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# Assessment and management of cerebral edema and intracranial hypertension in acute liver failure☆

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**Abstract** Acute liver failure is uncommon but not a rare complication of liver injury. It can happen after ingestion of acetaminophen and exposure to toxins and hepatitis viruses. The defining clinical symptoms are coagulopathy and encephalopathy occurring within days or weeks of the primary insult in patients without preexisting liver injury. Acute liver failure is often complicated by multiorgan failure and sepsis. The most life-threatening complications are sepsis, multiorgan failure, and brain edema. The clinical signs of increased intracranial pressure (ICP) are nonspecific except for neurologic deficits in impending brain stem herniation. Computed tomography of the brain is not sensitive enough in gauging intracranial hypertension or ruling out brain edema. Intracranial pressure monitoring, transcranial Doppler, and jugular venous oximetry provide valuable information for monitoring ICP and guiding therapeutic measures in patients with encephalopathy grade III or IV. Osmotic therapy using hypertonic saline and mannitol, therapeutic hypothermia, and propofol sedation are shown to improve ICPs and stabilize the patient for liver transplantation. In this article, diagnosis and management of hepatic encephalopathy and cerebral edema in patients with acute liver failure are reviewed.


## 1. Definition and epidemiology of acute liver failure

Acute liver failure (ALF) is a life-threatening multisystem illness resulting from massive liver injury. The defining clinical symptoms are coagulopathy and encephalopathy occurring within days or weeks of the primary insult in patients without preexisting liver injury [1]. Acute liver failure is a relatively uncommon disorder affecting approximately 2500 patients in the United States each year [2]. Acetaminophen and nonacetaminophen drug-induced hepatotoxicity account for more than 50% of cases of ALF in the United States [3]. Other identifiable causes of ALF include acute hepatitis B virus infection (7%); other viral infections (3%); autoimmune hepatitis (5%); ischemic hepatitis (4%); and various other causes (5%) such as Wilson disease, pregnancy-associated ALF, and other metabolic pathway abnormalities. Of importance, up to 15% of ALF cases remain of unclear etiology. In the developing countries, infectious hepatitis is the most common cause of ALF. However, less than 4% of cases

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of acute hepatitis B viral infection will lead to development of the ALF, but mortality is higher than that with hepatitis A or E infections [4].

## 2. Hepatic encephalopathy and brain edema in ALF

Hepatic encephalopathy is graded according to the degree of cognitive deficit. The West Haven criteria were originally developed for chronic liver disease but are used clinically for ALF as a bedside assessment tool (Table 1). Grades I and II have mild to moderate confusion and irritability with or without asterixis. Grade III has marked confusion with asterixis but still can follow commands. Grade IV patient is comatose [5]. In the earlier reports, the frequency of cerebral edema occurring in fulminant hepatic failure ranged from 50% to 85% [6-9]. Although the frequency of clinically overt brain edema in ALF patients has decreased over the past 2 decades, intracranial hypertension accounts for 20% to 35% of deaths and requires considerable resources in the intensive care unit setting [10,11].

The degree of hepatic encephalopathy on admission tends to predict outcome. In one of the largest prospective multicenter studies on 308 patients, 161 patients presented with grade I and II hepatic encephalopathy on admission; 52% survived without transplantation for 3 weeks. In contrast, of 147 patients who presented with grade III or IV hepatic encephalopathy, 33% survived 3 weeks without transplantation. The overall transplantation rate was 29% for all grades, but grade I and II had a survival rate of 77% compared with 56% in grade III and IV [12].

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

| Grade | Level of consciousness/ cognitive function | Psychiatric symptoms | Neuromuscular function |
|---|---|---|---|
| 1 | Sleep disturbance | Euphoria/ depression | Tremor |
| | Mild confusion | | Incoordination, ± asterixis |
| | Impaired computations | | |
| 2 | Inattentive | Irritability | Asterixis, slurred speech |
| | Moderate confusion | Decreased inhibitions | Impaired handwriting |
| | Disorientation to time | Personality changes | |
| 3 | Marked confusion | Anxiety or apathy | Slurred speech, ataxia |
| | Completely disoriented | Inappropriate | Asterixis, nystagmus |
| | Lethargic, but arousable | Bizarre behavior | Hypoactive or hyperactive reflexes |
| | Command following | Paranoia, anger or rage | |
| 4 | Non-command following | | Coma, dilated pupils |
| | | | Loss of cranial nerve reflexes |
| | | | Signs of herniation |
| | | | Flexor or extensor posturing |
| | | | Loss of reflexes |

## 3. Mechanism of brain edema

The pathogenesis of hepatic encephalopathy and cerebral edema is multifactorial, but it is well established that ammonia plays a central role and inflammatory cytokines accentuate the process [13]. According to the ammonia-glutamine hypothesis, the source of circulating ammonia is from glutamine metabolism in the intestinal epithelium and urease activity in the intestinal flora. In normal circumstances, the liver metabolizes all the ammonia coming from the small and large intestine via portal circulation. Ammonia is also produced in healthy individuals by muscle and the kidney. These 2 tissues have the ability to shift to ammonia detoxifying organs in the case of liver failure. However, because of loss of muscle mass in chronic liver failure, the physiologic efficiency and clinical benefits of this detoxifying process are not clear. Hyperammonemia induces accumulation of glutamine inside the astrocytes. Astrocytes are the only cells in the brain that can metabolize ammonia. The enzyme glutamine synthetase (present in the endoplasmic reticulum of astrocytes) is responsible for the conversion of equimolar concentrations of glutamate and ammonia to glutamine. Intracellular levels of glutamine, therefore, increase enormously as the ambient ammonia concentrations rise secondary to liver failure. The osmotic and metabolic effects of glutamine contribute to astrocyte swelling and cerebral edema in hepatic encephalopathy. Increased cerebral glutamine levels correlate with severity of psychoneurological signs and intracranial pressure (ICP) measurements. The “toxic liver hypothesis” implicates inflammatory cytokines and toxic products from the necrotic liver that correlate with central nervous system complication. There is evidence for neuroinflammation in ALF in experimental models and in patients with ALF showing efflux of tumor necrosis factor $\alpha$, interleukin $1\beta$, and interleukin 6 from the brain when measured in blood sampled from an artery and reverse jugular catheter [14]. Ultrastructural studies in brain sections from ALF patients have so far failed to provide evidence for blood-brain barrier breakdown, attributing brain edema and its complications to primarily cytotoxic rather than vasogenic mechanisms [15].