UT Southwestern Medical Center

Internal Medicine Grand Rounds

Cerebral Edema in Patients with Acute Liver and Renal Failure

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This is to acknowledge that Tamim Hamdi, MD has disclosed that he does not have any financial interests or other relationship with commercial concerns related directly or indirectly to this program. Dr Hamdi will not be discussing off-label uses in his presentation.

Presented by:

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I joined the Department of Internal Medicine, Division of Nephrology in the summer of 2014. My interests are wide and range from helping my clinic patient achieve stability and avoid dialysis, to managing the acutely ill patient with multi-system organ failure in the intensive care unit. I have a special passion to critical nephrology and all mechanical support devices, and for someone who has been "on both sides", I thrive to bridge the gap between intensive care medicine and nephrology to provide true interdisciplinary care to our severely ill and most vulnerable patients.

Purpose of the presentation:

1- To provide an overview of the pathogenesis of cerebral edema in patients with acute liver and renal failure, with special emphasis on the multifactorial nature of this condition.
2- To provide an overview of the management of cerebral edema from a nephrologist's perspective with a brief description of a novel approach for delivering osmotherapy.

Overview of the presentation:

The following topics will be covered chronologically:

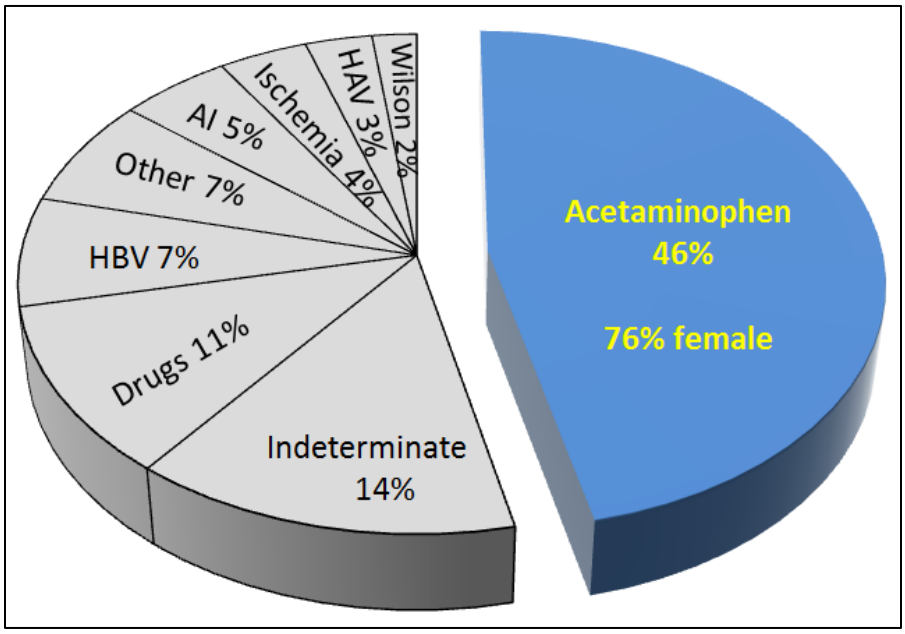
1- Epidemiology of acute liver failure.
2- Clinical presentation of acute liver failure with emphasis on concomitant renal failure, hemodynamic instability, hyponatremia, and systemic inflammation.
3- Pathogenesis of cerebral edema: role of the failed liver in generating cerebral edema; potential roles of the failed kidney, dialysis, hyponatremia, and systemic inflammation in worsening cerebral edema.
4- Management of cerebral edema from a nephrologist's perspective: effect of slow dialysis on intra-cranial pressures; description of dialysis-based osmotherapy and advantages over conventional delivery of osmotherapy

Educational objectives:
At the end of the presentation, the listener should be able to understand the various mechanism that lead to water entry into the brain cells and development of cerebral edema, how cautious renal support can help provide stability and provide a novel approach for providing osmotherapy.

Definition and Epidemiology

Acute liver failure (ALF) is defined as the sudden loss of liver function without preexisting liver disease[1] and affects approximately 2000 persons annually in the United States.[2] In a cohort of 1147 adult patients at 23 clinical sites between 1997 and 2008, ALF affected young patients with an average age of 38 years and twice more females than males. Acetaminophen toxicity is the leading cause of ALF in North American and Europe and accounts for about half of the cases (figure 1). Intentional and non-intentional acetaminophen ingestion are responsible for an equal number of ALF cases in the United States.[1]

Figure 1: Etiology of acute liver failure



Female patients constituted 67% of the whole acute liver failure cohort and 76% of the cases caused by acetaminophen toxicity. HBV: hepatitis B virus; AI: autoimmune; HAV: hepatitis A virus.

