

# Hepatic Encephalopathy

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## KEYWORDS

- Liver • Encephalopathy • Cancer • Emergency department
- Liver failure • Brain edema

Hepatic encephalopathy (HE) is a serious and progressive but potentially reversible disorder with a wide spectrum of neuropsychiatric abnormalities and motor disturbances that ranges from mild alteration of cognitive and motor function to coma and death.<sup>1</sup> It is a challenging complication of advanced liver disease where overt forms are estimated to occur in 30% to 45% of patients with liver cirrhosis and in 10% to 50% of patients with transjugular intrahepatic portosystemic shunts.<sup>2</sup> Minimal HE, which is characterized by more subtle motor and cognitive deficits, affects approximately 20% to 60% of patients with liver disease.

Cancer patients can be at risk for liver injury and HE due to multiple factors. The factors include preexisting liver disease, primary liver tumors, liver metastases of extrahepatic malignancies, compromised portal or hepatic venous circulation, hepatotoxicity due to chemotherapy, and bone marrow transplantation.<sup>3–11</sup>

Due to differences in etiology and severity, and subtle findings in mild HE, the diagnosis and management of HE may be challenging for physicians. This article aims to help with recognition and management of HE in the emergency department (ED) by reviewing its pathogenesis, classification, diagnosis, grading, and treatment.

## PATHOGENESIS

HE is a reversible metabolic encephalopathy associated with variable degrees of brain edema. The pathogenesis is multifactorial and includes neurotoxicity of ammonia, oxidative stress, endogenous benzodiazepine-like ligands, astrocyte swelling,  $\gamma$ -aminobutyric acid-like molecules, abnormal histamine and serotonin neurotransmission, endogenous opioids, neurosteroids, inflammatory cytokines, and potential manganese toxicity.<sup>12–14</sup> There is convincing evidence from animal and imaging studies about the role of ammonia and cerebral edema as major contributors to the development of HE.<sup>15</sup> Cerebral edema is partly due to uptake of ammonia into astrocytes, where it is combined with intracellular glutamate to produce glutamine, which causes

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Emerg Med Clin N Am 27 (2009) 401–414

doi:10.1016/j.emc.2009.04.005

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cellular swelling. In patients with acute liver failure, higher uptake of ammonia in the brain, increased cerebral edema, and intracranial pressure (ICP) resulting in increased mortality from cerebral herniation have been observed.<sup>16,17</sup>

The ammonia hypothesis does not fully explain the pathophysiology of HE because there are inconsistent changes in central nervous system functions when blood ammonia levels are increased. In contrast, HE is induced more consistently by rising ammonia levels in the presence of inflammatory mediators.<sup>12,18</sup> The precise mechanism underlying the synergism between inflammatory mediators and ammonia remains unclear.

## CLASSIFICATION

The World Congress of Gastroenterology has proposed three main categories of HE based on the underlying liver dysfunction (**Box 1**).<sup>1</sup> Type A HE is associated with acute liver failure and progresses rapidly to seizures, decerebrate rigidity, coma, and frequently death. Types B and C are chronic conditions and can manifest as minimal or overt HE. Overt HE can further be classified as episodic or persistent HE. Episodic HE is the more common form of overt HE and presents with short periods of changes in consciousness over hours to days. These periods are typically caused by increased blood ammonia levels or worsening liver disease. Patients with episodic HE usually return to a normal mental state with treatment and good supportive care. In persistent HE, despite fluctuating levels of consciousness, patients do not return to a normal mental state.

