Published in final edited form as:

J Hepatol. 2007 April ; 46(4): 564–569. doi:10.1016/j.jhep.2007.01.011.

BRAIN EDEMA IN ACUTE LIVER FAILURE:

Can it be prevented? Can it be treated?

Andres T Blei, MD

Northwestern University Feinberg School of Medicine, Chicago, IL

Keywords

Acute liver failure; Brain edema; intracranial pressure; Cerebral blood flow

The management of cerebral edema in Acute Liver Failure (ALF) is still imperfect, reflecting the limited tools to control brain swelling in this disease as well as in other neurological conditions (1). A better understanding of the unique mechanisms responsible for brain edema in ALF has emerged over the last years (2). Data arising from studies in experimental animals and in humans allow a more rational approach to the prevention and treatment of this serious complication of ALF.

A. THE PATHOGENESIS OF BRAIN EDEMA IN ALF

A net increase in water content defines the presence of brain edema. In the setting of an intact blood-brain barrier, water moves into brain via 3 possible routes: Via diffusion through the lipid bilayer of plasma membranes, via co-transport with organic and inorganic ions and through specialized water channels, aquaporins (2). Of special interest is aquaporin 4, the predominant aquaporin in brain. Mainly localized to cerebral endothelial cells and astrocyte foot processes that surround them, aquaporin-4 may play an important role in the pathogenesis of cytotoxic brain edema. Brain edema as a result of water intoxication is markedly reduced in aquaporin-4-deficient mice (reviewed in 3).

For many years, an accepted tenet has been the presence of an intact blood-brain barrier and a cytotoxic etiology to explain brain edema in ALF. This concept has been recently challenged (4) with the possibility of a “leaky” rather than a bona fide rupture of the barrier. Effects on endothelial tight-junction proteins could be present, a change potentially explained by the action of endotoxin and/or pro-inflammatory cytokines on cellular permeability (5). Still, cytotoxic mechanisms need to be considered as a major pathogenic factor. In a recent study, all 7 patients with ALF and deep encephalopathy showed evidence of cytotoxic edema using diffusion-weighted MRI of the brain (6).

Figure 1 depicts current views of the complex pathogenesis of brain edema in ALF. Astrocyte swelling is initiated by the accumulation of glutamine, the result of the detoxification of ammonia. As a result of swelling, ions (such as K^+) and other osmolytes

Correspondence: Andres T Blei, MD, Northwestern University Feinberg School of Medicine, Division of Hepatology, 303 E Chicago Avenue – Searle 10-574, Chicago, IL 60611, e-mail: a-blei@northwestern.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

(including myo-inositol, glutamate and taurine) are released. Ammonia-induced effects in vitro include an increase in aquaporin-4 expression in primary astrocytes (7).

Brain glutamine levels are clearly increased in human ALF, though they do not correlate with the degree of swelling in experimental ALF, suggesting the presence of additional pathways that lead to water accumulation. A consistent observation in animal models (8) and human disease (9) is an increase in cerebral blood flow independent from changes in systemic hemodynamics at the time of a rise in intracranial pressure. The mechanisms for this increase have not been fully explained. The signal may arise from factors released during astrocyte swelling or reflect the development of oxidative stress in glial cells, with the consequent generation of vasodilatory mediators (nitric oxide, carbon monoxide). Oxidative stress in astrocytes may arise from the effects of swelling itself (10) or be the result of glutamine-derived ammonia generated within mitochondria, which interferes with mitochondrial function giving rise to excessive production of free radicals and induction of the mitochondrial permeability transition (11). Under the latter view, the osmotic effects of glutamine may be less important for the induction of cellular swelling.

Inflammatory cytokines in the circulation bind to cerebral endothelial cells and can also activate perivascular cells (12). They are likely to amplify the effects of ammonia on cerebral metabolism and hemodynamics, a synergistic effect seen in both acute and chronic liver failure (reviewed in 13).