Clinical Presentation:

The hallmark of ALF is the combination of coagulopathy and encephalopathy[3] but patients with ALF frequently present or subsequently develop multi-system organ failure. Acute kidney injury (AKI) occurs in 75% of cases caused by acetaminophen toxicity[4,5] owing to the direct nephrotoxic effect of the acetaminophen metabolite N-para-aminoquinonimine (NAPQI), the same metabolite that mediates hepatotoxicity. Classical etiologies of AKI are usually present and include: reduced total blood volume secondary to poor oral intake; reduced effective arterial blood volume due to a combination of peripheral vasodilation, reduced serum albumin levels, and vascular leak induced by the acute inflammatory state; hemodynamic instability frequently present in ALF patients; and finally the use of nephrotoxic medications such as antibiotics. Acute kidney injury does not directly lead to death but worsens the overall outcome.[6]

Hyponatremia is almost universal in patients with ALF and is similarly multifactorial. The abovementioned reduced blood volume leads to a hypovolemic stimulus for antidiuretic hormone release with subsequent water retention. This condition can be iatrogenically

exacerbated if large volumes of hypotonic drips are infused to the patient such as when administering vasopressors, sedatives, analgesics, paralytics, antibiotics, or the antidote N-acetylcysteine.

Systemic inflammatory response syndrome (SIRS) and hemodynamic instability are common and mimic the features observed in patients suffering from septic shock. SIRS without infection is present in 40% of patients with ALF while an infection is documented in up to 47%.[7] Hypotension is multifactorial and shares some similarities with the hypotension associated with hepatorenal syndrome. Peripheral vasodilation is thought to result from increased level of vasoactive substances such as nitric oxide. Mice subjected to intraperitoneal carbon tetrachloride-induced ALF displayed a significantly increased level of nitric oxide synthase levels.[8] Other clinical manifestations include coagulopathy and acute lung injury.

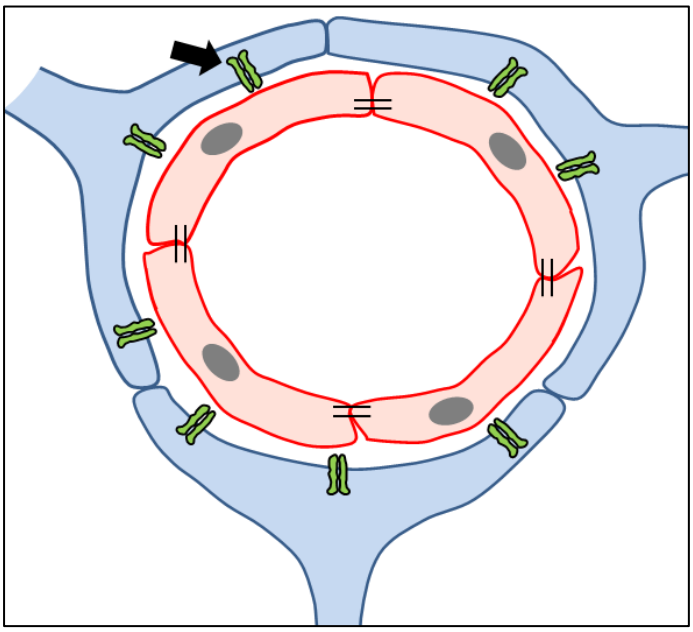
Cerebral edema is defined as the increase in the brain water content and is one of the most common and potentially fatal complications of ALF. Cerebral edema is directly related to the severity of hepatic encephalopathy, occurring in up to 80% of patients with grade IV encephalopathy.[2] About 30% of patients die in the setting of intractable cerebral edema, systemic infections, and hemodynamic collapse, 30% undergo orthotopic liver transplantation, and 40% recover.[2,5,7,9,10] In this paper, an overview of the pathogenesis of cerebral edema will be outlined followed by management plan as seen from the nephrologist's perspective.

Cerebral Edema:

Basic physiology of brain water homeostasis

The brain is encased in the rigid skull with little space for expansion and increase in its water content can lead to catastrophic implications thus the need for tight brain water content regulation. Astrocytes account for a third of the brain cells and are a key component of the blood brain barrier (BBB) and regulator of water and ion transport. Under normal physiologic conditions, the brain endothelial cells are known to lack any transmembrane water channels (aquaporins) and to possess tight junctions located toward their luminal sides. Additionally, endothelial cells are completely ensheathed by the foot processes of perivascular astrocytes. Those foot processes display a highly polarized expression of the water channel aquaporin-4 (AQP-4), specifically located on their perivascular side, rendering this cell a key component in regulating water influx and outflux of the brain (figure 2). AQP-4 is the most studied brain water channel and is reported to mediate cerebral edema under various pathological conditions. For example, wild-type mice subjected to hyponatremia through intraperitoneal free water injection developed an expected reduction in brain specific gravity reflecting an increase in brain water content, as well as hemispheric enlargement. Electron microscopic examination revealed swelling of the perivascular astrocyte foot processes indicating water entry into the brain. Both effects were significantly attenuated in AQP-4 knockout mice, confirming the pivotal role of the brain astrocytes and the AQP-4 channel in regulating brain water content.[11]