## DIAGNOSIS OF CHRONIC HEPATIC ENCEPHALOPATHY

Minimal HE is common in patients with cirrhosis, and it is characterized by normal neurologic findings and cognitive impairments that are detectable only by psychometric tests. Patients with minimal HE suffer from impaired psychomotor speed, visual perception, attention and concentration, slow mental processing, and memory loss. As a result of these alterations, patients often have difficulty with social interactions and in performing their work, leading to reduced health-related quality of life.<sup>19–22</sup>

The current definition of minimal HE is based on at least two psychometric tests. To meet the definition of HE, the results of each test should be two standard deviations less than normal. Despite their efficiency and sensitivity, routine use of these tests is challenged by copyright issues, need for psychological expertise for test interpretation, and time needed to perform them. If psychometric tests are not available and clinical suspicion of minimal HE is high, a trial of empiric therapy with lactulose can be initiated.<sup>23</sup>

Clinical symptoms, electroencephalography, neuroimaging, and blood ammonia testing are used for screening of patients for overt HE. It is characterized by alterations in mental status and generalized motor disturbance. Slow, monotonous speech and loss of fine motor skills are the hallmarks implicating the presence of overt HE. The clinical features of overt HE are shown in **Box 2**.<sup>24</sup> However, these manifestations are not specific and can be seen in other encephalopathies as well. The detection

### Box 1

#### Classification of HE

- 1) Type A: HE associated with acute liver failure
- 2) Type B: HE associated with portosystemic bypass and no intrinsic liver disease
- 3) Type C: HE associated with cirrhosis and portal hypertension

**Box 2****Clinical features of overt HE**

- 1) Slow, monotonous speech pattern
- 2) Loss of fine motor skills
- 3) Extrapyramidal type movement disorders
- 4) Hyperreflexia, Babinski sign, clonus
- 5) Asterixis
- 6) Hyperventilation
- 7) Seizures
- 8) Confusion, coma
- 9) Decerebrate/decorticate posturing

and differentiation of overt HE in cirrhotic patients has prognostic importance as these patients should be evaluated for liver transplantation. The diagnosis of overt HE is based on

- known or suspected liver disease and/or portosystemic shunt,
- neurologic and/or cognitive impairment found by specific testing or clinical examination,
- exclusion of other encephalopathies,
- identification and resolution of all precipitating factors (**Box 3**).<sup>25</sup>

Grading of HE carries prognostic and therapeutic importance. West Haven Criteria (**Box 4**) and the Glasgow Coma Scale can be used to grade the severity of HE.<sup>26,27</sup>

Neuroimaging studies are usually performed to rule out other potential causes of encephalopathy and to demonstrate the cerebral edema. Magnetic resonance imaging of brain is especially helpful in diagnosing HE in patients with portosystemic shunts but no intrinsic liver disease. As a result of decreased first-pass clearance of dietary manganese, these patients have accumulation of manganese in the basal ganglia. The accumulation of manganese is detected as hyperintensity of the basal ganglia on T1-weighted images and indicates significant portosystemic shunting.<sup>28</sup>

Blood ammonia levels can correlate with the severity of HE if measured appropriately.<sup>29-31</sup> The proper technique is to place the specimen on ice and perform the assay within 30 minutes of drawing blood. Failure to do so and performing the assay on post-prandial blood will result in artificial elevations. High ammonia levels in a comatose patient may be due to cirrhosis, a urea cycle disorder, or seizure activity. Ammonia levels in each stage of overt HE overlap widely; therefore, no consistent correlation exists between venous ammonia levels and risk for cerebral edema in patients with cirrhosis.<sup>17</sup>

## MANAGEMENT OF CHRONIC HEPATIC ENCEPHALOPATHY

The management of chronic HE includes exclusion of other causes of encephalopathy, identification and treatment of precipitating factors (see **Box 3**), supportive measures such as restoring electrolyte balance, fluid maintenance, aspiration precautions, and intubation for airway protection in grade 3 and 4 HE.

Based on the pathogenesis that intestinal-derived ammonia contributes to development of HE, current treatment measures are directed at reducing bacterial production of ammonia and enhancing its elimination.