B. PREVENTING BRAIN EDEMA (TABLE 1)

a) Before the development of encephalopathy

Bernauu has eloquently argued for the need to consider therapeutic measures before patients with hepatic failure develop changes in mental state (14). Early referral and treatment of the cause of ALF are the mainstay of such interventions. As such measures focus on treating the liver rather than the brain, they will not be reviewed here. Even if the question is reformulated by focusing on measures to prevent the development of encephalopathy, the evolution towards an altered mental state depends on the degree of liver failure. Of note, monitoring of factors V and VII levels were useful as predictors of the evolution towards a more severe course in patients with ALF without encephalopathy at admission (15). Nadir levels of the activity of factor V ($39 \pm 11\%$) and VII ($11 \pm 5\%$) were significantly lower in non-survivors (in survivors, $74 \pm 41\%$ and $30 \pm 16\%$, respectively).

b) A reduction of the ammonia load

Experimental and clinical evidence links hyperammonemia with the pathogenesis of brain edema. Indeed, brain edema occurs in “pure” hyperammonemic states, such as in children with urea cycle enzyme deficiencies. In a series of patients with ALF from Denmark, arterial ammonia levels $>150 \mu\text{mol/L}$ measured within 24 hs of reaching grade III hepatic encephalopathy, were associated with a higher likelihood of developing brain edema (16); levels $>200 \mu\text{mol/L}$ were seen in patients with cerebral herniation. The deleterious impact of higher ammonia levels in ALF has also been noted in a series from India (17). Patients should have ammonia measurements from an arterial site [the arteriovenous difference of ammonia is prominent in ALF (16)].

Pharmacological agents currently used for the treatment of hyperammonemia in chronic liver disease have not been formally tested in ALF. From a theoretical perspective, the colonic clearance of ammonia attainable with non-absorbable disaccharides is far inferior to the rate at which ammonia generated in the splanchnic bed is delivered to the systemic circulation. In addition, such agents may result in colonic distention and complicate the performance of an emergency liver transplantation. Nonetheless, a preliminary observation

from the ALF Study Group noted a delayed mortality in patients treated with lactulose (18). Though the number of patients was large (70 treated vs 47 untreated) and the 2 groups were well matched at baseline, the study was observational and no definitive conclusions can be reached.

Increasing ammonia disposal by muscle was shown to be the mechanism by which ornithine-aspartate prevented the development of brain edema in rats after hepatic devascularization (19). The amino acid mixture induced a post-translational increase in the activity of muscle glutamine synthetase, with a reduction in ammonia levels. The safety of this approach in humans has not been evaluated.

Ammonia can be removed by dialytic methods, the efficacy of which depends on the rate of countercurrent flow and the total filtration surface (20). Continuous veno-venous hemofiltration/dialysis is the usual renal replacement therapy in human ALF. High-flow dialysis, potentially the most effective method to remove ammonia, is difficult to perform in the vasodilated patients with ALF and may result in the development of acute fluid shifts in the brain.

c) Correcting hyponatremia

Hyponatremia is frequently observed in patients with ALF, noted in approximately a third of patients with ALF at admission (21). Hyponatremia, if severe, may cause brain swelling by itself and has been shown to potentiate ammonia-induced swelling in animal models. The pathogenesis of hyponatremia in ALF may share mechanisms with those seen in patients with chronic liver failure, including the non-osmotic release of vasopressin as a result of arterial vasodilatation. The presence of renal failure may further complicate the clinical management, as the classic approach to hyponatremia (i.e. water restriction) may not be feasible. Maintenance of adequate filling of the central compartment, monitored via central venous pressure measurements and/or the use of methods to measure central transit time, are needed in such patients. Hydration is an important end-point both at the onset of therapy, when volume expansion to assure organ perfusion and prevent metabolic acidosis is a goal, and at a late stage, when the administration of blood products carries the risk of overexpansion and movement of fluid into brain following hydrostatic forces (22). Administration of hypertonic saline to induce hyponatremia may be used to treat brain edema (*vide infra*).

d) Treating inflammation/infection

Inflammation and infection are associated with the presence as well as progression of encephalopathy in ALF. An activated inflammatory state can be presumed even in the absence of positive microbiological results by the presence of SIRS (systemic inflammatory response syndrome). Patients in whom SIRS could be detected [body temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, WBC >12000 or $<4000/\text{ml}$, tachycardia (>90 beats/min) or hyperpnea (>20 resp/min)], had a higher prevalence of encephalopathy (23). Positive bacteriological cultures preceded the progression of mild to severe encephalopathy in approximately 70% of patients with ALF of both acetaminophen and non-acetaminophen etiologies (24). As brain edema is seen exclusively in patients with severe changes in mental state, it is logical to conclude that patients who have reached stage III–IV encephalopathy should be presumed to be infected and empirically treated with broad spectrum antibiotics.

