Brain and the Liver: Cerebral Edema, Hepatic Encephalopathy and Beyond

8

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Abstract

Occurrence of brain dysfunction is common in both chronic liver disease as well as acute liver failure. While brain dysfunction most commonly manifests as hepatic encephalopathy is chronic liver disease; devastating complications of cerebral edema and brain herniation syndromes may occur with acute liver failure. Ammonia seems to play a central role in the pathogenesis of brain dysfunction in both chronic liver disease and acute liver failure. In this chapter we outline the pathophysiology and clinical management of brain dysfunction in the critically ill patients with liver disease.

Keywords

Hepatic encephalopathy • Acute liver failure • Fulminant hepatic failure • Chronic liver failure • Acute-on-chronic liver failure • Hepatic coma • Intracranial hypertension

Learning Objectives

- Review the classifications, mechanisms and neuroimaging findings involved in hepatic encephalopathy
- Differentiate the risk factors and implications of hepatic encephalopathy in acute Liver failure and Chronic Liver Failure
- Recognize and distinguish the approach to evaluating and managing hepatic encephalopathy and its confounders in critically ill patients with acute and chronic liver failure
- Outline the organ system approach to ICU considerations in hepatic encephalopathy applicable to acute and chronic liver failure

8.1 Introduction

Hepatic encephalopathy (HE) represents brain dysfunction directly caused by liver insufficiency and or portosystemic shunting (PSS) that manifests as a wide spectrum of neurological and psychiatric deficits ranging from subclinical deficits to coma.

8.2 Classification of HE

To capture the complexity and breadth of HE, the recent 2014 combined EASL-AASLD guidelines have integrated four characteristic factors into the classification of HE (see Table 8.1): (1) underlying disease (2) severity of manifestation

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Table 8.1 Classification and grading of hepatic encephalopathy[a]

Classification of HE	Sub classification of HE	Defining feature and description	
1. Underlying disease[a]	Type A	**A**cute Liver Failure	
	Type B	Portal-systemic **B**ypass without intrinsic hepato-cellular damage	
	Type C	**C**irrhosis and portal hypertension with portal-systemic shunts	
2. Severity of Manifestation[b]	Grade 0	No HE	No HE
		Psychometric or neuropsychological alterations without clinical evidence of mental change	**Minimal HE or COVERT**
	Grade I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm	**COVERT**
	Grade II	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis	**OVERT**
	Grade III	Somnolence to semi stupor Responsive to stimuli Confused Gross disorientation Bizarre behavior	
	Grade IV	Coma	
3. Time course of presentation	Episodic	Single or episodes occurring >6 months	
	Recurrent	Episodes occur <6 months	
	Persistent	Behavioral alterations that are always present and interspersed with relapses of overt HE.	
4. Precipitating factors	None		
	Precipitated	Precipitating factors can be identified in nearly all bouts of episodic HE type C and should be actively sought and treated when found	

[a]AASLD-EASL Hepatic encephalopathy Guideline [2]
[b]Adapted from West Haven Criteria [1]

(3) time course and (4) precipitating factors. Severity of manifestation was adapted from West Heaven (WH) criteria and merged with three newer definitions: minimal HE, covert HE and overt HE. For this critical care review, we will limit our focus on overt HE (Type A and C). While the WH Criteria [1] remains the staging tool for severity of HE, there remains significant differences in the implications of the grade of HE across the disease categories.

8.3 HE, Cerebral Edema and Mortality in ALF and Overt Type C HE

Cerebral edema (CE) at the cellular level (cytotoxic edema) or interstitial level (vasogenic edema) is a pathophysiologic hallmark of HE in both acute and chronic liver failure. In chronic liver failure, the occurrence of CE is not apparent on a macroscopic level. Hence the edema is not visible on conventional brain imaging, causing the clinician no concerns for elevated intracranial pressure (ICP). In acute liver failure, intracranial hypertension (IH) is a looming concern to the clinician. The term intracranial hypertension (IH) specific to ALF, implies both a cause and effect. The cause refers to diffuse CE visible on brain imaging and the effect refers to elevated ICP and impending transtentorial herniation if left untreated.

Acute liver failure (ALF) is a devastating disease with mortality up to 40–50% due to progressive multiorgan failure [3]. Worsening HE in ALF heralds a grim a prognosis. Grade IV HE precedes the development of cerebral edema and IH culminating in transtentorial herniation. Historically the progression from HE to transtentorial herniation accounted for up to 75–80% of deaths in ALF [4, 5]. With improved ICU care focusing on neuroprotective interventions, the mortality attributable to IH is in the range of 10–20% [6].

Despite the absence of IH, the diagnosis of HE in chronic liver failure is associated with a 50% mortality at 1 year. The correlation between Type C HE and increased mortality in cirrhosis has been difficult to decipher due the heterogeneity of the occurrence and impact of accruing multi-organ failure. Acute-on-chronic liver failure (ACLF) remains a term in search of a more precise definition that accurately captures a dominant subset of decompensated cirrhotics with disproportionately high short-term mortality rates attributable to multiorgan failure. In the recent European Canonic study,

ACLF was distinctly defined by the sequence and severity of organ dysfunction, allowing for a better understanding of the implications of HE in this critically ill subgroup [7, 8]. HE in both decompensated cirrhosis and ACLF was independently associated with increased mortality. However, mortality from HE associated with ACLF was significantly worse than the HE associated decompensated cirrhosis [9] and therefore warrants closer monitoring and early transfer to the ICU.

Unlike ALF, IH does not occur in decompensated cirrhosis but is infrequently reported in ACLF [10, 11]. The rare occurrence IH in ACLF is predicated upon the acuity of the liver injury rather than the chronicity of the liver disease [12]. A more recent retrospective study noted that cerebral edema leading to tonsillar herniation and death was observed in 4% (3/48) of patients with ACLF [13].

8.4 Pathophysiology

There remains no singular attributable etiology for HE. HE is a result of a complex interplay between brain ammonia, inflammation, altered neurotransmission pathways and cerebral hemodynamic dysautoregulation. Hyperammonemia continues to play a significant role in pathogenesis of HE [14, 15]. Ammonia is also thought to result in both cytotoxic and vasogenic brain edema, cerebral energy failure, excessive intracellular accumulation of the osmolyte glutamine and alterations in aquaporin-4 integral membrane proteins [16–19]. Ammonia also causes membrane depolarization, calcium influx, glutamate release, activation of proteases and production of free radicals which causes nitration of neuronal proteins and mitochondrial damage [19–21]. Figure 8.1

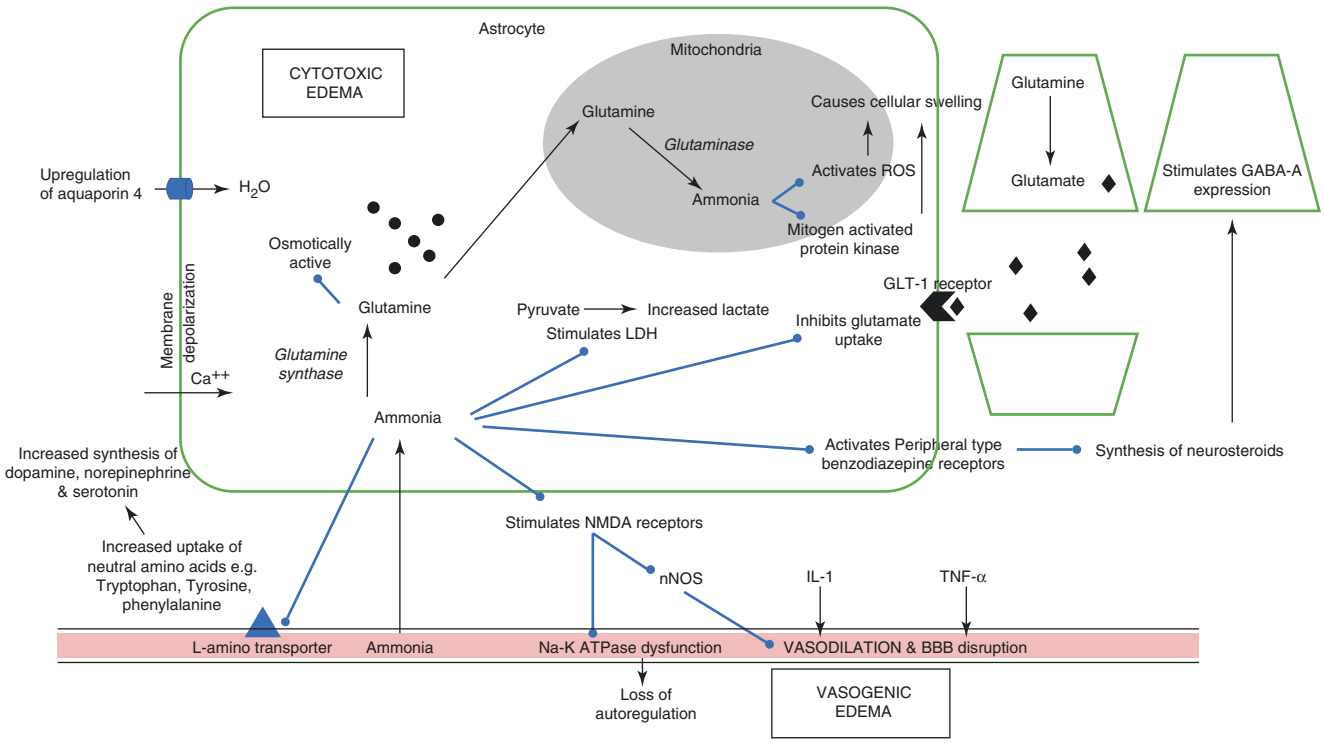


Fig. 8.1 Hypothesized neurotoxic mechanisms of hyperammonemia: Multiple pathways of ammonia related neurotoxicity have been discovered and postulated. Most significantly they affect astrocytes where ammonia is converted into glutamine. Glutamine has multiple deleterious effect in the CNS. Glutamine results in elevated synaptic glutamate levels and inhibits GLT-1 receptor thus preventing its reuptake. Glutamate stimulates postsynaptic receptors of neurons causing anxiety, agitation and convulsions. Glutamine is taken up by astrocyte mitochondria where it is reconverted into ammonia. This in turn stimulate ROS production in mitochondria, subsequently causing inflammation and cellular swelling through mitogen activated protein kinase. Glutamine is itself osmotically active and worsens swelling. Aquaporin 4 is upregulated by ammonia and IL-1 and is associated with cellular swelling. Ammonia also stimulates L-amino transporter in BBB, thus increasing uptake of neutral amino acids like tryptophan, tyrosine and phenylalanine. These compounds are building blocks for dopamine, norepinephrine and serotonin in CNS. It also results in stimulation of NMDA (N-methyl d-aspartate) receptors which mediates Na-K-ATPase dysfunction resulting in loss of autoregulation. Ammonia also causes membrane depolarization, calcium influx, glutamate release, activation of proteases and production of free radicals which causes nitration of neuronal proteins and mitochondrial damage. Ammonia also stimulates lactate dehydrogenase activity with subsequent formation of lactic acid and alanine. Hyperammonemia can result in increased neurosteroids production leading to elevated GABAergic tone in CNS. The loss of integrity of blood brain barrier results in formation of vasogenic edema. Hyperemia caused by failure of ATPase pump leads to loss of autoregulation of cerebral blood flow. Increased activity of neuronal nitric oxide synthase (nNOS) by ammonia toxicity results in nitric oxide production. In addition, cyclo-oxygenase gene is upregulated resulting in increased production of prostaglandins and eicosanoids which may contribute to hyperemia and increased cerebral blood flow. There is also evidence that there is microglial activation in ALF resulting in increased production of TNF alpha, IL-1 and IL-6