Figure 2: Astrocytes and blood brain barrier

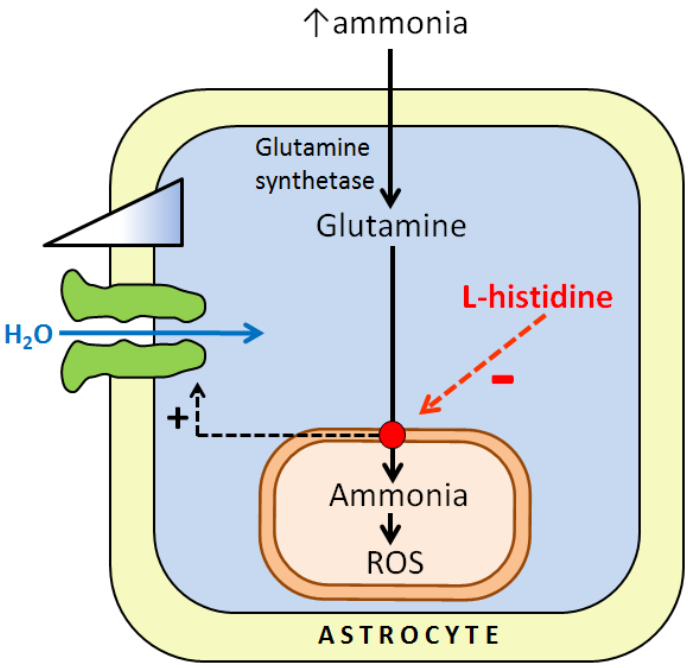


Blue: astrocyte foot processes; red: brain endothelial cells; arrow: aquaporin-4 water channels localized at the vascular side of the foot processes. Note the tight junctions between the endothelia cells towards their luminal sides

Pathogenesis of cerebral edema

The injured liver plays a pivotal role in the development of cerebral edema, but many of the failed organ systems mentioned above contribute to the development or worsening of this condition. ALF contributes through two potential mechanisms: cytotoxic and vasogenic cerebral edema.[12] Cytotoxic cerebral edema is thought to develop secondary to the resultant hyperammonemia because patients suffering from conditions that lead to elevated ammonia levels without liver failure such as valproate toxicity and urea cycle defects also develop cerebral edema. The astrocytes will uptake the ammonia and attempt its detoxification using the enzyme glutamine synthetase. The resultant production of the osmotically active glutamine leads to water influx into the cell. On the other hand, the "Trojan Horse" theory hypothesize that the resultant glutamine eventually enters into the mitochondria where it gets converted to glutamate and ammonia. The accumulation of ammonia inside the mitochondria leads to injury, impaired cell respiration, and cell swelling. Interestingly, thioacetamide-induced ALF in rats lead to an increase in brain water content along with increased expression of astrocytes APQ-4 water channels. The addition of L-histidine, an inhibitor or glutamine entry into the mitochondria, completely abrogated the increase in AQP-4 expression indicating that the brain swelling was indeed mediated by glutamine entry into the mitochondria and was facilitated by the resultant increased expression of AQP-4 (figure 3).[13] Vasogenic cerebral edema has been reported in patient with ALF using radiological studies and is less well understood or described in the literature. Patients with ALF are thought to have an increase in neuronal nitric oxide synthase leading to cerebral vasodilation, which along with impaired cerebral autoregulation result in increased cerebral blood flow and intra-cranial pressure. In patients with ALF, arterial ammonia level was found to correlate with cerebral blood flow which in turn correlated with the intra-cranial pressure.[14]

Figure 3: Effect of ammonia on astrocyte water influx



Production of glutamine mediates water entry into the astrocytes through the creation of an osmotic gradient or through the "Trojan Horse" effect, which involves glutamine entry into the mitochondria with subsequent damage and cell swelling. This process also increases expression of AQP-4 water channel and is abrogated using L-histidine. Triangle: glutamine-induced osmotic gradient

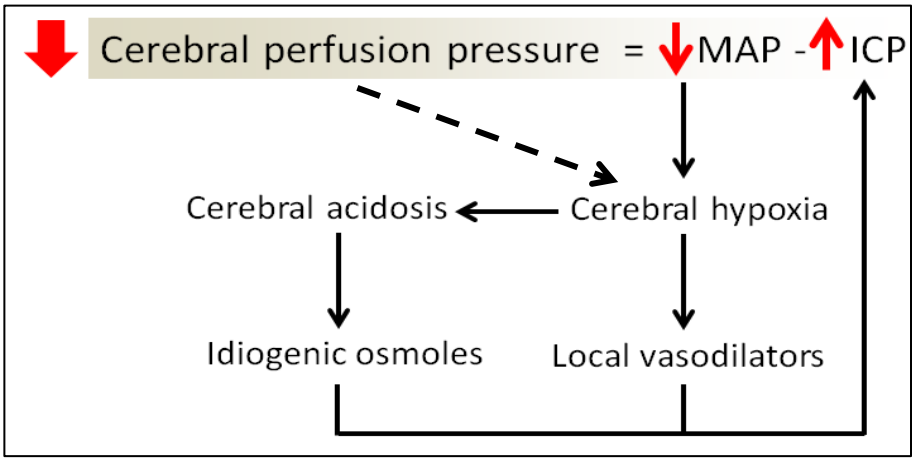
The concomitantly injured kidney might also contribute to the development or worsening of cerebral edema. Acute kidney injury is a systemic disease with remote manifestation and kidney-brain cross-talk has been described.[15,16] Mice subjected to bilateral ischemic reperfusion injury developed increase in brain permeability as measure by increase in Evans blue-bound albumin in the brain tissue. AKI also promotes brain inflammation with increase in keratinocyte-derived chemoattractant and granulocyte-colony stimulating factor which whether produced *in situ* or remotely lead to a significant increase in the number of activated microglial cells in the brain.[17] In a more chronic model of kidney injury, 5/6 nephrectomy in rats resulted in a 2.5 fold increase in the expression of brain AQP-4.[18]

