plasma ammonia and was shown to be safe with good inter-observer reliability, but proved unable to distinguish between early and advanced HE.⁶⁰ It is a promising technique but requires further validation in this cohort of patients.

Near-infrared spectrophotometry (NIS) is a non-invasive method which is based on the light absorption properties of haemoglobin. By utilising specifically up to 4 wavelengths of light in the infrared spectrum to penetrate the skull, regional cerebral oxygenated haemoglobin and deoxygenated haemoglobin concentration changes can be measured to determine cerebral oxygen saturation.⁶¹ In a study of 7 ALF patients where an infusion of noradrenalin was used to increase CBF, changes in cerebral oxygen saturation measured by NIS co-varied with changes in SvjO₂ in all but one patient,⁶² demonstrating utility of NIS to monitor changes in cerebral oxygenation. However, interference from raised bilirubin and haemoglobin in skin and subcutaneous tissues may interfere with values.⁶²

Neurophysiological monitoring of brain electrical activity with electroencephalography is useful given the high incidence of clinical and sub-clinical seizure activity in ALF.^{33,34} Prompt identification and treatment of seizures can prevent neurological injury and ameliorate spikes in ICP. Bispectral index may aid in clinical evaluation⁴⁹ but there is very limited data.

Serum Neuro-Biomarkers

Circulating markers of neurological dysfunction and injury may be used as biomarkers to predict ICH. S-100b (a marker of astroglial dysfunction) and Neuron Specific Enolase (NSE) (a glycolytic enzyme in the cytoplasm of neurons and marker of neuronal dysfunction) were measured in 35 patients with ALF.⁶³ S-100b levels did not correlate with cerebral herniation but, NSE blood levels were higher in patients, who subsequently developed cerebral herniation than in survivors (10.5 µg/L vs. 5.1 µg/L, $P = 0.05$).⁶³ Fatty acid binding protein 7 (FABP7) (expressed in astrocytes) was shown to be higher in survivors of ALF compared to non-survivors, but FABP7 levels did not correlate with the presence of ICH.⁶⁴

CONCLUSION

Although the incidence of ICH is reducing it remains a common complication of ALF leading to significant morbidity. ICPM may be considered for those at highest risk of ICH but the absence of a survival benefit may be a key factor to explaining its declining use. Additional semi and non-invasive methods are important offering significant potential to allow enhancement of monitoring in a multimodal fashion to optimise outcomes. However, more evidence is required for some of these techniques before they are employed in routine clinical practice.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Lee WM, Squires RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. *Hepatology*. 2008;47(4):1401–1415.
2. Bernal W, Wendon J. Acute liver failure. *N Engl J Med*. 2013;369(26):2525–2534.
3. Rao KV, Norenberg MD. Cerebral energy metabolism in hepatic encephalopathy and hyperammonemia. *Metab Brain Dis*. 2001;16(1–2):67–78.
4. Llansola M, Rodrigo R, Monfort P, et al. NMDA receptors in hyperammonemia and hepatic encephalopathy. *Metab Brain Dis*. 2007;22(3–4):321–335.
5. Albrecht J, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. *Hepatology*. 2006;44(4):788–794.
6. Kato M, Hughes RD, Keays RT, Williams R. Electron microscopic study of brain capillaries in cerebral edema from fulminant hepatic failure. *Hepatology*. 1992;15(6):1060–1066.
7. Chastre A, Bélanger M, Nguyen BN, Butterworth RF. Lipopolysaccharide precipitates hepatic encephalopathy and increases blood–brain barrier permeability in mice with acute liver failure. *Liver Int*. 2014;34(3):353–361.
8. Rai V, Nath K, Saraswat VA, Purwar A, Rathore RKS, Gupta RK. Measurement of cytotoxic and interstitial components of cerebral edema in acute hepatic failure by diffusion tensor imaging. *J Magn Reson Imaging*. 2008;28(2):334–341.
9. Murphy N, Auzinger G, Bernal W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology*. 2004;39(2):464–470.
10. Clemmesen JO, Larsen FS, Nordrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*. 1999;29(3):648–653.
11. Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*. 2007;46(6):1844–1852.
12. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. *Gut*. 2006;55(1):98–104.
13. Tofteng F, Hauerberg J, Hansen BA, Pedersen CB, Jorgensen L, Larsen FS. Persistent arterial hyperammonemia increases the concentration of glutamine and alanine in the brain and correlates with intracranial pressure in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab*. 2006;26(1):21–27.

14. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology*. 2000;32(4 Pt 1):734–739.
15. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology*. 2003;125(3):755–764.
16. Jiang W, Desjardins P, Butterworth RF. Cerebral inflammation contributes to encephalopathy and brain edema in acute liver failure: protective effect of minocycline. *J Neurochem*. 2009;109(2):485–493.
17. Wright G, Shawcross D, Olde Damink SWM, Jalan R. Brain cytokine flux in acute liver failure and its relationship with intracranial hypertension. *Metab Brain Dis*. 2007;22(3):375–388.
18. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension. *Gastroenterology*. 2004;127(5):1338–1346.
19. Bernal W, Murphy N, Brown S, et al. A multicentre randomized controlled trial of moderate hypothermia to prevent intracranial hypertension in acute liver failure. *J Hepatol*. 2016;65(2):273–279.
20. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. *Liver Transpl*. 2015;21(1):4–12.
21. Vaquero J, Chung C, Blei AT. Brain edema in acute liver failure. A window to the pathogenesis of hepatic encephalopathy. *Ann Hepatol*. 2003;2(1):12–22.
22. Aggarwal S, Kramer D, Yonas H, et al. Cerebral hemodynamic and metabolic changes in fulminant hepatic failure: a retrospective study. *Hepatology*. 1994;19(1):80–87.
23. Larsen FS, Adel Hansen B, Pott F, et al. Dissociated cerebral vasoparalysis in acute liver failure. A hypothesis of gradual cerebral hyperaemia. *J Hepatol*. 1996;25(2):145–151.
24. Larsen FS, Ejlersen E, Clemmesen JO, Kirkegaard P, Hansen BA. Preservation of cerebral oxidative metabolism in fulminant hepatic failure: an autoregulation study. *Liver Transpl Surg*. 1996;2(5):348–353.
25. Aggarwal S, Obrist W, Yonas H, et al. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: relationship to outcome. *Liver Transpl*. 2005;11(11):1353–1360.
26. Bernal W, Hyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol*. 2013;59(1):74–80.
27. Raschke RA, Curry SC, Rempe S, et al. Results of a protocol for the management of patients with fulminant liver failure. *Crit Care Med*. 2008;36(8):2244–2248.
28. Jalan R. Intracranial hypertension in acute liver failure: pathophysiological basis of rational management. *Semin Liver Dis*. 2003;23(3):271–282.
29. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342(8866):273–275.
30. Kitzberger R, Funk GC, Holzinger U, et al. Severity of organ failure is an independent predictor of intracranial hypertension in acute liver failure. *Clin Gastroenterol Hepatol*. 2009;7(9):1000–1006.
31. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715–735.
32. Shawcross DL, Wendon JA. The neurological manifestations of acute liver failure. *Neurochem Int*. 2012;60(7):662–671.
33. Bhatia V, Batra Y, Acharya SK. Prophylactic phenytoin does not improve cerebral edema or survival in acute liver failure – a controlled clinical trial. *J Hepatol*. 2004;41(1):89–96.
34. Ellis AJ, Wendon JA, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. *Hepatology*. 2000;32(3):536–541.
35. Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology*. 1991;13(2):209–212.
36. Keays RT, Alexander GJ, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. *J Hepatol*. 1993;18(2):205–209.
37. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology*. 2005;41(5):1179–1197.
38. Vaquero J, Fontana RJ, Larson AM, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl*. 2005;11(12):1581–1589.
39. Rabinowich L, Wendon J, Bernal W, Shibolet O. Clinical management of acute liver failure: results of an international multi-center survey. *World J Gastroenterol*. 2016;22(33):7595–7603.
40. European Association for the Study of the Liver. Electronic address eee. Clinical Practice Guidelines Panel. Wendon J, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol*. 2017;66(5):1047–1081.
41. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2012;55(3):965–967.
42. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet*. 1993;341(8838):157–158.
43. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. *Crit Care Med*. 2014;42(5):1157–1167.
44. Peck M, Wendon J, Sizer E, Auzinger G, Bernal W. Intracranial pressure monitoring in acute liver failure: a review of 10 years experience. *Crit Care*. 2010;14(1):P542.
45. Rajasee V, Fontana RJ, Courey AJ, Patil PG. Protocol based invasive intracranial pressure monitoring in acute liver failure: feasibility, safety and impact on management. *Crit Care*. 2017;21(1):178.
46. Fortea JI, Bañares R, Vaquero J. Intracranial pressure in acute liver failure: to bolt or not to bolt—that is the question. *Crit Care Med*. 2014;42(5):1304–1305.
47. Schell RM, Cole DJ. Cerebral monitoring: jugular venous oximetry. *Anesth Analg*. 2000;90(3):559–566.
48. Privitera GAB, Jalan R. Liver failure: pathophysiological basis and the current and emerging therapies. *EMJ Hepatol*. 2014;1:1.
49. Paschoal Jr FM, Nogueira RC, Ronconi Kde A, de Lima Oliveira M, Teixeira MJ, Bor-Sen-Shu E. Multimodal brain monitoring in fulminant hepatic failure. *World J Hepatol*. 2016;8(22):915–923.
50. Obrist WD, Thompson Jr HK, Wang HS, Wilkinson WE. Regional cerebral blood flow estimated by 133-xenon inhalation. *Stroke*. 1975;6(3):245–256.
51. Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler ultrasound: a review of the physical principles and major applications in critical care. *Int J Vasc Med*. 2013;2013:629378.
52. Abdo A, Lopez O, Fernandez A, et al. Transcranial Doppler sonography in fulminant hepatic failure. *Transpl Proc*. 2003;35(5):1859–1860.
53. Bellner J, Romner B, Reinstrup P, Kristiansson K-A, Ryding E, Brandt L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). *Surg Neurol*. 2004;62(1):45–51.
54. Kawakami M, Koda M, Murawaki Y. Cerebral pulsatility index by transcranial Doppler sonography predicts the prognosis of patients with fulminant hepatic failure. *Clin Imaging*. 2010;34(5):327–331.
55. Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer 2nd JF. Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. *Liver Transpl*. 2008;14(7):1048–1057.