Box 3 Precipitating factors for HE	
1) Increased nitrogen load	
	Gastrointestinal bleeding
	Excess dietary protein
	Azotemia
	Constipation
2) Electrolyte imbalance	
	Hyponatremia
	Hypokalemia
	Metabolic alkalosis/acidosis
	Hypoxia
	Hypovolemia
3) Drugs	
	Narcotics, tranquilizers, sedatives
4) Miscellaneous	
	Infection
	Surgery
	Superimposed acute liver disease
	Progressive liver disease
	Transjugular intrahepatic portosystemic shunt

Lactulose, a nonabsorbable disaccharide, remains the mainstay treatment for HE. Due to deficiency of specific disaccharidase, lactulose remains undigested until it reaches the colon, where it inhibits ammonia production and traps ammonia as non-diffusible ammonium. In the colon, lactulose is catabolized by colonic bacteria to form short-chain fatty acids such as lactic and acetic acid. These acids lower the colonic pH, which favors formation of insoluble ammonium from soluble ammonia, resulting in reduced plasma ammonia concentration. In addition, lactulose causes a fourfold increase in fecal nitrogen excretion due to its cathartic effects.<sup>32</sup> Lactulose can be administered orally or through a nasogastric (NG) tube (**Table 1**). Retention enema is preferred in patients with grade 3 and 4 HE, patients with ascites or peritonitis, and in those who are unable to tolerate NG. The side effects of lactulose seen after oral or NG administration include abdominal bloating and distention, cramping, and diarrhea.

Despite the widespread use of lactulose, evidence supporting its efficacy for the treatment of HE is limited. A systematic review of the literature found lactulose to be more effective than placebo in improving HE, but with no effect on mortality.<sup>33</sup> However, when only the highest-quality studies were included, no significant effect on improvement of HE was seen with lactulose therapy.

Alternative treatments for HE include antibiotics such as neomycin, metronidazole, and vancomycin. The goal of antibiotic treatment is to reduce the mass of enteric

Box 4 West Haven criteria for grading hepatic encephalopathy	
Grade 0	Lack of detectable changes in personality or behavior No asterixis
Grade 1	Trivial lack of awareness, shortened attention span, sleep disturbance, and altered mood Asterixis may be present
Grade 2	Lethargy, disorientation to time, amnesia of recent events, impaired simple computations, inappropriate behavior, slurred speech Asterixis is present
Grade 3	Somnolence, confusion, disorientation to place, bizarre behavior, clonus, nystagmus, positive Babinski sign Asterixis usually absent
Grade 4	Coma and lack of verbal, eye, and oral response

bacteria that produce ammonia. However, controlled studies have failed to show any difference in outcomes between patients with HE who were treated with neomycin and those treated with placebo.<sup>34</sup> No significant difference was found between lactulose and neomycin, lactulose and placebo, and lactulose and neomycin-lactulose combination.<sup>35–37</sup> The experience with metronidazole and vancomycin to date is limited to small, uncontrolled studies. Despite poor systemic absorption when taken orally, antibiotics may result in serious adverse effects due to cumulative systemic absorption after prolonged use. Chronic neomycin use is associated with ototoxicity and nephrotoxicity, and metronidazole is associated with neurotoxicity.

Rifaximin, a semisynthetic derivative of rifamycin, has also been found to be effective in HE at a dose of 1200 mg/d (see **Table 1**).<sup>38,39</sup> It is virtually nonabsorbable (<0.4%) from the gastrointestinal tract, and no dosage adjustments are necessary in

Table 1 Dosages of medications used for hepatic encephalopathy	
Lactulose (10 g/15 mL)	
Oral/NG	30 mL 2–4 times a day. Titrate dose until 2–3 soft stools a day
Retention enema	300 mL lactulose + 700 mL tap water or saline, every 4–6 h as needed
Neomycin	
Oral/NG	4–12 g/d divided every 46 h
Rifaximin	
Oral	1200 mg/d, divided every 8 h

patients with liver dysfunction or renal insufficiency.<sup>40</sup> Rifaximin was approved in the United States in 2004 for nondysenteric traveler's diarrhea caused by *Escherichia coli* and has been given "orphan status" by the Food and Drug Administration for use in the treatment of HE.