ALF patients undergoing hemodialysis in particular face a heightened risk of developing or worsening cerebral edema. Patients receiving standard (rapid and of short-lasting) hemodialysis developed reduction in their brain density (caused by water influx) as measured by CT scans performed after hemodialysis.[19] The exact mechanism underlying the water shift into the brain is unclear but two main theories might explain this process. The theory of "reverse urea effect" hypothesizes that standard hemodialysis result in faster and more efficient removal of urea from the blood when compared to the brain. This renders the once osmotically inactive urea compartmentalized in the brain and thus creates and osmotic gradient leading to water shift and brain swelling. This mechanism was documented in nephrectomised rats where hemodialysis resulted in about 5 times more urea clearance from the blood than the brain resulting in 6% increase in brain water content.[20] On the other hand, the theory of "idiogenic osmoles" states that urea is efficiently removed from the brain with standard dialysis and thus is not to blame for the water shift. Standard dialysis in dogs subjected to bilateral ureteral ligation lead to a 13% increase in brain water content. Although urea was efficiently removed from the brain, the brain osmolality was not reduced, indicating that other non-urea solutes were produced in response to

hemodialysis.[21] In a subsequent experiment, the pH of the CSF was reduced despite the increase in plasma pH as expected with dialysis, thus the authors concluded that the brain is producing acidic and osmotically active solutes in response to rapid dialysis.[22] The nature of those solutes was unknown so were termed "idiogenic osmoles" but were later identified as products of intracellular metabolism and included the amino acids glycine and taurine and the sugar alcohol polyol myoinositol. It is worthy to mention that brain edema did not develop in uremic dogs subjected to slow dialysis or control dogs subjected to rapid dialysis which indicates that uremia and rapid dialysis are both required for the generation of idiogenic osmoles. Aside from the effect of urea on brain water content, the rapid rise of serum bicarbonate occurring with standard hemodialysis contributes to the development of brain swelling. The buffering of the hydrogen ions leads to the production of carbon dioxide which rapidly diffuses into the cells and result in "paradoxical intracellular acidosis." This effect is more pronounced when the intracellular bicarbonate is already depleted as usually seen in acutely ill patients with AKI and acidosis.[23] The intracellular acidosis is believed to result in breakage of phosphate moieties and production of the same osmotically active idiogenic osmoles with resultant water shift and brain swelling.

Beside the effect of dialysis on urea and bicarbonate levels, hemodialysis can induce an independent increase in intracranial pressure especially in the hemodynamically unstable patient. When patients with ALF, AKI, and grade IV encephalopathy received standard hemodialysis, an early drop in the mean arterial pressure was noted, even before any fluid removal was performed. This reduction in the mean arterial pressure was shortly followed by an increase in the intracerebral pressure.[24] None of the theories mentioned above (urea shift, idiogenic osmoles, and rapid rise in serum bicarbonate level) can explain this hemodynamic instability which was observed before any meaningful changes in any solute level has occurred, suggesting that those changes were volume and solute-independent. It is believed that the rapid contact of the patient blood with the dialyzer membrane leads to auto-activation of factor XII (with resultant production of bradykinin), activation of monocytes (with resultant release of inflammatory mediators), and activation of the alternative complement pathway. The resultant hypotension in the hemodynamically fragile ALF patient coupled with impaired cerebral autoregulation lead to cerebral hypoxia. The end result is release of local vasodilators and production of idiogenic osmoles which will further increase the intracranial pressure and reduce the cerebral perfusion pressure (Figure 4), and effect that will further potentiate this vicious circle.