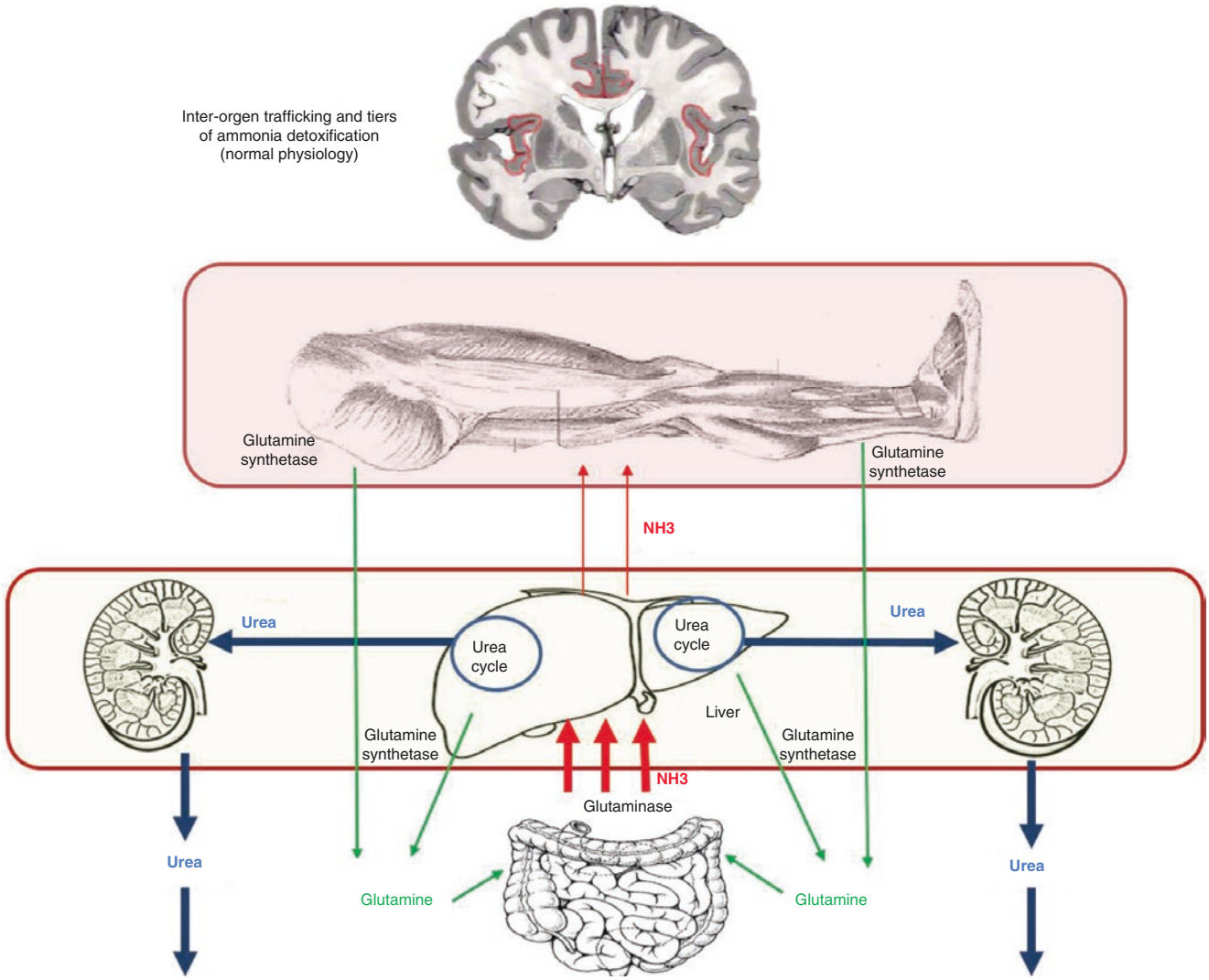


Fig. 8.2 Simplified conceptual model of interorgan trafficking and tiers of detoxification of ammonia in normal physiology: Dietary and circulating glutamine are converted by bowel endothelial cells to ammonia in the in the entero-hepatic circulation. Abnormal liver function and portosystemic shunting results in a large amount of ammonia entering the systemic circulation and breaching the first tier of detoxification. In end-stage cirrhosis, the significant loss of muscle mass further compromises the second tier of ammonia detoxification and exposes the brain to higher concentration of plasma ammonia. Astrocytes particularly in select regions of the cortical grey matter have the capacity to detoxify ammonia to glutamine by using glutamine synthetase enzyme. However, when overwhelmed with this process, glutamine accumulates intracellularly in the astrocytes and becomes osmotically active and causes a cytotoxic edema. Note that ammonia detoxification generates large amount of circulating glutamine which cannot be eliminated except indirectly via the kidneys. Renal impairment which is common in cirrhosis will intensify the severity and frequency of hepatic encephalopathy

provides a graphic representation of the various neurotoxic mechanisms in hyperammonemia. The homeostasis of ammonia is complex process dependent on multiple organ systems. Ammonia generated in the gut is detoxified to glutamine and urea by the liver and urea in turn is excreted by the kidneys. Defective sequential detoxification of ammonia by liver and kidney due to multi-organ failure in ALF and ACLF appreciably accounts for worsening HE. Muscle and brain (astrocytes) represent auxiliary ammonia detoxification systems that convert toxic ammonia to glutamine. Resultant glutamine accumulation in astrocyte is osmotically active and thus causes intracellular swelling (cytotoxic edema) [16, 22, 23] Hence, in the cachectic and catabolic end-stage cirrhotic, skeletal muscle provides minimal refuge to the brain from ammonia. A measured plasma ammonia level in a patient only discloses a small fraction of the proverbial ice berg, with the net bulk of the ammonia concealed in the form of glutamine. Excess glutamine can only be cleared indirectly via intact liver and renal function [24–26], without which glutamine becomes a precursor to generating more ammonia. Figures 8.2 and 8.3 provides a simplified graphic representation of this process.

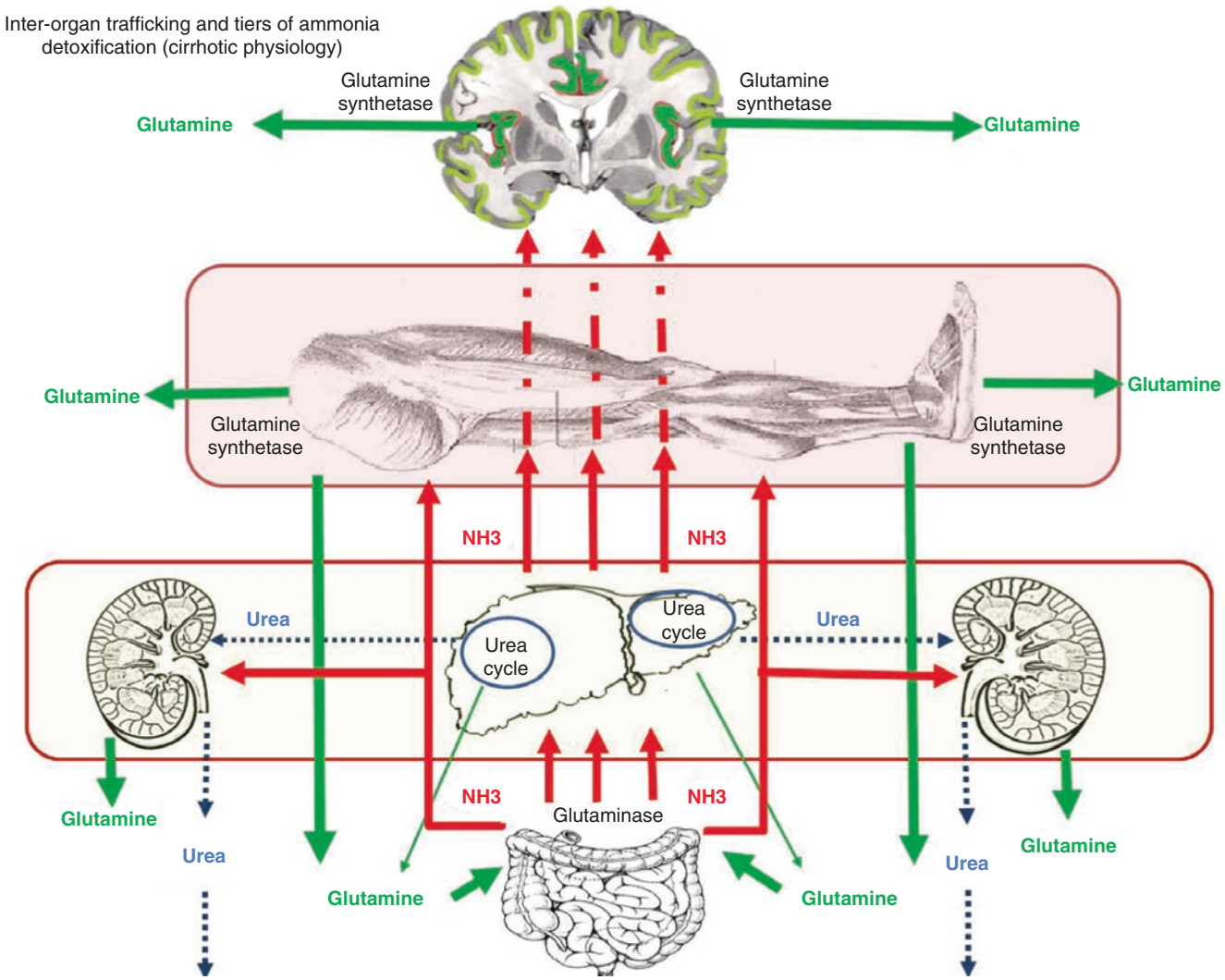


Fig. 8.3 Simplified conceptual model of interorgan trafficking and tiers of detoxification of ammonia in cirrhotic physiology: Dietary and circulating glutamine are converted by bowel endothelial cells to ammonia in the in the entero-hepatic circulation. Abnormal liver function and portosystemic shunting results in a large amount of ammonia entering the systemic circulation and breaching the first tier of detoxification. In end-stage cirrhosis, the significant loss of muscle mass further compromises the second tier of ammonia detoxification and exposes the brain to higher concentration of plasma ammonia. Astrocytes particularly in select regions of the cortical grey matter have the capacity to detoxify ammonia to glutamine by using glutamine synthetase enzyme. However, when overwhelmed with this process, glutamine accumulates intracellularly in the astrocytes and becomes osmotically active and causes a cytotoxic edema. Note that ammonia detoxification generates large amount of circulating glutamine which cannot be eliminated except indirectly via the kidneys. Renal impairment which is common in cirrhosis will intensify the severity and frequency of hepatic encephalopathy

Malignant cerebral edema resulting in intracranial hypertension and brain herniation appears to rely on secondary mechanisms specific to ALF. While cytotoxic edema is an explicit feature in HE, its immediate contribution to malignant edema or intracranial hypertension is dubious. In cirrhotics with HE, cytotoxic edema is present on a cellular level but often unappreciable on CT imaging. Vasogenic edema it thought to lag temporally behind cytotoxic edema and is both direct and indirectly attributable to ammonia [27–29]. Luxury perfusion due to increased cerebral blood flow and impaired autoregulation appears to be a process specific to ALF that accounts for the development of malignant cerebral edema and intracranial hypertension. Mechanisms driving this process include the loss of integrity of blood brain barrier [18], failure of ATPase pump with resultant hyperemia due to loss of cerebrovascular autoregulation, increased NO production due to increased activity of neuronal nitric oxide synthase [30], up regulation of cyclooxygenase with increased production of prostaglandins and eicosanoids resulting in hyperemia and increased cerebral blood flow [30]. Hyponatremia frequently occurs in ALF and likely contributes to increased interstitial water and the cerebral edema. Targeting higher plasma sodium goal is associated with a lower incidence of intracranial hypertension.

In chronic liver failure, the brain has time to adapt to the deleterious effects of chronic ammonia exposure. Cerebral astrocytes have the capacity to convert ammonia into glutamine. In chronic liver failure, intracellular glutamine accumulation is offset by the export of organic osmoles (myo-inositol and taurine) from astrocytes to maintain osmotic balance and mitigate the development of cytotoxic edema.