Current data suggest that rifaximin is as effective as lactulose and neomycin in the treatment of HE and has a favorable safety and tolerability profile.<sup>41,42</sup> In retrospective studies, it significantly reduced the number and length of hospitalizations resulting in lower hospitalization charges when compared with lactulose.<sup>43,44</sup> In a study comparing the cost-effectiveness of multiple treatment strategies in HE, including no treatment, lactulose monotherapy, neomycin monotherapy, rifaximin monotherapy, and rifaximin salvage (lactulose with crossover to rifaximin in lactulose-refractory or intolerant patients), lactulose monotherapy was found to be the least expensive and rifaximin monotherapy, the most expensive.<sup>45</sup> The authors concluded that reserving rifaximin for lactulose-refractory or intolerant patients may be more cost-effective. In one randomized double-blind study, rifaximin was not found to improve mental status better than placebo.<sup>46</sup> Rifaximin use for HE is currently being evaluated in a multicenter trial in the United States.

Sodium benzoate, an ammonia-reducing agent used for urea cycle defects, has been studied as a treatment option for HE. Benzoate reduces serum ammonia levels by increasing its urinary excretion. Sodium benzoate was found to be comparable to lactulose in improving symptoms of HE.<sup>47</sup> However, it was shown to cause increased ammonia levels in some animal and human studies; therefore, its use in patients without overt HE has not been recommended.<sup>48</sup>

Endogenous benzodiazepines have been suggested to cause neuroinhibition in patients with HE by binding to the  $\gamma$ -aminobutyric acid–benzodiazepine receptor complex. Antagonism of this effect with flumazenil, a benzodiazepine receptor antagonist, has been proposed as possible treatment of HE. In one study, intravenous flumazenil was found to be beneficial only in cirrhotic patients with severe HE.<sup>49</sup> Thirteen randomized, double-blind trials that compared flumazenil to placebo were evaluated by meta-analyses. Flumazenil was found to have significant beneficial effect on short-term improvement of HE in patients with favorable prognosis; however, it had no effect on recovery or survival.<sup>50,51</sup> It was concluded that until future trials reveal sustained improvement or increased recovery or survival, flumazenil cannot be recommended for routine clinical use.

L-ornithine-L-aspartate administration has been shown to improve ammonia detoxification in patients with chronic mild to moderate HE.<sup>52,53</sup> Although promising as a treatment option for HE, it is not available in the United States. Other treatments with the ketoanalogues of branched chain amino acids have been investigated but currently are not in use because of inefficacy and poor palatability. Extracorporeal albumin dialysis has been shown to be effective in HE and may serve as a bridge to liver transplantation.<sup>54,55</sup>

The recommended dietary protein intake for patients with a history of HE is 0.81.5 g/kg/d. Patients with grade 3 and 4 HE often have low or no protein intake for a few days due to an inability to ingest meals. However, they should resume protein intake as soon as they are ready to be fed orally or enterally to avoid a catabolic state associated with prolonged protein deprivation.<sup>56</sup>

## PROGNOSIS OF CHRONIC HEPATIC ENCEPHALOPATHY

Chronic HE is almost always reversible. If it does not resolve within 72 hours of treatment, an ongoing precipitating factor, another cause of encephalopathy, or

suboptimal treatment should be considered. Patients should be evaluated for low-grade gastrointestinal bleeding and excess dietary protein ingestion. Persistent HE related to worsening liver function or a transjugular intrahepatic portosystemic shunt may require chronic treatment with lactulose or nonabsorbable antibiotic. Because of lower survival rates, episodic or persistent HE in a patient with cirrhosis is an indication for liver transplant evaluation.