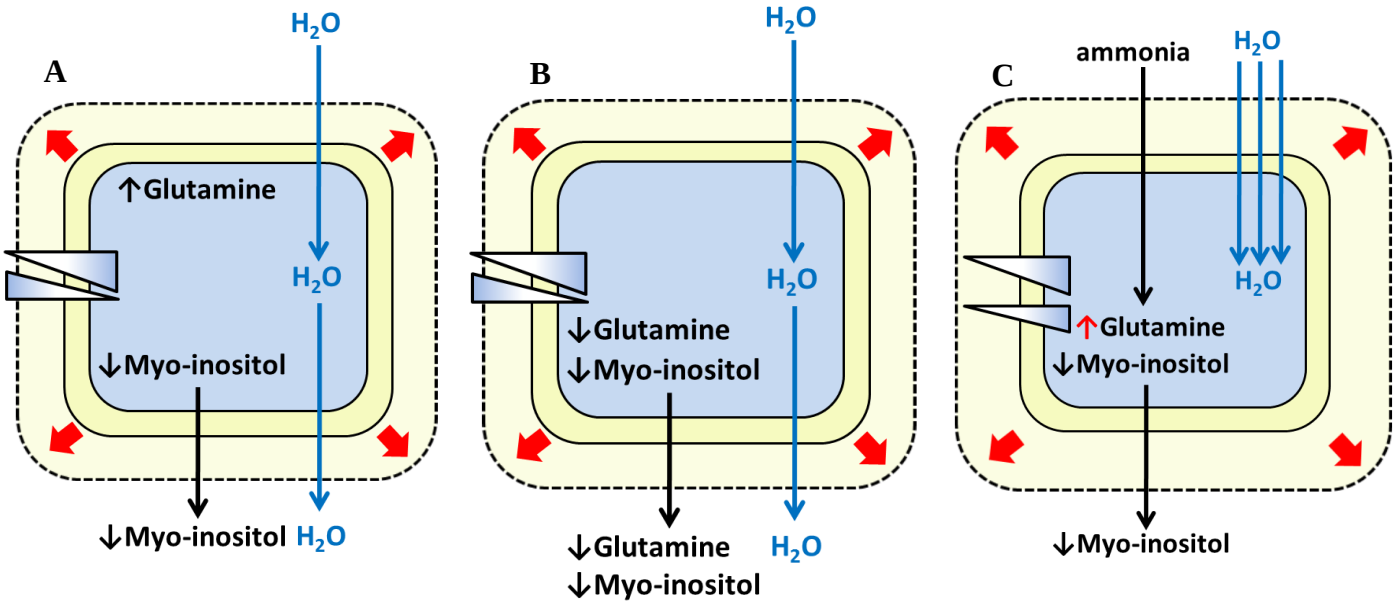
Figure 4: Effect of dialysis-induced hypotension in cerebral perfusion pressure



Dialysis-induced, volume-independent reduction in mean arterial pressure (MAP) leads to a solute-independent increase in the intracranial pressure (ICP) with resultant reduction in the brain perfusion pressure. The latter will further exacerbate the cycle (broken arrow).

The presence of hyponatremia in patients ALF worsens the cerebral edema as it present a hypotonic load on the brain cells which exhausts their adaptive responses. In an elegant study[25] examining the effect of concomitant hyperammonemia and hyponatremia, rats were subjected to either conditions or a combination of both and their brain concentration of glutamine, myoinositol and taurine were examined along with a measure of the brain water content. Rats subjected to portocaval anastomoses and ammonia infusion developed and increase glutamine concentration as expected in this condition along with a 0.8% increase in brain water (figure 5A). However, the cellular content of myoinositol and taurine were decreased, reflecting a cellular adaptive response: the increase in intra-cellular glutamine created and osmotic gradient followed by water shift into the cell, and the reduction of the other organic solutes is an attempt to reverse this gradient and move water outside the cell. Hyponatremia induced by dDAVP infusion resulted in 1% in brain water content. Hyponatremia resulted in a relatively hypertonic intracellular medium with subsequent intracellular water shift. The adaptive defense mechanism in this case involves reduction of all three organic solutes to allow water exit outside the cells (figure 5B). When both interventions were combined with resultant hyperammonemia and hyponatremia, there was an additive 1.8% increase in brain water content. The presence of hyponatremia exhausted the cell adaptive response with reduction in taurine and myoinositol and depletion of the available organic solutes, leaving it vulnerable to the hypertonic effect of ammonia-induced increase in glutamine (figure 5C).

Figure 5: Effect of hyperammonemia, hyponatremia, and combination of both on brain water content



Taurine was similar to myoinositol and is not shown. Panel A: hyperammonemia leads to increased glutamine and reduced myoinositol and taurine levels. Upper triangle represents glutamine-induced osmotic gradient while lower (reversed) triangle represents cellular attempt at reversing this gradient by extrusion of organic solutes. Panel B: hyponatremia leads to reduction in all three organic solutes. Upper triangle represents hyponatremia-induced osmotic gradient while lower triangle is similar to Panel A. Panel C: concomitant hyperammonemia and hyponatremia exerts an additive effect on brain water content. Upper triangle represents glutamine-induced osmotic gradient while lower triangle of similar orientation represents additive hyponatremia-induced osmotic gradient.

Finally, the presence of systemic inflammation in patients with ALF might induce subtle alteration in the blood brain barrier (BBB) and perhaps facilitate the influx of solutes and water. Patients with ALF show similar features to patients with septic shock and display an increase in various pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukins 1 and 6, among others. Mice subjected to intraperitoneal injection of the hepatotoxin carbon tetrachloride developed almost a 6 fold increase in serum TNF-α level with similar increase in TNF-α mRNA levels extracted from the liver tissue confirming its hepatic origin.[8] A patient who developed intractable cerebral edema and reduced cerebral perfusion pressure was temporarily stabilized with native hepatectomy before successful liver transplant. The TNF-α levels decreased significantly following the hepatectomy along with immediate improvement in cerebral perfusion pressure.[26] Even the brain of patient with ALF is reported to produce TNF-α and other inflammatory cytokines.[27] On the other hand, the detrimental effect of TNF-α on the integrity of the BBB was reported in animal models where injection of TNF-α resulted in opening of the BBB, an effect replicated when sepsis was induced by intraperitoneal bacterial injection. Interestingly, the addition of a TNF-α antibody completely blocked the alteration in BBB permeability, indicating that TNF-α indeed is responsible for those changes rather than the bacterial infection per se[28]. The topic of systemic inflammation in patients with ALF is an area of active research and was the subject of a recent review.[29]