However, the ability to counteract the effects of inflammation/infection may be limited in the setting of ALF. Prophylactic antibiotics administered at an earlier stage of ALF did not result in an improvement in survival. Encephalopathy progressed to a similar degree in those patients treated with prophylactic antibiotics as compared to those “on demand.”(reviewed

in 25). The cascade of biological events that surround the development of sepsis includes the release of both inflammatory and anti-inflammatory cytokines. The complex interaction between such opposing effects is reflected by a reduced monocyte HLA-DR expression, a poor prognostic finding in patients with acetaminophen-induced ALF (26).

e) Should seizures be prevented?

Subclinical seizure activity was detected using continuous EEG in approximately 45% of patients with severe encephalopathy (27). It was less prevalent in another report from India (21). While the administration of phenytoin was purportedly associated with a lower degree of brain edema at autopsy (27), it was ineffective when assessed using clinical parameters (21).

Theoretical reasons for the development of brain excitability and seizure activity may lie in the increase in extracellular brain glutamate seen in ALF (28). However, the incidence of overt seizures in ALF is relatively low and could also reflect the role of other confounding events (hydration, renal failure, medications) rather than being a primary expression of encephalopathy. At this time, phenytoin is not recommended for prevention of brain edema. However, if suspected, seizures should be actively sought and immediately treated.

C. TREATING BRAIN EDEMA (TABLE 2)

a) Monitoring intracranial pressure

Brain edema is life-threatening when it progresses to intracranial hypertension. Clinical symptoms have a low sensitivity for the diagnosis of an increased intracranial pressure (ICP). Continuous monitoring for the development of long-tract signs, decerebrate posturing, alterations in pupillary reactivity or of the oculo-vestibular reflex is impractical. Imaging of the brain cannot be used as a tool to follow the evolution of the brain picture, with the associated risk of patient mobilization. The role of ICP monitoring in ALF is still highly controversial, as noted in recent publications (29,30). A non-invasive system that provides equivalent information is not yet available.

The main concern with ICP monitoring is the development of intracranial hemorrhage. The frequency of bleeding was estimated to be 22% from the response to a questionnaire in the early 90's (31). More recently, it was 10% in more precisely gathered data from the US Acute Liver Failure group (32). Deaths attributed to hemorrhage were noted in both time periods. On the flip side, the use of ICP monitors was associated with a higher use of medications for intracranial hypertension (32), suggesting that a high intracranial pressure is underdiagnosed and undertreated without the information obtained by invasive monitoring.

The principle of "*primum non nocere*" applies to both sides of the argument. For those opposed to the placement of such monitors, the development of a fatal complication from the procedure is sufficient reason not to use the equipment (29). For those in favor of their use, avoiding irreparable brain damage is critical for the successful outcome of patients awaiting emergency liver transplantation (30). This controversy could be solved with effective measures to prevent bleeding. Recombinant factor VIIa could be of benefit (33), but the effectiveness and safety of this approach has not been fully elucidated.

Not all patients with ALF and deep encephalopathy develop clinically significant brain edema. It is more likely to occur in hyperacute liver failure and in the setting of arterial hyperammonemia, especially if $> 200 \mu\text{mol/L}$ (16). In deeply encephalopathic patients, administration of pressors to correct arterial hypotension or to maintain the cerebral perfusion pressure is made more rational by the use of ICP monitoring; indeed, the resulting

increase in arterial pressure carries the risk of worsening ICP in view of the failure of cerebral autoregulation seen in ALF (reviewed in 25).

b) Monitoring cerebral blood flow

Aggarwal et al have described several stages in the evolution of the clinical picture of ALF with severe encephalopathy (9). Their observations note the importance of an increased cerebral blood flow (CBF) preceding the rise in ICP. Cerebral blood flow can be lower at an earlier stage of the course (34), reflecting a reduction in cerebral oxidative metabolism and/or peripheral vasodilatation, as well as seen during the pre-terminal course, when the elevated ICP increases resistance to cerebral perfusion.