56. Moretti R, Pizzi B, Cassini F, Vivaldi N. Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage. *Neurocrit Care*. 2009;11(3):406–410.
57. Rajajee V, Fletcher JJ, Rochlen LR, Jacobs TL. Comparison of accuracy of optic nerve ultrasound for the detection of intracranial hypertension in the setting of acutely fluctuating vs stable intracranial pressure: post-hoc analysis of data from a prospective, blinded single center study. *Crit Care*. 2012;16(3):R79-R.
58. Kim Y-K, Seo H, Yu J, Hwang G-S. Noninvasive estimation of raised intracranial pressure using ocular ultrasonography in liver transplant recipients with acute liver failure – a report of two cases. *Korean J Anesthesiol*. 2013;64(5):451–455.
59. Krishnamoorthy V, Beckmann K, Mueller M, Sharma D, Vavilala MS. Perioperative estimation of the intracranial pressure using the optic nerve sheath diameter during liver transplantation. *Liver Transpl*. 2013;19(3):246–249.
60. Das MC, Srivastava A, Yadav R, Yachha SK, Poddar U. Role of bedside ultrasound guided measurement of optic nerve sheath diameter in children with acute liver failure – a prospective observational pilot study. *Hepatology*. 2017;66:. 20a-a.
61. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth*. 2009;103(suppl 1):i3-13.
62. Nielsen HB, Tofteng F, Wang LP, Larsen FS. Cerebral oxygenation determined by near-infrared spectrophotometry in patients with fulminant hepatic failure. *J Hepatol*. 2003;38(2):188–192.
63. Strauss GI, Christiansen M, Møller K, Clemmesen JO, Larsen FS, Knudsen GM. S-100b and neuron-specific enolase in patients with fulminant hepatic failure. *Liver Transpl*. 2001;7(11):964–970.
64. Karvellas CJ, Speiser JL, Tremblay M, Lee WM, Rose CF. For the USALFSG. The association between FABP7 serum levels with survival and neurological complications in acetaminophen-induced acute liver failure: a nested case-control study. *Ann Intensive Care*. 2017;7:99.