Management of cerebral edema: a nephrologist's perspective

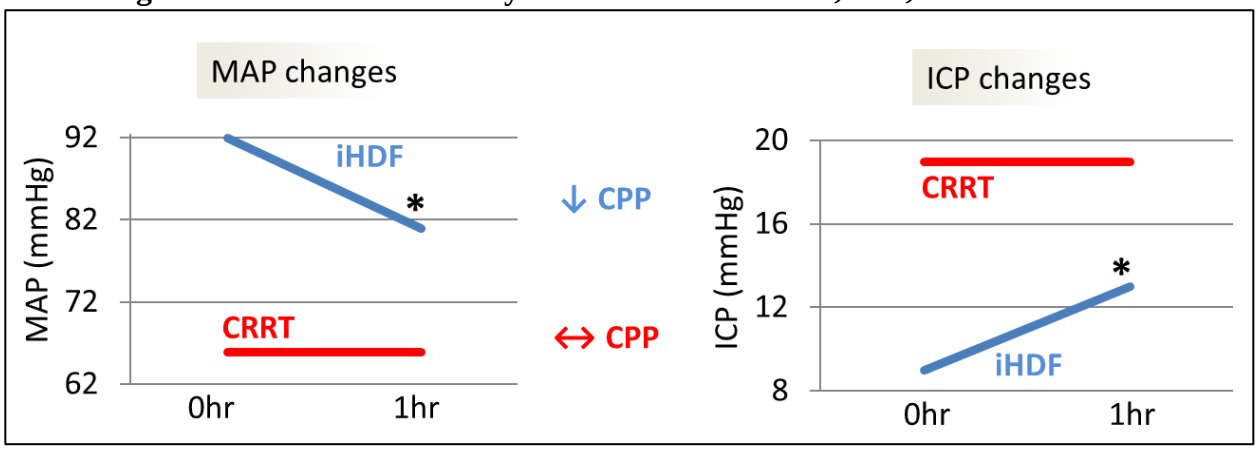
Multiple approaches are simultaneously implemented to control the cerebral edema in this severely ill group of patients. Head of bed elevation, hypothermia, hyperventilation, and relief of any venous outflow obstruction from the brain (midline head position, avoidance of internal jugular lines, etc.) can help reduce the brain swelling but hypertonic therapy remains the cornerstone of management. For patients requiring dialysis, the modality of renal replacement therapy is of paramount importance. Continuous renal replacement therapy (CRRT, slow and long lasting) is the modality of choice and provides the advantages outlined in table 1. Of note, the hemodynamic changes reported in figure 4 did not occur when patients received CRRT despite having lower baseline mean arterial pressure and higher intracranial pressure (figure 6).[24] The slower blood-membrane contact results in less systemic inflammation and some of the membranes used in CRRT machines possess adsorptive capabilities that can reduce the levels of factor D for example, the rate limiting enzyme of the alternate complement pathway activation.[30]

Additionally, CRRT can easily clear many water soluble toxins known to be elevated in patient with ALF, including phenols, mercaptans, and ammonia. Ammonia is easily removable given its small molecular size, water solubility, and absence of protein binding. However, ammonia is usually produced in large amounts and although can be cleared with standard short dialysis, rebound is seen immediately after discontinuation of dialysis and only CRRT is able to prevent this rebound. Despite the physiologic plausibility, little data exist whether dialytic removal of ammonia confers any clinical benefits.[31]

Table 1: advantages of continuous renal replacement therapy

Advantage	Result
Slow urea removal	No urea compartmentalization; No production of idiogenic osmoles
Slow rise in bicarbonate	No paradoxical acidosis with production of idiogenic osmoles
Slow blood flow	No hypotension, cerebral hypoxia, acidosis, and production of idiogenic osmoles
Slow blood flow	Convective heat loss helps establishing hypothermia
Removal of ammonia	Theoretical benefit
Providing osmotherapy	

Figure 6: Effects of hemodialysis and CRRT on MAP, ICP, and CCP



Left panel: reduction in MAP was only noted in the intermittent hemodialysis group (blue) despite higher baseline values. Right pane: increase in the ICP was only noted in the hemodialysis group despite lower baseline values. Middle: resultant reduction in CPP with HD and stability with CRRT. iHDF: intermittent hemodiafiltration (a form of rapid dialysis); CRRT: Continuous renal replacement therapy; MAP: mean arterial pressure; ICP: intracranial pressure; CCP: cerebral perfusion pressure. *$p < 0.05$

Induction of systemic plasma hypertonicity using hypertonic saline or mannitol therapy remains the cornerstone of management of cerebral edema. Urea has fell out of favor due to its low reflection coefficient indicating that after initial urea-induced water outflux from the brain, the effect will be reversed as urea diffuses into the brain followed by water. Mannitol and hypertonic saline are both acceptable alternatives[32] as there are no standardized protocols for treatment of cerebral edema in patients with ALF. The details related to each therapeutic option are beyond the scope of this paper which will focus on the delivery of hypertonic saline through dialysis. In patients suffering from concomitant kidney injury, plasma hypertonicity can be regulated by adjusting the prescription of CRRT to achieve and maintain a specific higher systemic sodium level. CRRT has been classically used to remove wastes and provide useful solutes such as bicarbonate and calcium, without much impact on the serum sodium level. However, just like any other solute, serum sodium levels can be manipulated and increased to any desired level.