Glutamine in turn prevents reuptake of glutamate which accumulates in post synaptic space. In chronic liver failure, there is compensatory decrease in glutamate receptors in post synaptic membrane which may account for the psychomotor slowing and drowsiness seen in HE. Other mechanisms of HE includes the elevated GABAergic tone produced by stimulation of TGR5 receptors and increased neurosteroid production by activation of peripheral type benzodiazepine receptors.

The failing liver triggers a systemic inflammatory response with activation of immune system and release of cytokines including IL-6, IF-α, TNF-α. The mechanism of increased cytokines involves activation of toll like receptors which activate Kupffer cells that activate signaling cascades and transcription of proinflammatory cytokines. These cytokines increase cerebral blood flow and increase permeability for ammonia. While this process contributes to HE in chronic liver failure, it transpires on a mammoth scale in ALF.

8.5 Clinical Features of Hepatic Encephalopathy in Chronic Liver Disease

In the undifferentiated liver failure patients with abnormal synthetic liver function, the absolute first critical step is to distinguish if the HE is type A (ALF) or type C (Chronic). This step helps stratify risk attributable to the HE and designates appropriate neuromonitoring and neuroprotective interventions. While this may seem intuitive, confusing these disease entities is not uncommon in clinical practice and results in unnecessary delays that affect patient outcome. In autoimmune hepatitis, differentiating the two can at times be difficult due to derangements in synthetic function common to both in early stages. A careful history, and longitudinal monitoring of neurological status and synthetic function will be needed to make this determination. In the indeterminate phase, it is prudent to adopt an ALF management strategy until the clinician can safely determine the acuity and chronicity of the disease.

If the initial presentation of HE in chronic liver failure is atypical or severe (grade 3 or 4 HE), excluding an alternate etiology due to infection, metabolic anomaly, toxidrome, neurovascular event or seizures through an accurate history, physical exam, laboratory work up and brain imaging is paramount. If the mental status decline of HE (grade 1 to grade 4) is witnessed with typical features and a precipitant identified, extensive work up for an alternate etiology is less warranted.

8.6 Neurological Assessment in Early HE

Evaluating orientation and serial subtraction test to assess attention are one of the more objective determinations of earlier stages of HE specifically WH grade I to II. Other neuropsychiatric findings are more subjective and can be difficult to quantify and trend. The more contemporary Confusion Assessment Method (CAM ICU) and Agitation Sedation Scale (RASS) used in ICUs may provide some additional benefits to discriminating the neuropsychiatric changes and the level of arousal respectively, however, neither have been adequately validated in HE [31].

An additional efficient and objective method to monitor progression or recovery from HE focusses on grading asterixis by quantifying the number for flaps over 30 s (see Table 8.2) [32]. Coarse tremor or jactitation [33], while common to HE should not be mistaken for asterixis. Negative myoclonic jerks differentiable from asterixis in HE can be observed frequently in opioid toxicity and uncompensated respiratory acidosis and less commonly in severe uremia and other neurological disorders.

In more severe grades of HE, using the Glasgow Coma Scale is useful, appropriate and has been validated in HE and may provide more immediate information about the neurological trajectory. One limitation WH criteria as well as other developed HE scales [34, 35] have is the ceiling effect for patients in who are in coma. Glasgow Coma Score allows a more refined discrimination of advanced grades of HE (see Table 8.3).

Table 8.2 Grading asterixis to monitor progression of hepatic encephalopathy [32]

Grade of asterixis	Description	Number of flaps/30 s
Grade 0	No flapping motions	0
Grade I	Rare flapping motion	1–2
Grade II	Occasional, irregular flaps	3–4
Grade III	Frequent flaps	5–30

Table 8.3 Comparable Glasgow Coma Scale to Modified West Haven Criteria adapted from Bernal et al. [36]

West Haven Criteria Grade	GCS
I	14–15
II	12–15
III	7–12
IV	<7

8.7 Physical Exam in HE

A complete neurological examination in severe HE is likely to uncover false localizing signs including transient pupillary dysfunction, dysconjugate gaze, gaze deviation, ocular bobbing, decorticate and decerebrate posturing, hyperreflexia, up going plantar as well as other less common findings. These findings are usually transient and resolve or change within hours. Cases of reversible focal deficits mimicking stroke attributable to severe HE has been reported but fortunately these are not common.

8.8 Brain Imaging in Overt Type C HE

In patient with low grade HE (WH grade I or II) developing sudden focal deficits i.e. face, arm and leg weakness that is clinically localizable, a CT if negative for hemorrhage should be followed up by an immediate CT-Angiogram before considering thombolytics. MRI would also be helpful in this situation if it can be performed quickly. Initiating thombolytics with a negative CT alone would not suffice due to the coagulopathy and higher bleeding risk in cirrhotics and the potential that the source of the deficit was predominantly a metabolic abnormality and not a vascular phenomenon.

In a single center study of 158 cirrhotic patients scanned for altered mental status, Joshi et al. revealed that 30% of head CTs were normal, 30% demonstrated increased atrophy, 17% with small vessel disease and 16% with intracranial hemorrhage [13]. The prevalence of intracranial hemorrhage (ICH) in ACLF was higher than decompensated cirrhosis: noted to be 23% versus 9% [13]. Given this finding, the decision to image a patient HE requires clinical discretion. If a patient with recurrent HE, presents with his/her usual presentation for HE that was witnessed by family or hospital staff, then imaging would less likely be of use. If an unresponsive patient was found on the ground, demonstrates evidence of trauma from a fall, witnessed fall or atypical presentation of HE, imaging with CT should be performed. Findings by Joshi et al. also implies that a lower threshold for performing CT should be considered in patients with ACLF possibly due to the more coagulopathic state evidence by lower platelet counts, higher INRs and lower fibrinogen levels.

While the risk of IH leading to herniation is low in cirrhosis, the infrequent occurrence IH in ACLF (4%) is predicated upon the acuity of the liver injury rather than the chronicity of the liver disease [12, 13]. Therefore, infrequently, an obtunded ACLF patient with abrupt deterioration in synthetic liver function, who is relatively young, with significant hyperammonemia, hemodynamic instability, multiorgan failure, hyponatremia, very recent TIPSS procedure or volume overload should be considered for imaging to evaluate for cerebral edema and herniation.

MRI may be useful in evaluating atypical features or refractory HE for alternate causes, both common and rare. More recently, an underrecognized complication of prolonged course of metronidazole used for management of HE in cirrhotics with impaired renal function has been identified with explicit MRI finding [37–39]. MRI may also detect cerebral edema more precisely than CT however, the infrequent ACLF patients suspected of having cerebral edema is likely too critically ill to tolerate an MRI.

8.9 Precipitating Factors for Overt Type C HE

Reversible precipitating factors have been reported in up to 80% of patients with cirrhosis. Prompt recognition of precipitating factors and common confounders help identify a reversible cause and refines the approach to investigation and treatment (see Table 8.4). In addition to well-known precipitating factors for HE, Table 8.4 also delineates frequently overlapping confounders seen in patients with cirrhosis that should be considered and assessed when deemed clinically relevant by history and physical exam.

In the recent European Canonic study, infection remains a major precipitant of episodic HE, recurrent HE as well as HE in ACLF. Unlike prior studies, GI bleeding appeared to confer a lower risk for developing HE [2, 40]. Earlier endoscopic interventions and improved management strategies for GI bleeds may have contributed to this paradigm shift. More notably, the European Canonic Study was able to identify a distinctive difference in clinical characteristics of patients with HE due to ACLF compared with HE associated with decompensated cirrhosis (see Table 8.5). Active alcohol use surfaced as a precipitant of HE that was unique to patents with ACLF. Table 8.5 differentiates clinical features and precipitants of HE in ACLF versus decompensated cirrhosis.

Table 8.4 Precipitating factors, HE-confounders and underlying mechanisms in hepatic encephalopathy

Mechanism	Precipitating Factor and HE-confounders	Work up to consider
Excess nitrogen burden	Gastrointestinal bleed[a] Blood transfusions Constipation[a] Azotemia Excess dietary protein Protein catabolism in starvation and insulin resistance due to Diabetes Mellitus[a] Portosystemic shunt[a] (iatrogenic and spontaneous)	Complete blood count BUN and Creatinine Micronutrients—B12, B6, Thiamine, Carnitine level Plasma ammonia levels Blood Glucose and HBa1c Abdominal venous imaging
Infection and inflammation	Infection[a] SBP[a] Septic shock Viral or Autoimmune Encephalitis Cryptococcal Meningitis HIV/AIDS Pancreatitis	Blood, Urine, CSF, Sputum culture, C. difficile toxin Ascitic fluid cell count and culture ScvO2 and Lactate Serum and CSF Cryptococcus antigen HIV serology Lipase and amylase
Compromised toxin clearance	Dehydration due excessive fluid restriction, diuretic use[a] or paracentesis[a], diarrhea Acute Kidney Injury, Hepatorenal Syndrome Hypotension due to bleeding[a], or systemic vasodilatation Abdominal Compartment syndrome due to severe ascites	Renal function Electrolytes (serum Sodium) ScvO2 and Lactate Monitor Bladder Pressures
Compromised neurotransmission and metabolism	Endozepines and neurosteroids Benzodiazepine use Coinciding Alcohol withdrawal Opioid Use Psychoactive drugs Hypoglycemia Hypoxemia and Hypercarbia Thyroid dysfunction	Urine Toxicology Blood alcohol level Blood Glucose ABG TSH
Acute hepatocellular damage	Alcoholic hepatitis[a] Drugs Other acute hepatitis Development of hepatocellular carcinoma Undiagnosed Wilsons Disease	Liver function panel Acetaminophen Level Acute Hepatitis work up Alpha fetoprotein level Serum and 24-h urinary Copper, Ceruloplasmin,
Other confounders: metabolic abnormalities, neurological injury	Intracranial Hemorrhage (Subdural Hemorrhage is most common cause) Dementia Wernicke's encephalopathy Metronidazole induced encephalopathy Central Pontine Myelinolysis Brain Stem Strokes Severe Hyperammonemia Seizure disorder	Head CT MRI brain with and without gadolinium EEG

ABG arterial blood gas, *CSF* cerebrospinal fluid, *HIV* human immunodeficiency virus, *ScvO2* central venous oxygen saturation, *TSH* thyroid-stimulating hormone

[a]Precipitating factors of HE specific to chronic liver failure. Data from American Association for the Study of Liver Diseases, European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014;61(3):642–59; and Cordoba J, Ventura-Cots M, Simon-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol 2014;60(2):275–81.

Table 8.5 List of clinical features and precipitating factors for HE in decompensated cirrhosis versus ACLF—canonic study[a]

	HE in decompensated cirrhosis	HE in ACLF
Clinical features	• Older Cirrhotics • Inactive Drinkers • Less impairment of Liver function • Minimal inflammatory reaction • Low prevelance of organ failure • Lower mortality	• Young Cirrhotics • More frequently Alcoholics • More Impairment in Liver function • Increased inflammatory response • High prevalence of organ failure • Higher mortality
Precipitating factors	• Long term diuretic use	• Active alcohol use • Bacterial infections • Hyponatremia

[a]Data from Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, Angeli P, Domenicali M, Gines P, Bernardi M et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). Journal of hepatology 2014, 60(2):275–281.

Case 1

55 year old male with Hepatitis C related Cirrhosis is having recurrent HE occurring frequently and causing recurrent admissions. In addition to his liver disease, he has stage III Chronic Kidney Disease for which is being evaluated for a combined Liver and Kidney Transplant. He is being treated with a HE regime of daily doses of Lactulose, Rifaximin, Zinc and Metronidazole for the last 12 weeks for the refractory HE. He has become increasingly altered in the past week and presents to the Emergency department with seizures that subsided with Ativan 2 mg and was subsequently intubated.