### HEPATIC ENCEPHALOPATHY IN ACUTE LIVER FAILURE

HE has prognostic importance in acute liver failure. Among 136 patients from the United States Acute Liver Failure Study, 31% with mild HE either underwent liver transplantation or died.<sup>57</sup> Liver transplantation or death occurred in 74% of 217 patients with severe HE in the United Kingdom.<sup>58</sup>

Brain edema and intracranial hypertension (ICH) are serious consequences of severe HE in acute liver failure. The risk of edema is very low in grade 1 and 2 HE, but increases to 25% to 35% in grade 3 HE and to 65% to 75% or higher in grade 4 HE.<sup>59</sup>

Ammonia, infection/inflammation, and hyponatremia are the main contributors to the development of brain edema in acute liver failure. Higher arterial ammonia levels were found to be predictive of higher mortality and are associated with more complications including cerebral edema, seizures, and ventilation requirement.<sup>16</sup> Among patients with grade 3 and 4 HE, arterial ammonia values above 200  $\mu\text{mol/L}$  were found to be almost invariably associated with cerebral uncal herniation, and levels below 150  $\mu\text{mol/L}$  appeared to be protective.<sup>60</sup> Venous ammonia levels are less informative due to large arteriovenous variation of ammonia in acute liver failure. When ammonia concentration cannot be lowered with conventional treatments, continuous venovenous hemofiltration may be used to reduce arterial ammonia concentration significantly. Infection/inflammation have been shown to be associated with development and progression of HE in acute liver failure.<sup>61,62</sup> Approximately 25% of patients with acute liver failure have hyponatremia, which is more prominent in those with severe encephalopathy.<sup>16</sup> The pathogenesis of hyponatremia in acute liver failure remains unclear, but volume overload and vasopressin secretion are believed to be contributing factors.

In patients with acute liver failure, decerebrate posturing, pupillary changes, and oculovestibular reflex abnormalities all indicate increased ICP. Unfortunately, the sensitivity of imaging studies with regard to information about brain edema in acute liver failure is low. Invasive monitoring is the most accurate tool to measure ICP; however, intracranial bleeding in the setting of coagulopathy remains a serious complication. The prevalence of bleeding ranges between 10% and 22%.<sup>63,64</sup> Aggressive correction of coagulation parameters, with the addition of recombinant factor VIIa, may reduce the risk of bleeding.

### MANAGEMENT OF HEPATIC ENCEPHALOPATHY IN ACUTE LIVER FAILURE

It is preferable to follow patients with acute liver failure and grade 1 HE in the intensive care unit. However, they can also be admitted to a medicine ward with skilled nursing care and frequent neurologic monitoring. A quiet environment is preferred to avoid agitation.

Patients with grade 2 HE should be admitted to intensive care units. Sedation should be avoided if possible. Small doses of short-acting benzodiazepines can be used if needed. Head imaging is helpful to exclude other possible causes of encephalopathy. Patients with grade 2 HE can be treated with lactulose to lower ammonia levels. Data from the United States Acute Liver Failure Study Group suggest that

lactulose use is associated with a small increase in survival but no difference in severity of HE or overall outcome.<sup>65</sup>

Patients with grade 3 and 4 HE require intubation for airway protection. Short-acting agents such as propofol are preferred for sedation. Identification of early cerebral edema at this stage is important as brain perfusion must be preserved and herniation prevented until transplantation. Clinical symptoms of elevated ICP such as hypertension, bradycardia, and irregular respiration may not be present at this stage. Therefore, ICP monitoring devices are helpful in identifying early cerebral edema. These devices can show elevations in ICP and reductions in cerebral perfusion pressure (CPP). ICP should be maintained below 20 to 25 mm Hg with CPP above 50 to 60 mm Hg.<sup>66</sup> Prolonged ICP greater than 40 mm Hg and CPP less than 50 mm Hg have been shown to be associated with poor outcome.<sup>67</sup> Refractory ICH and decreased CPP are contraindications for liver transplantation.