The arteriovenous oxygen difference across the brain is used to monitor cerebral perfusion, albeit imperfectly. The (artery-jugular vein) difference varies inversely with the value of CBF. However, it may also be affected by the degree of cerebral oxidative metabolism. Other tools to estimate cerebral perfusion (such as Doppler measurements in the middle cerebral artery) are more complex and require expertise with their use (reviewed in 35).

c) Therapeutic options

- i. Adequate management in the intensive care unit is critical. Patients need to be adequately sedated with short-acting agents, especially propofol, and be mechanically ventilated. The latter is not without cost, as an increase in end-expiratory pressures may reduce venous return, drop cardiac output and reduce splanchnic perfusion. With regards to propofol, its duration of action is short, but may become longer due to its accumulation in fatty tissues. Elevation of the head of the bed provides improved venous drainage and lowers ICP as long as the cerebral perfusion pressure is acceptable (1). Fever and hyperglycemia should be avoided as they aggravate the clinical picture via an increase in CBF in the former and possibly via osmotic effects in the latter.
- ii. To control cerebral swelling, osmotic-based therapy can be used. Mannitol may provide a rapid fluid shift, though its entry into brain may impair repeated usage. Administration of hypertonic saline to induce hyponatremia (aiming at 150 mmol/L) may be especially useful to control early increases in ICP (36). The risk of congestive heart failure needs to be considered and avoidance of hyperchloremic metabolic acidosis may require the addition of acetate. Corticosteroids do not improve brain edema
- iii. Other approaches can be used to reduce CBF. Hyperventilation results in precapillary vasoconstriction (37) and while not recommended as a prophylactic measure, it is especially useful to control surges of ICP, a “pressure wave” that requires immediate medical therapy. A similar use can be assigned to indomethacin, a cerebral vasoconstrictor (38); the effects of the drug on the gastric mucosa and renal circulation preclude a prophylactic role.
- iv. Extracorporeal approaches. Many of these patients receive renal replacement therapy, which may play a role in preventing rather than treating brain swelling (volume control, removal of ammonia). The role of artificial/bioartificial systems to control brain edema and ICP is uncertain (see article by Dr. Singhal and Dr. Neuberger in this Forum). Reports of a decrease of ICP with the use of extracorporeal albumin dialysis (39) need to be viewed with caution: Not only the reported experience arises from a few patients, but a reduction in body temperature was concomitantly present.

- v. Mild hypothermia is of interest. It reduces an elevated ICP in patients with ALF and severe intracranial hypertension (40). The effects are prompt and body temperatures of 32°–34°C can be easily attained with external cooling blankets (or via connection to the external circuit used in renal replacement therapy). Patients who are cooled require neuromuscular paralysis to avoid shivering. The reduction in ICP can be maintained in the operating room during emergency liver transplantation (41).

The mechanisms by which hypothermia reduces brain edema and ICP are multiple (reviewed in 42) but they affect all parameters shown in figure 1. They include a decrease in CBF without impairing cerebral oxidative metabolism. From this perspective, mild cooling is preferable to alternative methods, such as the induction of coma with barbiturates (43). The reduced entry of ammonia into brain results in a decrease in the toxin load, manifested by a lesser degree of osmolyte release from astrocytes. Oxidative stress is ameliorated, with a reduction in anaerobic glycolysis. The production of putative vasodilators, such as nitric oxide and carbon monoxide, is reduced. In addition, hypothermia can change the circulating cytokine profile from a pro- to an anti-inflammatory milieu.

In animal models, mild hypothermia can prevent the development of brain edema (44). Furthermore, it improves survival in acetaminophen-induced acute liver failure in mice (45). In the latter study, the effects on the liver were multiple, including a reduction in necrosis without loss of regenerative activity. Maintenance of regeneration is important if cooling would be targeted for non-transplant candidates. From this perspective, acetaminophen-induced ALF may be the optimal etiology to apply hypothermia, as a critical stem-cell compartment for regeneration appears preserved with such injury (46).