Exam:

Heart rate: 90 bpm Respiratory Rate: 12 bpm BP: 112/70 Temperature: 36.8 °C

Neuro: Pupils 3 mm reactive to light. Brisk reflexes throughout with upgoing plantar reflexes. Remains minimally responsive with GCS 7. Moving all four extremities with equal strength.

CVS: Normal heart sounds. Sinus rhythm. No murmurs

Pulmonary: Clear to auscultation bilaterally

GI: Ascitic abdomen and nontender to palpation.

Extremities: Normal pulses. Trace edema.

Laboratory and Diagnostics:

His plasma ammonia level is 89 mmol/L. He is afebrile. Ascetic fluid cell count is normal. Urine analysis with 12 wbc and the urine has been sent for culture. His chemistry panel and liver function panel remains unchanged from his last outpatient visit. EEG revealed periodic lateralizing discharged from both parietal lobes suggesting cortical irritability for which Levetiracetam IV has been initiated.

Question:

1. What diagnostic test would you order?
2. How would you treat his encephalopathy?

Answer:

1. MRI brain
2. Discontinue Metronidazole. Continue Lactulose and Rifaximin.

This is a case of Metronidazole Induced Encephalopathy (MIE). The patient is at risk due to decreased clearance with both liver and kidney dysfunction. Metronidazole is not infrequently used off label to treat refractory HE. When used indiscriminately, accumulation of Metronidazole causes neurotoxicity affecting both peripheral nerve and central white mater. This patient had bilateral symmetrical parietal white mater demyelination and edema seen on MRI which is consistent with MIE. With supportive care, management of seizure and discontinuing metronidazole, most patient will improve with time. Limit Metronidazole use in cirrhosis to 7 days or less when possible.

8.10 Goals of Therapy for HE in Chronic Liver Failure

1. Identifying if HE is presenting with decompensated cirrhosis versus ACLF.
   (a) ACLF patient will require earlier transfer to the ICU due to imminent short-term mortality
2. Treatment of precipitating factors in parallel with intensive care supportive strategies for multiorgan failure
3. Initiation of first tier therapeutic strategies specific to HE
   (a) Reduction of intestinal ammonia production and absorption
   (b) Nutritional and micronutrient supplementation
4. Initiation of second tier therapeutic strategies specific to HE
   (c) Plasma ammonia lowering devices and non-pharmacological interventions
   (d) Eliminating large spontaneous portosystemic shunts (SPSS)
   (e) Alternative pathway therapies
   (f) Neurotransmitter blockade

Distinction of ACLF has been discussed previously and the importance of this will not be repeated here. Vast majority of patients with HE have a precipitating cause: some of the commoner precipitating causes are upper GI bleeding, infections including spontaneous bacterial peritonitis, hypovolemia and over-diuresis, hypokalemia, metabolic alkalosis, concomitant use or abuse of other sedating drugs, particularly benzodiazepines. Precipitating cause should be actively sought and treated in parallel with best supportive care. Most patients with cirrhosis have protein energy malnutrition and as such there is no role of protein restriction in management of acute or chronic HE. Hypokalemia should be corrected. Hyponatremia should be avoided particularly in ALF and ACLF: however rapid correction of Na avoided due to risk of osmotic demyelination syndrome.

8.11 Therapeutic Strategies for Managing Type C HE in the ICU

8.11.1 Plasma Ammonia Lowering Strategies (First Tier)

1. **Reduction of intestinal ammonia production and absorption**
   (a) **Lactulose (beta-galactosidofructose) and Lactitol (beta-galactosidosorbitol)**

   Despite the absence of mortality benefit, both these nonabsorbable disaccharides are currently first line agents for the treatment of HE. Lactitol is not available in the United States. Since there is absence of specific disaccharidases on the villous membranes of the human small bowel, these disaccharides freely reach the colon. In the colon, they are broken by the colonic bacteria into acids which lowers the pH. This acidification favors conversion of ammonia (NH3) into ionic ammonium ($NH4^+$). Because of its very nature, ammonium ion is less permeable than ammonia and less absorbed into portal circulation. In addition, both lactulose and lactitol inhibit ammoniagenic coliform bacteria and clear ammonia by decreasing transit time. Lactulose is superior to placebo and tap water enemas and comparable to neomycin [41, 42]

   Lactulose is usually given orally in patients who are awake enough to swallow. Initial dose of 30–60 ml can be repeated hourly till there is a bowel movement and then dose titrated to 2–3 soft bowel movements per day. Caution should be exercised in patients with significant alteration in mental status and high aspiration risk. In addition, it should be recognized that goal of lactulose administration is not profuse diarrhea: resulting hypovolemia may actually make encephalopathy worse. Finally, lactulose can cause significant gaseous small bowel distension in paralytic ileus and make it worse. A distended abdomen in a critically ill cirrhotic patient receiving lactulose should be evaluated for an ileus and not assumed to be increased ascites. Lactulose can also be given as enema in comatose patients and those unable to swallow or lacking enteral access.

(b) **Polyethyelene Glycol (PEG)**

A small randomized single center study demonstrated that a 4 L PEG administered orally or via NG over 4 h led to more rapid HE resolution despite less ammonia difference at 24 h compared to standard therapy with Lactulose. PEG's safety profile and balanced electrolytes make it an attractive adjunct to Lactulose in the ICU setting. Volume of 4 L remains a concern for aspiration especially in later grades of HE.

2. **Ammonia lowering antibiotics (First Tier)**
   (a) **Rifaximin**: Rifaximin is an oral nonsystemic antibiotic with <0.4% absorption. Rifaximin has *in vitro* antimicrobial activity against Gram-positive and Gram-negative, aerobic and anaerobic flora. Current AASLD/EASL guidelines only recommend rifaximin as an add-on therapy for prevention of overt HE recurrence. Data is insufficient regarding the use of rifaximin as a first line therapy or stand-alone therapy for treatment of overt HE. Rifaximin may be used in combination with lactulose in patients with overt HE as the combined effect leads to reversal of the condition in 76% of patients *vs.* 50.4% in those on lactulose alone. In absence of more robust data, rifaximin 550 mg po q12h is a reasonable adjunct for severe or refractory HE, especially since it has a better side effect profile than neomycin and metronidazole. Rifaximin added to lactulose is more efficacious than lactulose alone in prevention of overt HE (43)
   (b) **Neomycin**: Oral neomycin is minimally absorbed, yet chronic administration can result in nephrotoxicity and ototoxicity. Evidence for use and efficacy of neomycin in HE is not robust at all, yet it is FDA approved [43, 44]. For acute HE, 1 g q6h for up to 6 days and for chronic HE, 1–2 g daily is prescribed. Given other alternatives and lack of strong evidence, use of neomycin should probably be limited
   (c)**Metronidazole**: Not FDA approved for management of HE. One small study revealed at it is as effective at Neomycin at a dose of 250 mg twice daily [45]. The concern for resistant clostridium difficile colitis and neurotoxic effects of metronidazole are valid. Liver failure and renal impairment are both predisposing factors to developing metronidazole encephalopathy (MIE), a toxidrome more recently characterized by both reversible and irreversible findings on MRI [37–39].

3. **Nutritional and micronutrient supplementation (First Tier)**
   (a) **Zinc**: There are a number of small studies on Zinc supplementation in cirrhosis resulting in lower plasma ammonia levels and improved hepatic encephalopathy. The biochemical rational is predicated on Zinc being a co-factor in the urea cycle. Two recent meta-analysis on zinc in HE revealed a significant neuropsychiatric improvement measured using the number correction test [46]. In the meta-analysis by Timbol et al. published in abstract form., zinc supplementation provided for a statistical significant reduction in serum ammonia levels [47]. Zinc levels are tightly associated with liver function. Cirrhotics with low zinc levels have a higher risk of hepatic decompensation and hepatic encephalopathy. In cirrhosis with

hypoalbuminemia, low zinc levels may be reported since 80% of zinc in blood is albumin bound. Zinc levels are not routinely monitored unless a way to measure free plasma zinc level is developed. In the critically ill patient with HE, including zinc supplementation has the potential to improve ammonia metabolism with minimal side effects. However, long term use of zinc supplementation in concomitant renal failure does increase the possibility of zinc toxicity.

(b) **L-Carnitine**: There are numerous small studies and anecdotal reports about the ammonia lowering effects of oral supplementation with L-Carnitine which requires further study. Carnitine is a co-factor in the metabolism of long chain fatty acids. It facilitates mitochondrial membrane transport by binding acyl-CoA molecules and promotes translocation from cytoplasm to mithochondrial matrix for B-Oxidation. Disruption in Carnitine transport results in cytosolic accumulation of fatty acyl-CoA molecules which is postulated to inhibit the urea cycle [48]. Patient with carnitine deficiency due to malnutrition or short gut, valproate acid, primary deficiency due to mutations in organic cation transporter gene (OCTN2) have been reported to manifest with symptomatic hyperammonemia which improves with carnitine supplementation. There is limited evidence on use L-Carnitine routinely in the management of HE, however, in cirrhotic patients with a significant history of malnutrition and refractory hyperammonemia, checking L-Carnitine levels followed by supplementing L-Carnitine pending the return of these levels is physiologically sound and may provide a benefit with minimal risk until further evidence is available.

(c) **Branched-chain amino acid (BCAA) supplementation**: Improvement in HE has been noted in patients predominantly treated in the outpatient setting without improvement in mortality. Existing evidence revealed no difference between BCAA, lactulose and neomycin It did however increase the risk of nausea and vomiting. Its role in the ICU remains unproven. Having an alternative to lactulose in patients on vasopressors or at risk of developing an ileus could be useful in the critical care setting.

4. **Plasma Ammonia lowering devices and non-pharmacological interventions (second Tier)**

(a) **Continuous Renal Replacement Therapy**

Continuous renal replacement therapy using continuous veno-venous hemofiltration with high filtration volume (90 ml/kg/h) is an effective method of rapidly lowering serum plasma ammonia levels [49, 50]. Ammonia clearance is closely associated with ultrafiltration rate. More than likely, CRRT will be used in such a patient for acute kidney injury needing renal replacement; and not hyperammonemia per se. However, one can make a case for CRRT for severe hyperammonemia particularly in ALF or ACLF where the risk of intracranial hypertension and herniation is significantly higher. Hemodialysis and CRRT remains the mainstay for the management of hyperammonemia in patients with urea cycle disorders with a proven track record.

(b) **Molecular Adsorbent Recirculating System (MARS) and Bio-artifical devices**

Molecular Adsorbent Recirculating System (MARS) is a blood detoxification system based on albumin dialysis that removes protein bound (bile acids, bilirubin, endogenous benzodiazepines, nitrous oxide) and water soluble toxins (ammonia, creatinine). In the US, MARS is FDA approved for management of ALF due to drug overdose or toxic exposures and for management of HE in decompensated cirrhosis. MARS trials thus far have failed to show a survival benefit; however they have consistently demonstrated improvement in HE and a satisfactory safety profile. Using MARS for refractory HE is thus a potential option. In the case of bioartificial systems, the extracorporeal circuit includes bioreactors loaded with liver cells, thus theoretically having potential to improve synthetic function as well. These extra-corporeal liver assist devices are as of now far from ideal and not widely available; these are subject of research.

(c) **Therapeutic Hypothermia (Goal Temperature of 34 °C)**

There remains limited clinical experience in the use of mild hypothermia in chronic liver failure [51]. Its appeal in liver disease is that it counteracts many of the metabolic effects of ammonia, slows protein catabolism and production of ammonia by bacteria and the kidneys [52]. The predominant concern with using hypothermia in cirrhotic patients is its potential to worsen the existing coagulopathy in patients who are high risk for bleeding and the predisposition to infection. In rare cases of extreme refractory hyperammonemia, hypothermia can be used as a transient neuroprotective strategy while pursuing clearance of plasma ammonia through other avenues.