CRRT is delivered through various machines and dialysis fluid preparations. When using machines that utilize premixed fluid bags with fixed serum sodium level, the sodium concentration for example can be raised from 140 mEq/L to 154 mEq/L by the addition of 17.5 mL of 23.4% hypertonic saline (sodium concentration of 4 mEq/mL). The major drawback for this approach is the risk of contamination and errors during the injection of hypertonic saline into the fluid bags. Fatal errors during the compounding of replacement fluid bags have been reported.[33] In a previous experience,[34] eleven consecutive patients with acute liver failure, renal failure and cerebral edema were treated with hypertonic CRRT of whom five patients had an intra-cranial pressure (ICP) monitor inserted. Table 2 summarizes the patients' demographics and relevant clinical settings. The duration of hypertonic CRRT ranged from 4 to 13 days. Within 24 hours, all patients had their sodium levels at or around the specified target. Severe hypernatremia or unexpected changes in serum sodium did not occur in any patient. Similarly, serum sodium was maintained throughout the duration of therapy and was not significantly lowered despite the large loads of hypotonic IV fluids. Figure 7 provides details regarding the actual serum sodium level, the desired serum sodium level (as requested by the intensivist or neurointensivist), and the prescribed dialysis sodium concentration. For patients who had an ICP monitor, we observed an improvement in the ICP within 24 hours (figure 8). In this model, the desired serum sodium was smoothly maintained with less risk of hypernatremia, no fluctuations in serum sodium level, and gradual reversed at the end of therapy with less risk for rebound cerebral edema. Table 3 summarizes the advantages of this model over the conventional approach. The patient suffering from Budd-Chiari syndrome as well as one patient with acetaminophen toxicity died despite maintaining target serum sodium levels. Among the nine patients who survived, none required liver transplantation. Seven patients had normalization of their serum creatinine and liver function tests, while the remaining two had partial improvement in both organ functions and were discharged without requiring outpatient dialysis and were lost to follow-up.

Conclusion:

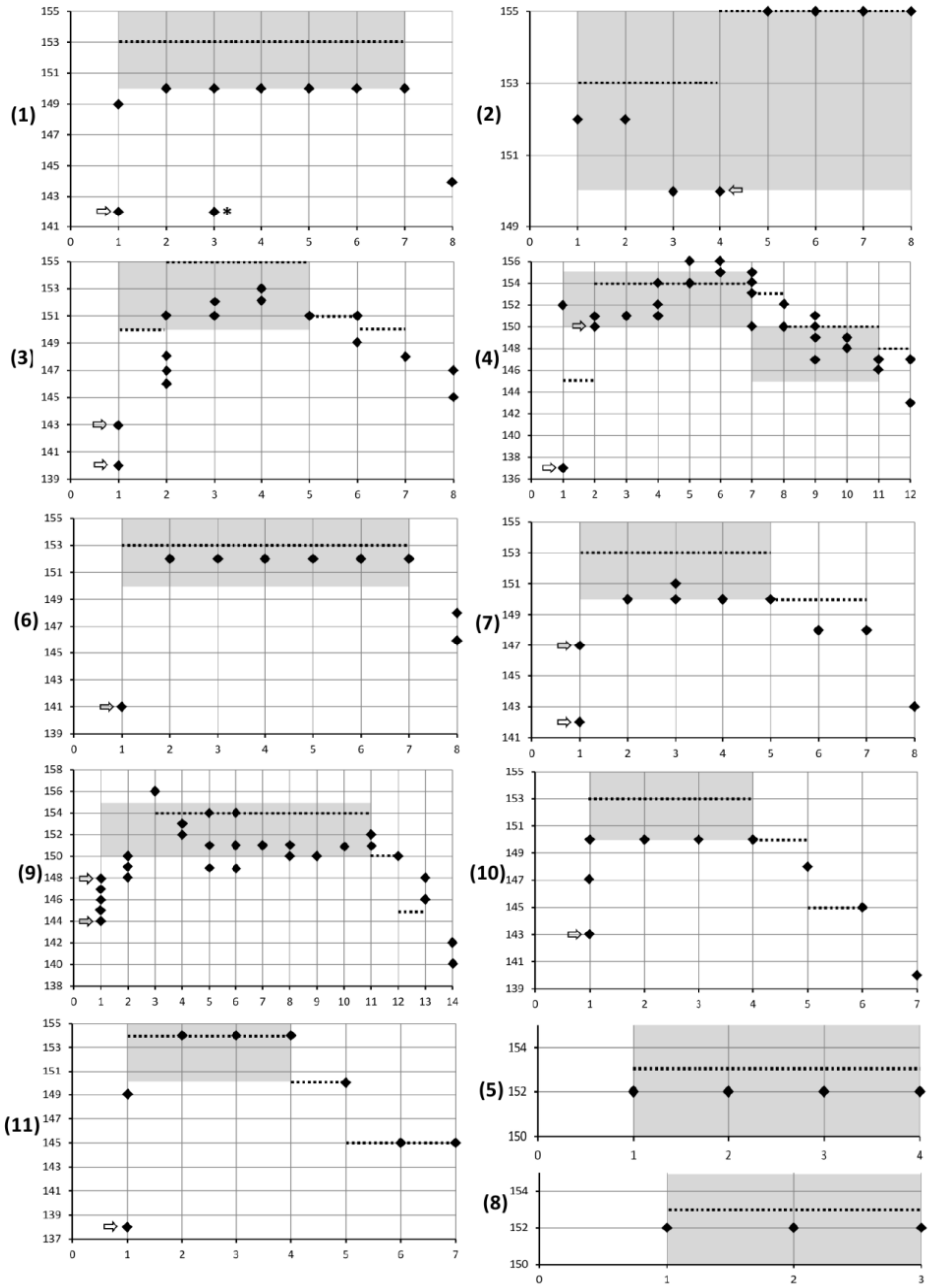
Acute liver failure is life threatening condition that usually present as a syndrome involving multiple system failures. Many of the concomitantly failed organs such as the kidneys and the cardiovascular system as well as some of the medical interventions can exacerbate cerebral edema. Death occurs in the setting of cerebral edema and hemodynamic collapse. Osmotherapy is the cornerstone of the management of cerebral edema and can be efficiently delivered with dialysis. A true multidisciplinary approach is required to provide the optimal care for this severely ill group of patients.