The full potential of mild hypothermia to prevent and treat brain edema in ALF will require the performance of a controlled trial. Concerns with the safety of this approach have not been yet dispelled, including the risk of infection, coagulopathy and acute pancreatitis. At this time, mild hypothermia appears confined to patients in whom brain edema has become uncontrollable by medical means. The duration (more than 24 hours?) and extent of cooling (32° vs. 34°C) has not been systemically evaluated.

In conclusion, brain edema in ALF arises from the sum of osmotic, metabolic and hemodynamic changes in the brain triggered by liver injury (via ammonia, changes in serum osmolarity and circulating cytokines). A rational approach to the prevention of brain edema targets such factors. Once ICP has risen, osmotic therapy and control of cerebral circulation are foci of therapy. Mild hypothermia may be of special interest in view of its low cost and ready availability in the intensive care setting.

Acknowledgments

Supported by the Stephen B Tips Fund at Northwestern Memorial Hospital

Abbreviations

ALF	acute liver failure
ICP	intracranial pressure
CBF	cerebral blood flow
SIRS	systemic inflammatory response syndrome

References

1. Rubinstein AA. Treatment of Cerebral Edema. *The Neurologist*. 2006; 12:59–73. [PubMed: 16534443]
2. Agre P, Nielsen S, Ottersen OP. Towards a molecular understanding of water homeostasis in the brain. *Neuroscience*. 2004; 129:849–50. [PubMed: 15561402]
3. Manley GT, Binder DK, Papadopoulos MC, Verkman AS. New insights into water transport and edema in the central nervous system from phenotype analysis of aquaporin-4 null mice. *Neuroscience*. 2004; 129:983–91. [PubMed: 15561413]
4. Nguyen JH, Yamamoto S, Steers J, Sevillever D, Lin W, Shimojima N. Matrix metalloproteinase-9 contributes to brain extravasation and edema in fulminant hepatic failure mice. *J Hepatol*. 2006; 44:1105–14. Epub 2005 Nov 7. [PubMed: 16458990]
5. Bruewer M, Luegering A, Kucharzik T, Parkos CA, Madara JL, Hopkins AMA. Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. *J Immunol*. 2003; 171:6164–72. [PubMed: 14634132]
6. Ranjan P, Mishra AM, Kale R, Saraswat VA, Gupta RK. Cytotoxic edema is responsible for raised intracranial pressure in fulminant hepatic failure: in vivo demonstration using diffusion-weighted MRI in human subjects. *Metab Brain Dis*. 2005; 20:181–92. [PubMed: 16167196]
7. Rama Rao KV, Chen M, Simard JM, Norenberg MD. Increased aquaporin-4 expression in ammonia-treated cultured astrocytes. *Neuroreport*. 2003; 14:2379–82. [PubMed: 14663195]
8. Master S, Gottstein J, Blei AT. Cerebral blood flow and the development of ammonia-induced brain edema in rats after portacaval anastomosis. *Hepatology*. 1999; 30:876–80. [PubMed: 10498637]
9. Aggarwal S, Obrist W, Yonas H, Kramer D, Kang Y, Scott V, Planinsic R. Cerebral hemodynamic and metabolic profiles in fulminant hepatic failure: relationship to outcome. *Liver Transpl*. 2005; 11:1353–60. [PubMed: 16237715]
10. Haussinger D, Schliess F. Astrocyte swelling and protein tyrosine nitration in hepatic encephalopathy. *Neurochem Int*. 2005; 47:64–70. [PubMed: 15908046]
11. Albrecht J, Norenberg MD. Glutamine: a Trojan horse in ammonia neurotoxicity. *Hepatology*. 2006; 44:788–94. [PubMed: 17006913]
12. Schiltz JC, Sawchenko PE. Signaling the brain in systemic inflammation: the role of perivascular cells. *Front Biosci*. 2003; 8:s1321–9. [PubMed: 12957837]
13. Blei AT. Infection, inflammation and hepatic encephalopathy, synergism redefined. *Hepatology*. 2004; 40:327–30.
14. Bernuau J. Acute liver failure: avoidance of deleterious cofactors and early specific medical therapy for the liver are better than late intensive care for the brain. *J Hepatol*. 2004; 41:152–5. [PubMed: 15246223]
15. Elinav E, Ben-Dov I, Hai-Am E, Ackerman Z, Ofran Y. The predictive value of admission and follow up factor V and VII levels in patients with acute hepatitis and coagulopathy. *J Hepatol*. 2005; 42:82–6. [PubMed: 15629511]
16. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology*. 1999; 29:648–53. [PubMed: 10051463]
17. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. *Gut*. 2006; 55:98–104. Epub 2005 Jul 15. [PubMed: 16024550]
18. Hay JE, Angulo P, Lee WM. Lactulose treatment in acute liver failure. *J Hepatol*. 2002; 36 (Suppl 1):33.
19. Rose C, Michalak A, Rao KV, Quack G, Kircheis G, Butterworth RF. L-ornithine-L-aspartate lowers plasma and cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure. *Hepatology*. 1999; 30:636–40. [PubMed: 10462368]
20. Cordoba J, Blei AT, Mujais S. Determinants of ammonia clearance by hemodialysis. *Artif Organs*. 1996; 20:800–3. [PubMed: 8828772]
21. 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; 41:89–96. [PubMed: 15246213]