5. **Alternative pathway therapy (second Tier):**

(a) **Ammonia scavengers: Sodium Benzoate, phenylacetate, glycerol phenylbutyrate, Ornithine phenylacetate**

(b) **L-Ornithine L-Aspartate (LOLA)**

Ammonia scavengers help to increase ammonia clearance and thus reduce systemic concentrations of ammonia. These compounds provide an alternative

pathway wherein ammonia is excreted in the urine as phenylacetylglutamine. Whereas small randomized studies show encouraging results, larger trials are needed to define the role of these in HE in daily practice. Limitation of these therapies include the need for intact renal function for elimination of phenylacetylglutamine. Efficacy of therapy with dialysis remains unclear. Sodium benzoate is an FDA approved food additive/preservative and is infrequently off-lable in refractory hyperammonemia by adding it to enteral feeding in patients with refractory hyperammonemia and intact renal function. However, the efficacy of this therapy in cirrhosis have not been verified in large trials.

L-ornithine L-aspartate (LOLA): LOLA is substrate for urea cycle and stimulates enzymatic activity in residual hepatocytes leading to increased urea excretion. LOLA significantly improves HE and ammonia levels when compared to placebo; however it demonstrated no difference compared with lactulose. Oral LOLA is more frequently used for treatment of HE outside the US.

6. **Neurotransmitter Blockade (second Tier)**
   Flumazenil: In a systematic review involving 13 controlled trials with a total of 805 patients, the use of flumazenil was associated with significant improvement in HE but failed to show long term benefits or improvement in outcome [53]. As a short acting benzodiazepine antagonist, flumazenil is postulated to inhibit endogenous GABAergic substances and previous residual effects of long acting benzodiazepine. Cirrhotics have also been shown to have increased benzodiazepine receptor activation but only a subset of patients will demonstrate response to Flumazenil. Flumazenil should be used in a closely monitored environment as it has a potential of provoking seizures. A trial of 1–2 mg of Flumazenil in 20 mL saline solution by intravenous infusion for 3–5 min may be considered in patients with stage 3–4 encephalopathy who have low serum ammonia level and have not responded to Lactulose.

7. **Surgical Treatment Options if applicable (second Tier)**
   (a) **Embolization of large portosystemic shunts (PSS)**: A review by Lyn AM et al. of their carefully selected 20-patient experience with embolization of portosystemic shunt for refractory HE revealed that durable benefit in HE was achieved in majority of patients with reduction in hospitalization for HE [54]. Increased ascites was noted in a about 50% of these patients. Multiple case reports and case series have corroborated these findings, however, larger supporting studies especially in the ICU setting remains deficient. PSS embolization could be considered in the refractory, recurrent or persistent HE in select patients. At present, this option is probably underutilized given that imaging for large portosystemic shunts are often not routinely performed for evaluation of refractory HE.
   (b) **Liver transplantation**: is the definitive treatment for HE [55]. Tier 1 and 2 interventions should be thoughtfully and diligently employed to patients eligible for transplant as pre-transplant encephalopathy post-transplant metabolic encephalopathy. An awake, oriented and responsive candidate is also a more attractive candidate for transplantation.

8.12 Acute Liver Failure

8.12.1 Clinical and Laboratory Assessment Specific to Type A HE (ALF)

In type A HE due to ALF, grading scales for HE do not differ from type C HE (see Neurochecks in HE) which include clinical assessment WH grading, asterixis grading, GCS. However, the consequences of progressing to grade 4 HE is significantly worse in ALF due to the significantly higher risk of IH resulting in brain herniation. It is imperative that early determination of acuity of the liver failure need to be ascertained which should trigger a rapid transfer of the patient to a regional liver transplant program. ALF patients can rapidly decline clinically with distributive shock and multiorgan failure after which they are too unstable to a transfer.

8.12.2 Neuro Checks in ALF

Monitoring pupillary function is important in WH grade 3 and 4 HE. Pupillary light reaction frequently progresses from normal to hyper-responsive in early in WH grade 2-3 HE and hypo-responsive in WH grade 4 [56]. Loss of pupillary function may be a metabolic phenomenon in late stages however it may also signify brain herniation due to uncal compression or stretching of ciliary fibers of cranial nerve III. Hence, despite the false positive findings, close monitoring of pupils is critical in ALF. Reversal of brain herniation using osmotherapy is possible if detected early.

Reports of up to one third of WH grade IV ALF patients may develop subclinical seizures. Presence of subclinical seizures are of uncertain relevance but could contribute to elevated ICP inpatients with IH. Continuous EEG should be considered during the management of Grade IV HE with risk factors for developing IH.

8.12.3 Objectives of Serial Laboratory Testing Relevant to HE and IH in ALF

1. Analyze and monitor the onset and severity ALF and examine for evidence spontaneous recovery of liver function. Risk of cerebral edema is analogous to severity of liver dysfunction and hyperammonemia but resolution of cerebral edema may lag behind the recovery of synthetic liver function.
2. Decelerating the development cerebral edema:
   (a) Monitor plasma sodium levels, osmolarity, pH, CO_2, plasma ammonia levels
   (b) Correct hyponatremia, severe acidosis, hypercarbia
   (c) Augment plasma sodium levels and osmolarity
3. Monitoring other organ function, detection of infection and hemodynamic laboratory markers pertinent to cerebral perfusion and brain edema.
4. Triggering the decision to transplant based upon clinical picture in conjunction with biochemical markers before losing the hemodynamic window.

8.12.4 Risk Factor for Development of IH in ALF

Plasma ammonia level of more than 150–200 μmol/L is associated with the development of IH in ALF. More recently, Kitzberger at al. reported that 25% of ALF patients developed IH despite relatively low plasma ammonia levels (NH3 < 146 μmol/L) [57]. The disproportionately higher extracerebral severity of organ failure (SOFA) score in these patients emphasizes the substantial role of inflammation and shock organ failure in the development cerebral hyperemia and diffuse cerebral edema. Other common associations for ICP elevation include hyponatremia, volume overload, severe hypercarbia, severe acidosis, pain and ventilator dyssynchrony.

8.12.5 Brain Imaging in ALF and IH

Utility of brain CT for assessment of cerebral edema and IH remains in question especially when interpretation of CT is performed without a comparator. Imaging is useful for excluding other intracranial processes or evaluating for complications of placing intracranial devices [58, 59]. If imaging is to be used for CE detection and to assess risk of herniation, performing serial imaging with a baseline scan performed early on before onset of severe HE may be more useful [60].

Brain MRI may help exclude CNS infection, brainstem stoke, Wernicke's encephalopathy, metronidazole encephalopathy, and central pontine myelinolysis not visible on CT and should only be pursued if there is a high index of suspicion. If clinically unstable and MRI is necessary, the patient should be monitored by intensive care unit (ICU) clinicians throughout image acquisition.

A recent MRI finding associated with sustained hyperammonemia reinforces the idea that ammonia is neurotoxic and not just an epiphenomenon in HE [61, 62]. Restricted diffusion limited to bilateral insular cortex, cingulate gyrus, and thalamus when mild (limited cortical restricted diffusion [LCRD]) and can involve bilateral temporal, parietal, and frontal lobes and sparing the occipital poles, when severe (diffuse cortical restricted diffusion [DCRD]). This MRI finding is associated with severe hyperammonemia, cognitive decline, matching downstream cortical atrophy, and worse outcome (see Figs. 8.4 and 8.5).

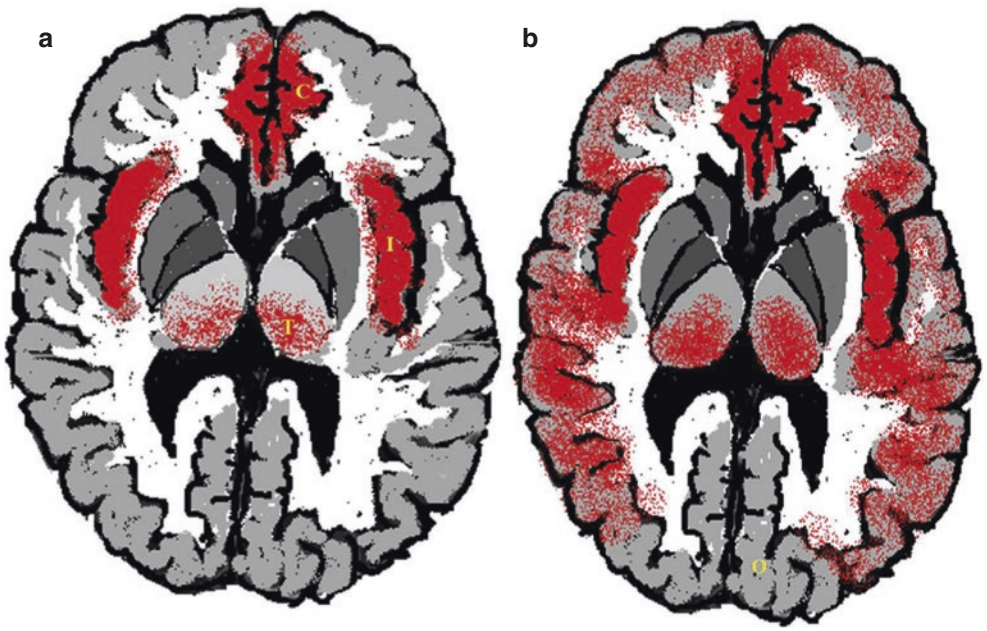


Fig. 8.4 (**a**) LCRD—Initial pattern of cytotoxic edema in severe hyperammonemia. Involves insular cortex (*I*), cingulate gyrus (*C*), and thalamus (*T*) with good outcome. (**b**) DCRD—Diffuse pattern of cytotoxic edema with variable outcome. Involves all cortical grey matter and thalamus with sparing of the occipital poles (*O*)