Table 2: Baseline characteristics and clinical settings

Case no.	Age, gender	Etiology of ALI	SOFA score	MELD score	Baseline renal function	Vaso-pressors	MV	ICP monitor
1	43, F	Septic shock	17	39	Normal	Yes	No	No
2	50, F	Budd-Chiari	10	45	Normal	No	No	No
3	24, F	APAP	14	23	unknown	Yes	No	No
4	40, F	APAP	16	35	Normal	Yes	Yes	Yes
5	34, F	APAP	16	33	Normal	Yes	Yes	Yes
6	42, F	APAP	14	42	Normal	Yes	No	No
7	25, M	APAP	14	45	unknown	Yes	No	No
8	19, F	APAP	11	51	unknown	No	No	No
9	36, F	APAP	14	36	Normal	Yes	Yes	Yes
10	54, F	APAP	13	37	Normal	Yes	Yes	Yes
11	44, F	unknown	9	29	Normal	Yes	Yes	Yes

ALI: acute liver in injury; APAP: N-acetyl-para-aminophenol; SOFA: sequential organ failure assessment. Initial score of more than 11 is associated with a mortality rate >90%, while a score of 8-11 is associated with a mortality rate of 60%; MELD: model for end-stage liver disease score at time of initiation of ol-CVVHD-RCA; MV: mechanical ventilation; ICP: intra-cranial pressure. Patients 2 and 5 did not survive. ol-CVVHD-RCA: online continuous veno-venous hemodialysis with regional citrate anticoagulation (a form of CRRT)

Figure 7: Individual serum, dialysis fluid, and target sodium levels



X-axis indicates time in days and Y-axis denotes serum sodium concentration (mEq/L). Filled diamonds (♦) and broken (- - -) lines indicate achieved serum sodium levels and dialysate sodium concentrations, respectively. Solid arrows indicate administration of 20 ml of 23.4% saline bolus. Shaded areas indicate desired serum sodium concentration range. Note that identical serum sodium values throughout a day are superimposed. The decrease in the dialysate sodium indicates the weaning from osmotherapy and the disappearance of the broken line indicated the stopping of CRRT. Patients (2) and (5) died. Patients (5) and (8) depicted in the right lower corner underwent the shortest duration of therapy. * Sodium level likely a laboratory error; rechecked immediately and was 150 mEq/L.

Figure 8: Intracranial pressure (ICP) changes after initiation of hypertonic CRRT

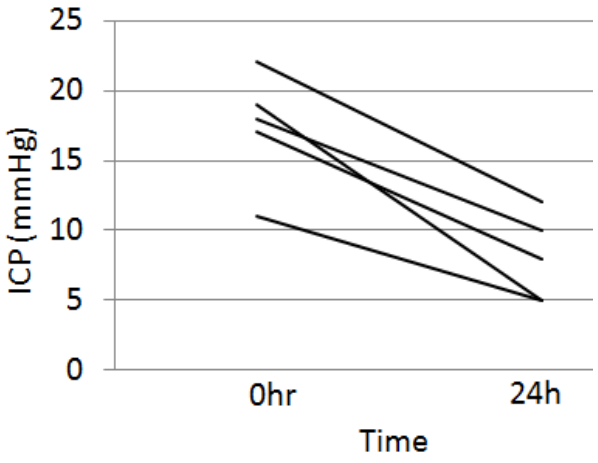


Table 3: Comparison of standard vs CRRT-based hypertonic therapy

Drawbacks of standard hypertonic saline drips	Hypertonic CRRT
• Rapid/unpredictable increase in initial sodium levels	• Controlled increase
• Fluctuations in serum Na levels	• Stable serum Na levels
• Difficult weaning	• Smooth weaning
• Additional workload	• none

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