22. Larsen FS, Wendon J. Brain edema in liver failure: basic physiologic principles and management. *Liver Transpl.* 2002 Nov; 8(11):983–9. [PubMed: 12424710]
23. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. *Hepatology.* 2000; 32:734–9. [PubMed: 11003617]
24. Vaquero J, Polson J, Chung C, Helenowski I, Schiodt FV, Reisch J, Lee WM, Blei AT. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology.* 2003; 125:755–64. [PubMed: 12949721]
25. Vaquero J, Chung C, Cahill ME, Blei AT. Pathogenesis of hepatic encephalopathy in acute liver failure. *Semin Liver Dis.* 2003; 23:259–69. [PubMed: 14523679]
26. Antoniadou CG, Berry PA, Davies ET, Hussain M, Bernal W, Vergani D, Wendon J. Reduced monocyte HLA-DR expression: a novel biomarker of disease severity and outcome in acetaminophen-induced acute liver failure. *Hepatology.* 2006; 44:34–43. [PubMed: 16799971]
27. Ellis AJ, Wenson J, Williams R. Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial. *Hepatology.* 2000; 32:536–41. [PubMed: 10960446]
28. Vaquero J, Butterworth RF. The brain glutamate system in liver failure. *J Neurochem.* 2006; 98:661–9. Epub 2006 Jun 12. [PubMed: 16771837]
29. Bernuau J, Durand F. Intracranial pressure monitoring in patients with acute liver failure: A questionable invasive surveillance. *Hepatology.* 2006; 44:502–4. [PubMed: 16871566]
30. Wendon JA, Larsen FS. Intracranial pressure monitoring in acute liver failure. A procedure with clear indications. *Hepatology.* 2006; 44:504–7. [PubMed: 16871578]
31. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet.* 1993; 341:157–8. [PubMed: 8093756]
32. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl.* 2005; 11:1581–9. [PubMed: 16315300]
33. Shami VM, Caldwell SH, Hespdenheide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transpl.* 2003; 9:138–43. [PubMed: 12548507]
34. Strauss GI, Knudsen GM, Kondrup J, Moller K, Larsen FS. Cerebral metabolism of ammonia and amino acids in patients with fulminant hepatic failure. *Gastroenterology.* 2001; 121:1109–19. Erratum in: *Gastroenterology* 2002; 122:250. [PubMed: 11677203]
35. Blei AT. Monitoring cerebral blood flow: a useful clinical tool in acute liver failure? *Liver Transpl.* 2005; 11:1320–2. [PubMed: 16237697]
36. 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; 39:464–70. [PubMed: 14767999]
37. Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol.* 1986; 2:43–51. [PubMed: 3081622]
38. Tofteng F, Larsen FS. The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure. *J Cereb Blood Flow Metab.* 2004; 24:798–804. [PubMed: 15241188]
39. Ben Abraham R, Szold O, Merhav H, Biderman P, Kidron A, Nakache R, Oren R, Sorkine P. Rapid resolution of brain edema and improved cerebral perfusion pressure following the molecular adsorbent recycling system in acute liver failure patients. *Transplant Proc.* 2001; 33:2897–9. [PubMed: 11543780]
40. 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; 127:1338–46. [PubMed: 15521003]
41. Jalan R, Olde Damink SW, Deutz NE, Davies NA, Garden OJ, Madhavan KK, Hayes PC, Lee A. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. *Transplantation.* 2003; 75:2034–9. [PubMed: 12829907]