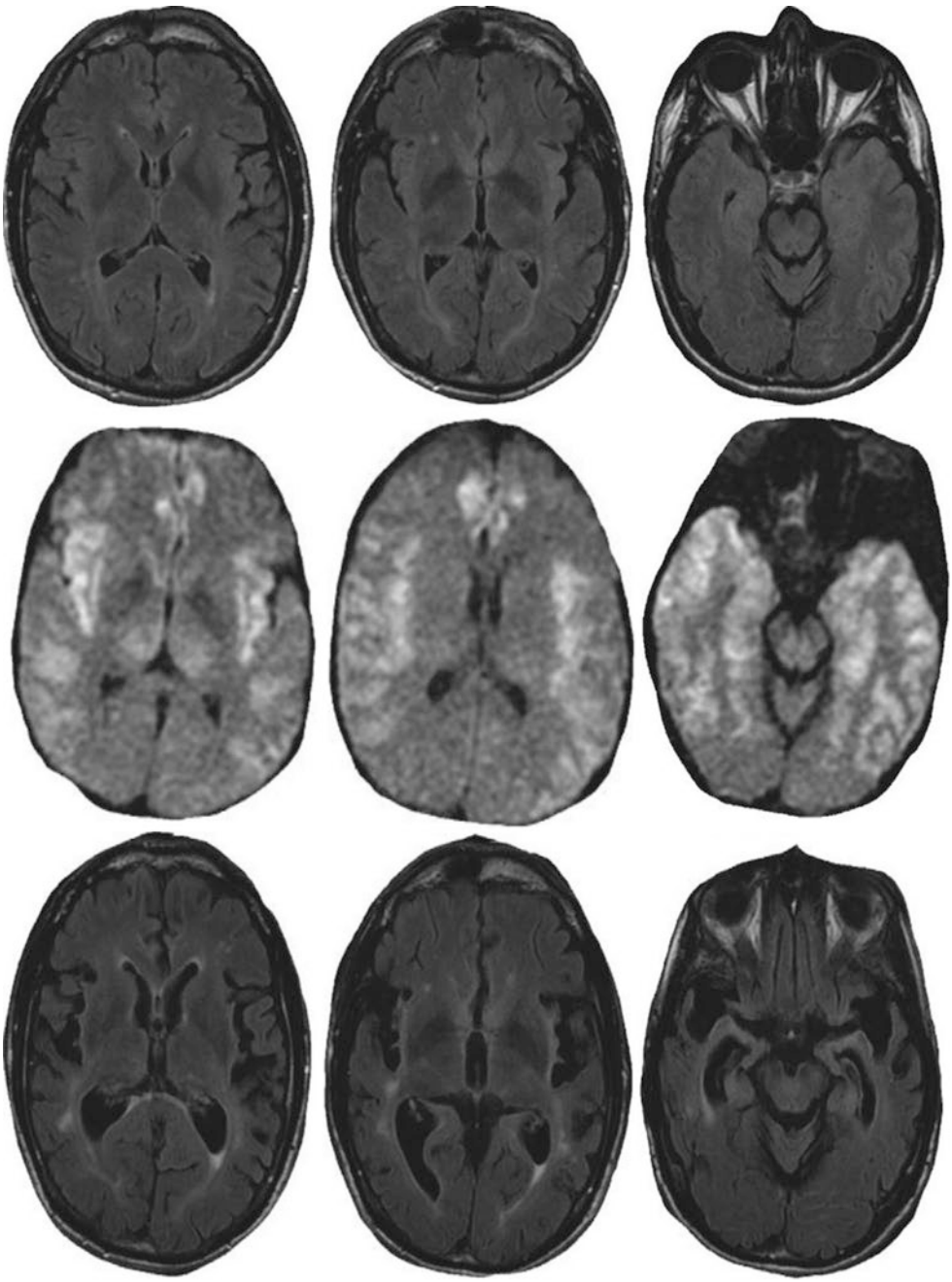


Fig. 8.5 MRI features of hyperammonemia in a patient with liver failure. A 49-year-old man with hepatitis C, MELD score 17, with accidental chronic acetaminophen overdose, SOFA score 11, and peak plasma NH3 level of 606 mmol/L. Plasma ammonia level was <100 mmol/L for 6 days. (*Top*) Baseline outpatient MRI findings 6 months prior for headache workup. (*Middle*) Diffusion weighted images during admission for liver failure. DCRD involving bilateral cingulate gyrus, insular cortex, temporal lobes, frontal lobes, and posterior thalamus. (*Bottom*) Cortical atrophy matching areas of restricted diffusion on 9-month follow-up MRI. Moderate-to-severe static cognitive impairment (From Kandiah PA, Pandya D, Lynch JR, et al. Catastrophic hyperammonemia: a case series. Neurocritical care 2008;8(1):61–232; and Kandiah PA, Pandya D, Nanchal R, et al. Metaanalysis of magnetic resonance imaging findings and neurological outcomes in liver failure and severe hyperammonemia. In: 15th International Society for Hepatic Encephalopathy and Nitrogen Metabolism: 2012. Grenaa, Denmark, 2012. pp. 25–6; with permission.)

8.13 Pharmacologic Treatment Options

8.13.1 Outline of management of HE in ALF

1. Identify and treat cause of ALF to minimize further injury
2. Identify risk factors for mortality and IH (Table 8.6) and evaluate candidacy for liver transplant if high risk
3. Elect neuromonitoring strategy
   (a) Invasive—intracranial monitoring devices
   (b) Noninvasive—GCS, neuro checks, pupillary exam, serial brain imaging, transcranial Doppler (TCD), jugular bulb oxymetry, optic nerve sonography
4. Initiate neuroprotective strategies to delay development of CE and IH
   (a) Head of bed elevation with neck in neutral position
   (b) Initiate osmotherapy with hypertonic saline or mannitol
      - Crucial to plan an effective osmotherapy strategy taking into account continuous reno-renal replacement therapy (CRRT)
      - Hypertonic saline with sodium goal of 145–150
   (c) Initiate plasma ammonia lowering strategies
      - Early initiation of CRRT
      - Targeted temperature management (Mild hypothermia 35 °C) [36, 63, 64]

- Avoid hypokalemia and metabolic alkalosis [65]
- Other plasma ammonia lowering interventions

(d) Consider intensive care supportive strategies for multiorgan failure directed at cerebral edema (see Table 8.7)

5. Rescue maneuvers to control elevated intracranial pressure or refractory IH
   (a) Maintain adequate cerebral perfusion pressure
   - Vasopressors for shock

   (b) Increased sedation for metabolic suppression
   - Thiopental or Pentobarbital only as a last resort

   (c) Maximize osmotherapy with hypertonic saline
   - Hypertonic saline with goal sodium of 150–155
   - 20% Mannitol with

   (d) Consider continuous neuromuscular blockade infusion for high central venous pressures (>20 mmHg) or sustained refractory ICP

Table 8.6 Risk factors associated with intracranial hypertension in ALF

Risk factors of IH	Possible mechanisms and rational
1. Meets Kings college Criteria	Correlates with severity of liver injury, luxury cerebral perfusion due to inflammation
2. Plasma ammonia level >150 μmol/L [28, 29, 57]	Neurotoxic effects of plasma ammonia • Predicts IH with specificity of 84% and a sensitivity of 60%
3. Plasma ammonia level >200 μmol/L [29]	Neurotoxic effects of plasma ammonia
4. Partial Pressure of ammonia or unionized ammonia (pNH3) [57]	Neurotoxic effects of plasma ammonia
5. Sustained elevation on plasma ammonia levels	Neurotoxic effects of plasma ammonia
6. Acute renal failure requiring CRRT [29]	i) Volume overload impeding venous return. ii) Severe acidosis iii) Decreased clearance of ammonia and glutamine.
7. Young age (<35 years) [29]	Limited intracranial space with limited age related atrophy
8. Vasopressor use [29]	i) Inflammation and multi-organ failure causing vasogenic CE from luxury cerebral. ii) Volume overload due to excessive volume resuscitation
9. Severity of Organ failure (SOFA score) [57]	i) Inflammation and multi-organ failure causing vasogenic CE from luxury cerebral. ii) Volume overload due to fluid resuscitation and oliguric renal failure iii) Decreased ammonia clearance with renal failure • Predicts IH with specificity of 62% and a sensitivity of 94%

Table 8.7 Intensive care supportive strategies directed at cerebral edema in ALF

Organ system	Intensive care supportive strategies
Neurological	Use short acting sedatives and opiates once intubated. Propofol and low dose fentanyl are sedatives of choice. Avoid intermediate or long acting benzodiazepines.
Respiratory	**Intubation** for airway protection needs to be considered early in later stages of HE before significant aspiration and lung injury occurs. **Low tidal volume** lung protective strategy to prevent ARDS. High intrathorasic pressures result in cerebral venous outflow obstruction [66] **High Peep** → Use cautiously as very high peep can theoretically add to hepatic congestion **CO_2 goal**: 30–40 mmHg → Hypercarbia causes vasodilatation
Cardiovascular	**Noninvasive approach** and IH suspected → Target a higher MAP goal (≥80 mmHg) **Invasive approach** → Cerebral perfusion pressures (CPP) should be maintained between 50 and 60 using vasopressors [67] **In refractory shock** → consider plasma exchange to maintain optimal CPP. Plasma exchange was associated with reduction in SIRS response, reduction in SOFA scores and decline in need for vasopressor support [63, 68] **CVP goal < 20** → Increased CVP may impede venous return from the brain [69]. Maintain euvolemia. Consider paralysis.
Renal, acid base disorders and electrolytes	**Early CRRT** → To maintain euvolemia, augment ammonia clearance [49], correction of electrolyte and acidosis correction Formulate strategy to maintain sodium goal (145–150) while on CRRT. Options include preparation of hypertonic prismasate or hypertonic saline infusion in post filter return arm of CRRT. **Caution**: Initiating CRRT with isotonic prismsate in patient with IH and induced hypernatremia can cause rebound edema from dialysis disequilibrium syndrome and precipitate brain herniation. **Hypokalemia and metabolic acidosis** increases renal ammonia production. **Metabolic alkalosis** promotes formation of NH3+ from (NH4+) augmenting its passage across the blood brain barrier (15, 16)
GI, liver and nutrition	Abdominal compartment syndrome may indirectly worsen ICP. **Lactulose** → Avoid lactulose via oral or NG route in ALF as it may cause bowel distention, worsening ileus and complicating transplant surgery. Limited evidence supporting it use in ALF. If used, it is safer to be given rectally
Endocrine	**Avoid hypoglycemia** → may add to metabolic injury to the brain. Initiate 10% or 20% Dextrose preemptively in ALF
Hematologic and immune system	**Disseminated intravascular coagulation** → Consider repeating head CT the patient if DIC occurs as spontaneous intracranial hemorrhages may occur.

ARDS acute respiratory distress syndrome, *CVP* central venous pressure, *DIC* disseminated intravascular coagulation, *MAP* mean arterial pressure, *PEEP* positive end-expiratory pressure, *SIRS* systemic inflammatory response syndrome

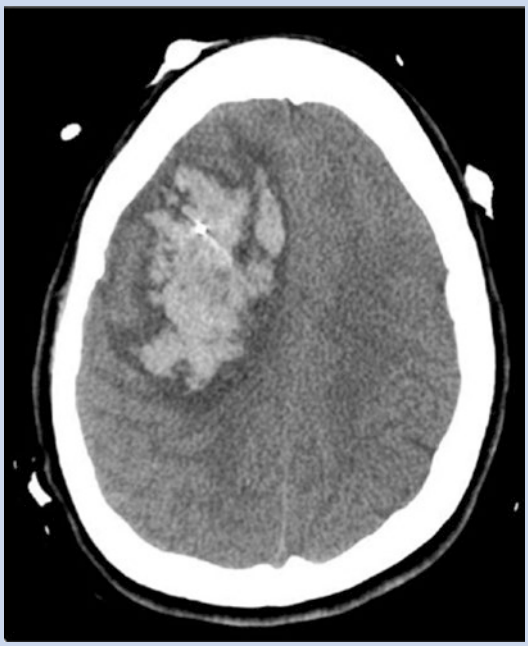
(e) Targeted temperature management (Moderate hypothermia 33–34 °C)
(f) Consider using IV indomethacin 0.5 mg/kg bolus for refractory ICP
(g) Correct severe acidosis with sodium bicarbonate infusions

6. Slow de-escalation of neuroprotective therapies post-liver transplant or in transplant free recovery
   - IH frequently lag behind liver recovery.
   - Slow normalization of serum sodium levels
   - Monitor for rebound edema or dialysis disequilibrium syndrome
   - Slow rewarming to if induced hypothermia initiated

Case 2

26 year old woman with cerebral edema after acetaminophen overdose now with grade 4 encephalopathy, renal failure, NH3 of 300 mmol/L. The decision to place an intraparenchymal ICP monitor (Camino) was made given the high risk status and that patient was not a transplant candidate. She remained hemodynamically stable and on minimal ventilator settings. Intraparenchymal catheter placed after 2 units of FFP, 1 unit of Cryoprecipitate, 1 pack of platelets, and within 1 h of dosing recombinant factor VIIa which produced a resultant INR of 1.4. Platelet count was 104. Post ICP monitor placement, the patients ICP climbs from 15 to 30 mmHg and subsequently 40 mmHg despite sedation and osmotherapy with hypertonic saline.

What is your immediate next step?



Answer: Emergent Head CT

CT head revealed a large right intraparenchymal hemorrhage with midline shift in the region of the ICP pressure probe. Correction of coagulopathy my not be completely protective. Hyperemia of the brain likely contributes to the brisk bleeding when it does occur.

8.14 Invasive Neuromonitoring Strategy in ALF

ICP monitoring has been used to identify and treat elevated ICP aggressively especially when brain edema was the predominant cause of death [28, 70]. With improvement in ICU interventions and lower incidence of IH, the utility of invasive intracranial monitoring has been steadily decreasing. Intracranial hemorrhage from bolt placement is reported to range from 2.5% to 10% [71, 72]. While observational studies have not found overall survival advantages in those receiving ICP monitoring [73, 74], the possibility of benefit in a subset of high risk brain edema patients remains unanswered. Recombinant Factor VII_a is frequently used to help correct the coagulopathy associated with ALF before the procedure [75, 76]. When ICP monitoring is performed, the mean cerebral perfusion pressures (CPP) should be maintained between 50 and 60 using vasopressors [67].

8.14.1 Noninvasive Neuromonitoring Strategy in ALF

A non-invasive strategy would be reliant upon empiric use of cerebral edema-preventing interventions as listed below without the reassurance of having a pressure reading. Serial CT imaging [58, 59], Transcranial Doppler, jugular bulb oximetry, pupillometry neurological exam would be complimentary to this approach.

Transcranial Doppler ultrasound (TCD) is a non-invasive method to estimate ICP based on waveform characteristics due to resistance in cerebral blood flow in proximal cerebral circulation [77]. Its utility in ICP detection in ALF has not been validated prospectively and has to be interpreted with caution. Trends in TCD indicating cerebral perfusion could be useful however an easy method for continuous monitoring is not yet available [78]. Other non-invasive devices such as optic nerve sonography, technologies using near infrared spectroscopy and pupillometry have not been validated in ALF.

8.14.2 Neuroprotective Strategies in ALF

Hyponatremia can worsen cerebral edema and thus should be treated but care must be taken to avoid rapid correction.

Hypertonic saline used to prophylactically to elevate serum sodium level between 145 and 155 meq/L has been demonstrated to reduce the incidence and severity of IH in HE grade 3 and 4 patient a single center study [79]. 30% hypertonic saline infusion titrated between 5 and 20 mL per h to maintain serum sodium levels at 145–155 mmol/L was used in this study.

Hyperosmotic agents have been traditionally used to reduce ICP. This approach may also be used in patients with elevated ICP in ALF patients [80]. Twenty percent Mannitol in bolus doses of 0.5–1 g/Kg bodyweight can be used to reduce ICP. Serum osmolality should be monitored while on mannitol and should be kept <320 mOsm/L due to risk for renal tubular toxicity. However there is no evidence for this number [81]. Care should be taken in patients with ARF, use of mannitol can cause volume overload from osmotic effect of drawing water from interstitial space.

Hyperventilation causes hypocapnia that induces alkalosis which in turn produces vasoconstriction and thereby a decrease in CBF and cerebral blood volume hence decreasing ICP. However, there is a serious concern of hypocapnia causing or worsening cerebral ischemia and rebound cerebral edema [82]. Moderate short term hyperventilation reduces global cerebral blood flow without compromising cerebral oxidative metabolism [83]. Pa_{CO2} should be monitored and should be targeted between 30 and 40 mmHg [84].

Barbiturate coma may be considered with pentobarbital in selected cases [85]. Thiopental and pentobarbital have been shown to reduce brain oxygen utilization, however, in setting of ALF, neurological assessment cannot be done due to induced coma and the half-life is prolonged due to hepatic metabolism of this drug. Pentobarbital is associated with hemodynamic instability due to the direct myocardial suppression effect and should be used and monitored with caution. Bowel dysmotility and frequent occurrence small bowel ileus is a well knows adverse effect of barbiturates. Therefore, NG lactulose should be avoided in barbiturate use altogether.

Hypothermia has been successful in decreasing ICP and has been reported to help to bridge to liver transplant [86–88]. Its use in ALF remains controversial as two studies (Temp 33–34 °C) have demonstrated both absence of benefit and harm [64, 89]. Sustained and significant reduction in plasma ammonia levels [87] and its utility in controlling ICP remains an attractive intervention in the ICU and perhaps should be reserved for refractory IH or refractory hyperammonemia.

Indomethacin reduced ICP by cerebral vasoconstriction in a porcine model [90]. In a physiological study of 12 patients with ALF, IV bolus of indomethacin dose of 0.5 mg/kg reduced ICP and increased CPP without compromising cerebral perfusion. Further studies need to be performed prior to considering it for routine use. IV formulation of indomethacin is not easily available in the US.

Seizures can worsen cerebral edema and increase ICP. Since one third of patients with ALF have seizures, continuous EEG monitoring should be considered in patients who are both sedated and paralyzed [91]. Phenytoin was shown to reduce breakthrough seizures in one small study while using it prophylactically was of no benefit in another [92]. While phenytoin is indicated in breakthrough seizures in ALF, its side effect profile and liver induction effects should preclude its prophylactic use. It is not unreasonable to consider the use of newer antiepileptic medications with less side effect profiles and not metabolized by the liver to treat breakthrough seizures in HE.

CRRT is recommended over hemodialysis due to lower fluctuations in ICP and improved hemodynamic stability [93, 94]. CRRT is particularly effective at lowering plasma ammonia levels [49] and correcting hyponatremia. Appropriate consideration should be given to sodium concentration in dialysate for CRRT and intravenous hypertonic saline dosing when determining goal serum sodium level.

8.14.3 Plasma Ammonia Lowering Strategies in ALF

Ammonia plays a significant but fragmented role in the development of cerebral edema and IH. There remains a paucity of studies that show therapeutic benefit to ammonia reduction. While Lactulose and Rifaximin may offer a nominal plasma ammonia reduction effect, they are likely deficient in preventing IH in ALF. Unlike cirrhosis, ALF patients are not preconditioned to deal with hyperammonemia and are likely more susceptible to ammonia related toxicity. In practice, plasma ammonia reduction is ALF is frequently orchestrated habitually and serendipitously by using CRRT [49] for acute renal failure and therapeutic hypothermia [87] IH. Earlier use of CRRT for significant hyperammonemia, despite relatively preserved renal function, may delay the development of cerebral edema.

8.14.4 Summary

Over the last three decades, consistent mortality reduction in subsets of liver failure not attributable to transplantation has been evident. Death from cerebral edema and brain herniation in ALF has also significantly decreased. There is not a defining therapeutic intervention that's has resulted in this

change. Perhaps this is the net result of improved and nuanced critical care delivery and the enhanced recognition of how dysfunction of other organ systems and their respective interventions affect cerebral metabolic and hemodynamic physiology.

8.15 Review Questions

Question: Plasma NH3 level has to exceed 150 mmol/L in ALF before they are at risk of developing intracranial hypertension. **True or False ?**

Answer: False

An elevated plasma ammonia level (>150 mmol/L) in acute liver failure increases the risk of intracranial hypertension; however, a low level (<146 mmol/L) does not preclude it when associated with multiorgan failure. Vasogenic edema from hyperperfusion of the brain can occur independently of an elevated plasma ammonia levels due to the cytokine storm produced by the dying liver.

Question: Brain imaging for evaluating severe hepatic encephalopathy in patients with Acute-on-chronic Liver failure is unnecessary. **True or False ?**

Answer: Acute-on-chronic liver failure patients admitted with overt hepatic encephalopathy have a significantly higher short-term mortality rate and small but devastating risk of brain herniation (4%) and are at an increased risk of intracranial hemorrhage (16%). Atypical presentation of HE in these patients may warrant a head CT. In chronic liver disease without acute multiorgan failure, the yield from neuroimaging is low unless features are very atypical or there is a history of trauma.

Question: Hyperammonemia in chronic liver failure causes worsening encephalopathy leading to coma, however, the effect on the brain is always reversible with treatment. **True or False ?**

Answer: False

Ammonia is neurotoxic however patients with cirrhosis have a relative tolerance to hyperammonemia. Severe and sustained hyperammonemia in cirrhosis can cause irreversible brain injury akin to patients with urea cycle disorders. The threshold at which the injury is irreversible remain unclear. Brain MRI pattern of restricted diffusion (cytotoxic edema) in hyperammonemia states correlates in severity with plasma ammonia levels and clinical outcome.

Question: Induced hypothermia improves outcome in ALF by controlling ICP? **True or False ?**

Answer: False

Therapeutic hypothermia controls ICP, reduces plasma ammonia levels and is safe but does not confer a clear mortality benefit in acute liver failure.

Question: Monitoring and treating ICP in ALF using invasive intracranial monitoring devices result in improved control in ICP with a clear evidence of mortality benefit. **True or False ?**

Answer: False

Invasive intracranial pressure monitoring used in an estimate of 20–30% of patients with acute liver failure in North America yields a 2.5–10% risk of intracranial hemorrhage. Patient's with intracranial monitors in a retrospective review received more interventions for ICP control and increased sedation without a discernable mortality benefit.

References

1. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35(3):716–21.
2. American Association for the Study of Liver D. European Association for the Study of the L: Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol. 2014;61(3):642–59.
3. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21(1):240–52.
4. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137(12):947–54.
5. O'Grady J. Modern management of acute liver failure. Clin Liver Dis. 2007;11(2):291–303.
6. Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol. 2013;59(1):74–80.
7. Arroyo V, Moreau R, Jalan R, Gines P, Study E-CCC. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol. 2015;62(1 Suppl):S131–43.
8. Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, Laleman W, Trebicka J, Elkrief L, Hopf C, et al. Clinical Course of acute-on-chronic liver failure syndrome and effects on prognosis. Hepatology. 2015;62(1):243–52.
9. Romero-Gomez M, Montagnese S, Jalan R. Hepatic encephalopathy in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure. J Hepatol. 2015;62(2):437–47.
10. Donovan JP, Schafer DF, Shaw BW Jr, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. Lancet. 1998;351(9104):719–21.
11. Jalan R, Bernuau J. Induction of cerebral hyperemia by ammonia plus endotoxin: does hyperammonemia unlock the blood-brain barrier? J Hepatol. 2007;47(2):168–71.
12. Jalan R, Dabos K, Redhead DN, Lee A, Hayes PC. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. J Hepatol. 1997;27(5):928–33.

13. Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int. 2014;34(3):362–6.
14. Zieve L. Pathogenesis of hepatic encephalopathy. Metab Brain Dis. 1987;2(3):147–65.
15. Albrecht J, Jones EA. Hepatic encephalopathy: molecular mechanisms underlying the clinical syndrome. J Neurol Sci. 1999;170(2):138–46.
16. Thumburu KK, Taneja S, Vasishta RK, Dhiman RK. Neuropathology of acute liver failure. Neurochem Int. 2012;60(7):672–5.
17. Raghavan M, Marik PE. Therapy of intracranial hypertension in patients with fulminant hepatic failure. Neurocrit Care. 2006;4(2):179–89.
18. Nguyen JH. Blood-brain barrier in acute liver failure. Neurochem Int. 2012;60(7):676–83.
19. Desjardins P, Du T, Jiang W, Peng L, Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure: role of glutamine redefined. Neurochem Int. 2012;60(7):690–6.
20. Butterworth RF. Pathogenesis of hepatic encephalopathy and brain edema in acute liver failure. J Clin Exp Hepatol. 2015;5(Suppl 1):S96–S103.
21. Ott P, Vilstrup H. Cerebral effects of ammonia in liver disease: current hypotheses. Metab Brain Dis. 2014;29(4):901–11.
22. Cordoba J, Blei AT. Brain edema and hepatic encephalopathy. Semin Liver Dis. 1996;16(3):271–80.
23. Wright G, Noiret L, Olde Damink SW, Jalan R. Interorgan ammonia metabolism in liver failure: the basis of current and future therapies. Liver Int. 2011;31(2):163–75.
24. Karim Z, Szutkowska M, Vernimmen C, Bichara M. Renal handling of NH3/NH4+: recent concepts. Nephron Physiol. 2005;101(4):77–81.
25. Olde Damink SW, Dejong CH, Deutz NE, Redhead DN, Hayes PC, Soeters PB, Jalan R. Kidney plays a major role in ammonia homeostasis after portasystemic shunting in patients with cirrhosis. Am J Physiol. 2006;291(2):G189–94.
26. Olde Damink SW, Jalan R, Deutz NE, Redhead DN, Dejong CH, Hynd P, Jalan RA, Hayes PC, Soeters PB. The kidney plays a major role in the hyperammonemia seen after simulated or actual GI bleeding in patients with cirrhosis. Hepatology. 2003;37(6):1277–85.
27. 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):21–7.
28. 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(3):648–53.
29. 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):1844–52.
30. Scott TR, Kronsten VT, Hughes RD, Shawcross DL. Pathophysiology of cerebral oedema in acute liver failure. World J Gastroenterol. 2013;19(48):9240–55.
31. Orman ES, Perkins A, Ghabril M, Khan BA, Chalasani N, Boustani MA. The confusion assessment method for the intensive care unit in patients with cirrhosis. Metab Brain Dis. 2015;30(4):1063–71.
32. Conn H, Bircher J. Quantifying the severity of hepatic encephalopathy. Bloomington, IL: Medi-Ed Press; 1994.
33. Wijdicks EF. Hepatic Encephalopathy. N Engl J Med. 2016;375(17):1660–70.
34. Ortiz M, Cordoba J, Doval E, Jacas C, Pujadas F, Esteban R, Guardia J. Development of a clinical hepatic encephalopathy staging scale. Aliment Pharmacol Ther. 2007;26(6):859–67.
35. Conn H. Portal-systemic encephalopathy (PSE) after transjugular intrahepatic portal-systemic stent-shunts (TIPS). Ital J Gastroenterol. 1993;25(7):397–9.
36. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2014;370(12):1170–1.
37. Hobbs K, Stern-Nezer S, Buckwalter MS, Fischbein N, Finley Caulfield A. Metronidazole-induced encephalopathy: not always a reversible situation. Neurocrit Care. 2015;22(3):429–36.
38. Kato H, Sosa H, Mori M, Kaneko T. Clinical characteristics of metronidazole-induced encephalopathy: a report of two cases and a review of 32 Japanese cases in the literature. Kansenshogaku Zasshi. 2015;89(5):559–66.
39. Sandip S, Afshan I, Khandelwal RK. MR features of metronidazole-induced encephalopathy. BMJ Case Rep. 2015;2015:bcr2015212609.
40. Cordoba J, Ventura-Cots M, Simon-Talero M, Amoros A, Pavesi M, Vilstrup H, Angeli P, Domenicali M, Gines P, Bernardi M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol. 2014;60(2):275–81.
41. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. Cochrane Database Syst Rev. 2004;2:CD003044.
42. Uribe M, Campollo O, Vargas F, Ravelli GP, Mundo F, Zapata L, Gil S, Garcia-Ramos G. Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial. Hepatology. 1987;7(4):639–43.
43. Conn HO, Leevy CM, Vlahcevic ZR, Rodgers JB, Maddrey WC, Seeff L, Levy LL. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. Gastroenterology. 1977;72(4 Pt 1):573–83.
44. Strauss E, Tramote R, Silva EP, Caly WR, Honain NZ, Maffei RA, de Sa MF. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. Hepatogastroenterology. 1992;39(6):542–5.
45. Morgan MH, Read AE, Speller DC. Treatment of hepatic encephalopathy with metronidazole. Gut. 1982;23(1):1–7.
46. Chavez-Tapia NC, Cesar-Arce A, Barrientos-Gutierrez T, Villegas-Lopez FA, Mendez-Sanchez N, Uribe M. A systematic review and meta-analysis of the use of oral zinc in the treatment of hepatic encephalopathy. Nutr J. 2013;12:74.
47. Timbol AB, Razo RI, Villaluna RA, Ong J. 740: Zinc supplementation for hepatic encephalopathy in chronic liver disease: a meta-analysis. Crit Care Med. 2013;41(12):A183.
48. Corvi MM, Soltys CL, Berthiaume LG. Regulation of mitochondrial carbamoyl-phosphate synthetase 1 activity by active site fatty acylation. J Biol Chem. 2001;276(49):45704–12.
49. Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, Sherwood R, Wendon JA, Bernal W. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014;34(1):42–8.
50. Cordoba J, Blei AT, Mujais S. Determinants of ammonia clearance by hemodialysis. Artif Organs. 1996;20(7):800–3.
51. Chawla R, Smith D, Marik PE. Near fatal posterior reversible encephalopathy syndrome complicating chronic liver failure and treated by induced hypothermia and dialysis: a case report. J Med Case Reports. 2009;3:6623.
52. Whitelaw A, Bridges S, Leaf A, Evans D. Emergency treatment of neonatal hyperammonaemic coma with mild systemic hypothermia. Lancet. 2001;358(9275):36–8.
53. Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. Cochrane Database Syst Rev. 2004;2:CD002798.
54. Lynn AM, Singh S, Congly SE, Khemani D, Johnson DH, Wiesner RH, Kamath PS, Andrews JC, Leise MD. Embolization of

portosystemic shunts for treatment of medically refractory hepatic encephalopathy. Liver Transpl. 2016;22(6):723–31.
55. Keays R, Potter D, O'Grady J, Peachey T, Alexander G, Williams R. Intracranial and cerebral perfusion pressure changes before, during and immediately after orthotopic liver transplantation for fulminant hepatic failure. Q J Med. 1991;79(289):425–33.
56. Yan S, Tu Z, Lu W, Zhang Q, He J, Li Z, Shao Y, Wang W, Zhang M, Zheng S. Clinical utility of an automated pupillometer for assessing and monitoring recipients of liver transplantation. Liver Transpl. 2009;15(12):1718–27.
57. Kitzberger R, Funk GC, Holzinger U, Miehsler W, Kramer L, Kaider A, Ferenci P, Madl C. Severity of organ failure is an independent predictor of intracranial hypertension in acute liver failure. Clin Gastroenterol Hepatol. 2009;7(9):1000–6.
58. Wijdicks EF, Plevak DJ, Rakela J, Wiesner RH. Clinical and radiologic features of cerebral edema in fulminant hepatic failure. Mayo Clin Proc. 1995;70(2):119–24.
59. Munoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B, Martin P, Maddrey WC. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology. 1991;13(2):209–12.
60. Thayaparajah SW, Gulka I, Al-Amri A, Das S, Young GB. Acute fulminant hepatic failure, encephalopathy and early CT changes. Can J Neurol Sci. 2013;40(4):553–7.
61. McKinney AM, Sarikaya B, Spanbauer J, Lohman BD, Uhlmann E. Acute hepatic (or hyperammonemic) encephalopathy: diffuse cortical injury and the significance of ammonia. Am J Neuroradiol. 2011;32(7):E142. author reply E143.
62. JM U-K-I, Yu E, Bartlett E, Soobrah R, Kucharczyk W. Acute hyperammonemic encephalopathy in adults: imaging findings. Am J Neuroradiol. 2011;32(2):413–8.
63. Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, Triantafyllou E, Bernal W, Auzinger G, Shawcross D, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. J Hepatol. 2016;64:69.
64. Karvellas CJ, Todd Stravitz R, Battenhouse H, Lee WM, Schilsky ML, Group USALFS. Therapeutic hypothermia in acute liver failure: a multicenter retrospective cohort analysis. Liver Transpl. 2015;21(1):4–12.
65. Tapper EB, Jiang ZG, Patwardhan VR. Refining the ammonia hypothesis: a physiology-driven approach to the treatment of hepatic encephalopathy. Mayo Clin Proc. 2015;90(5):646–58.
66. Citerio G, Vascotto E, Villa F, Celotti S, Pesenti A. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. Crit Care Med. 2001;29(7):1466–71.
67. Polson J, Lee WM. American Association for the Study of Liver D: AASLD position paper: the management of acute liver failure. Hepatology. 2005;41(5):1179–97.
68. Larsen FS, Hansen BA, Ejlersen E, Secher NH, Clemmesen JO, Tygstrup N, Knudsen GM. Cerebral blood flow, oxygen metabolism and transcranial Doppler sonography during high-volume plasmapheresis in fulminant hepatic failure. Eur J Gastroenterol Hepatol. 1996;8(3):261–5.
69. Scheuermann K, Thiel C, Thiel K, Klingert W, Hawerkamp E, Scheppach J, Konigsrainer A, Morgalla MH, Leckie P, Proven A, et al. Correlation of the intracranial pressure to the central venous pressure in the late phase of acute liver failure in a porcine model. Acta Neurochir Suppl. 2012;114:387–91.
70. Keays RT, Alexander GJ, Williams R. The safety and value of extradural intracranial pressure monitors in fulminant hepatic failure. J Hepatol. 1993;18(2):205–9.
71. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, Han S, Harrison ME, Stravitz TR, Munoz S, et al. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl. 2005;11(12):1581–9.
72. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet. 1993;341(8838):157–8.
73. Lidofsky SD, Bass NM, Prager MC, Washington DE, Read AE, Wright TL, Ascher NL, Roberts JP, Scharschmidt BF, Lake JR. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. Hepatology. 1992;16(1):1–7.
74. Karvellas CJ, Fix OK, Battenhouse H, Durkalski V, Sanders C, Lee WM, Group USALFS. Outcomes and complications of intracranial pressure monitoring in acute liver failure: a retrospective cohort study. Crit Care Med. 2014;42(5):1157–67.
75. Kositchaiwat C, Chuansumrit A. Experiences with recombinant factor VIIa for the prevention of bleeding in patients with chronic liver disease undergoing percutaneous liver biopsies and endoscopic retrograde cholangiopancreatography (ERCP). Thromb Haemost. 2001;86(4):1125–6.
76. Shami VM, Caldwell SH, Hespenheide 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(2):138–43.
77. Aggarwal S, Brooks DM, Kang Y, Linden PK, Patzer JF 2nd. Noninvasive monitoring of cerebral perfusion pressure in patients with acute liver failure using transcranial doppler ultrasonography. Liver Transpl. 2008;14(7):1048–57.
78. Abdo A, Lopez O, Fernandez A, Santos J, Castillo J, Castellanos R, Gonzalez L, Gomez F, Limonta D. Transcranial Doppler sonography in fulminant hepatic failure. Transplant Proc. 2003;35(5):1859–60.
79. Murphy N, Auzinger G, Bernel W, Wendon J. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. Hepatology. 2004;39(2):464–70.
80. Canalese J, Gimson AE, Davis C, Mellon PJ, Davis M, Williams R. Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure. Gut. 1982;23(7):625–9.
81. Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. Neurocrit Care. 2004;1(2):219–33.
82. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. Crit Care Med. 2010;38(5):1348–59.
83. Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. Dan Med Bull. 2007;54(2):99–111.
84. Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. J Hepatol. 1986;2(1):43–51.
85. Forbes A, Alexander GJ, O'Grady JG, Keays R, Gullan R, Dawling S, Williams R. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. Hepatology. 1989;10(3):306–10.
86. Jalan R, Olde Damink SW, Deutz NE, Lee A, Hayes PC. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. Lancet. 1999;354(9185):1164–8.
87. 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):1338–46.
88. Vaquero J. Therapeutic hypothermia in the management of acute liver failure. Neurochem Int. 2012;60(7):723–35.
89. Larsen F.S. Murphy N, Bernal W, Bjerring PN, Hauerberg J, Wendon J., 2011 EUROALF Group. The prophylactive effect of mild hypothermia to prevent brain edema in patients with acute liver failure: results of a multicenter randomized, controlled trial (abstract). J Hepatol, 54(Suppl 1):S26.

90. 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(7):798–804.
91. 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):536–41.
92. 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.
93. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. Crit Care Med. 1993;21(3):328–38.
94. William M. Lee, AM Larson, R. Todd Stravitz. AASLD Position paper: the management of acute liver failure: update 2011. 2011.

Further Readings

Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2014;370(12):1170–1.
Bernal W, Hyyrylainen A, Gera A, Audimoolam VK, McPhail MJ, Auzinger G, Rela M, Heaton N, O'Grady JG, Wendon J, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. J Hepatol. 2013;59(1):74–80.
Joshi D, O'Grady J, Patel A, Shawcross D, Connor S, Deasy N, Willars C, Bernal W, Wendon J, Auzinger G. Cerebral oedema is rare in acute-on-chronic liver failure patients presenting with high-grade hepatic encephalopathy. Liver Int. 2014;34(3):362–6.
Wijdicks EF. Hepatic encephalopathy. N Engl J Med. 2016;375(17):1660–70.
Al-Khafaii A, editor. ICU care of abdominal organ transplant patients. 1st ed. Oxford: Oxford University Press; 2013.