42. Vaquero J, Rose C, Butterworth RF. Keeping cool in acute liver failure: rationale for the use of mild hypothermia. *J Hepatol.* 2005; 43:1067–77. Epub 2005 Oct 10. [PubMed: 16246452]
43. Nemoto EM, Klementavicius R, Melick JA, Yonas H. Suppression of cerebral metabolic rate for oxygen (CMRO₂) by mild hypothermia compared with thiopental. *J Neurosurg Anesthesiol.* 1996; 8:52–9. [PubMed: 8719194]
44. Cordoba J, Crespín J, Gottstein J, Blei AT. Mild hypothermia modifies ammonia-induced brain edema in rats after portacaval anastomosis. *Gastroenterology.* 1999; 116:686–93. [PubMed: 10029628]
45. Vaquero J, Blei AT, Butterworth RF. Mild hypothermia improves survival in acetaminophen-induced acute injury in mice. *Gastroenterology.* (in press).
46. Kofman AV, Morgan G, Kirschenbaum A, Osbeck J, Hussain M, Swenson S, Theise ND. Dose- and time-dependent oval cell reaction in acetaminophen-induced murine liver injury. *Hepatology.* 2005; 41:1252–61. [PubMed: 15880565]

Figure 1. A model to explain the development of brain edema

Circulating factors include hypo-osmolality (as with hyponatremia), hyperammonemia and cytokines (which bind to endothelial cell receptors). The permeability of the blood-brain barrier is presumed intact, though this has been recently questioned (4). Water movement into astrocytes may proceed via specialized pores, including aquaporin 4 (Aq4) in the endothelium and astrocyte plasma membrane. The generation of glutamine (GLN) within astrocytes from the amidation of glutamate (GLU), a reaction catalyzed by glutamine synthetase (GS), results in cellular swelling as a result of osmotic (10) and/or non-osmotic (11) effects. A net consequence of the processes that lead to swelling is the generation of oxidative and nitrosative stress within glial cells, a mechanism involved in the induction of cerebral hyperemia. The latter is critical for the net gain in water that is needed to result in brain edema (35). Most of the elements of this model originate from studies in rats with ammonia-induced brain edema, a model where the development of brain swelling can be studied independently from the extent of liver failure.

TABLE 1**Measures to prevent brain edema**

1) <i>Prevention of encephalopathy</i>
Treatment of underlying liver disease (14)
Adequate hydration
Correcting potential precipitating factors
Monitoring of liver function (15)
No role for anti-seizure medication.
2) <i>Reducing the ammonia load</i>
? non-absorbable disaccharides (18)
Continuous veno-venous hemofiltration/dialysis
? ornithine-aspartate (19)
3) <i>Correcting hyponatremia</i>
Adequate hydration, hemodynamic monitoring.
Hypertonic saline (36)
4) <i>Treating inflammation/infection</i>
Monitor for manifestations of SIRS
Empiric antibiotics with progression of encephalopathy

SIRS= systemic inflammatory response syndrome

TABLE 2

Treating brain edema

1. <i>Osmotic therapy</i>
Mannitol, bolus dosing
Hypertonic saline (36)
2. <i>Controlling CBF</i>
Hyperventilation for sudden elevation of ICP (37)
Fluid removal with renal replacement therapy
Indomethacin for uncontrollable rise in ICP (38)
Mild hypothermia for uncontrollable rise in ICP (40)
3. <i>Emergency liver transplantation</i>
Mild hypothermia during the operative procedure (41)