Clinical trials have shown that control of elevated ICP improves survival.<sup>68,69</sup> Mannitol is effective in the short term to decrease cerebral edema. It is administered as an IV bolus of 0.5 to 1 g/kg. The dose may be repeated once or twice. Hypertonic saline to induce hypernatremia (150 mmol/L) may be used to control ICH based on data from patients with head injury. Two studies showed significant improvement in ICP and CPP after hypernatremia was induced with 3% saline in pediatric patients with head trauma and resistant ICH.<sup>70,71</sup> Moderate hypernatremia has also been shown to decrease ICP in patients with acute liver failure. In one study, 30% hypertonic saline was given to patients with acute liver failure and grade 3 or 4 HE.<sup>72</sup> The infusion rate was titrated between 5 and 20 mL/h to maintain serum sodium levels at 145 to 155 mmol/L. The authors concluded that patients with hypernatremia had significantly lower ICP and reduced incidence of clinically significant ICH. However, because hypertonic saline solutions are associated with very high sodium loads, caution is advised, especially for patients with renal dysfunction. Indeed, most patients in that study received continuous venovenous hemofiltration, which buffered sodium overload.

Hyperventilation to reduce PaCO<sub>2</sub> to 25 to 30 mm Hg may be used temporarily if ICH cannot be controlled with mannitol or other measures in patients with acute liver failure. However, both mannitol and hyperventilation are not recommended for routine or prophylactic use. Although controlled trials are lacking, some centers prefer to keep the core temperature at 36°C in those intubated for HE and at 34°C in those developing ICH.<sup>73</sup> Patients with acute liver failure and progressive HE are considered as potentially infected and should be started on empiric antibiotics.<sup>74</sup> Most patients with acute liver failure require renal replacement therapy, which is more effective in preventing brain edema rather than treating it. Intravenous administration of N-acetylcysteine has been reported to improve survival significantly in patients with acute liver failure and mild HE.<sup>75</sup> However, there was no impact on survival of patients with severe HE.

Acute liver failure is a rare condition; very few controlled trials exist for its treatment, and standards of care have not been established. The recommended management of HE in acute liver failure, based on expert opinions and data from limited studies, is summarized in **Box 5**.<sup>76</sup>

## HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CANCER

Patients with cancer have increased risk of acute or chronic liver injury and portal hypertension due to multiple factors (**Box 6**). HE can develop either due to progression

**Box 5****Management of cerebral edema and intracranial hypertension in acute liver failure****Grade 1 and 2 encephalopathy**

- Consider transfer to liver transplant facility
- Perform head imaging to rule out other causes of alterations in mental status
- Avoid stimulation
- Avoid sedation if possible
- Antibiotics: survey and treat infection, prophylaxis possibly helpful
- Lactulose possibly helpful

**Grade 2 and 3 encephalopathy**

- Continue management as above
- Intubate trachea
- Elevate head at 30°
- Consider placing ICP monitoring device
- Treat seizures (phenytoin)
- Mannitol for severe elevation of ICP or first clinical signs of herniation
- Hyperventilation may be used for impending herniation

of the liver injury or due to therapeutic measures such as transjugular intrahepatic portosystemic shunts. There might be several different presentations. First, patients with no previous history of malignancy may present with liver dysfunction and HE, which can be a diagnostic challenge. Second, patients with known malignancy but without previous history of liver involvement can present with liver dysfunction and HE. Finally, patients with known primary or secondary hepatic malignancy may present with HE as a terminal event. In the first scenario, diagnosis of hepatic infiltration should be considered in addition to nonmalignant liver diseases. Non-Hodgkin's lymphoma, Hodgkin's disease, and leukemias commonly infiltrate the liver. Colon, gastric, breast, and small-cell carcinoma and melanoma are less common causes of hepatic infiltration.<sup>4-6,77</sup> HE can be the initial presentation of hepatocellular carcinoma.<sup>78</sup> In the

**Box 6****Causes of liver injury in cancer patients**

- Primary liver tumors
- Metastatic infiltration of liver
- Nodular regenerative hyperplasia
- Compromised hepatic or portal venous circulation
- Hepatotoxicity of chemotherapeutic agents
- Hepatotoxicity due to nonchemotherapeutic agents
- Bone marrow transplantation
- Total parenteral nutrition
- Viral hepatitis
- Sepsis

second scenario, chemotherapy- or radiotherapy-induced liver failure, metastatic infiltration, and reactivation of underlying chronic hepatitis B should be considered.<sup>79</sup> In the third scenario, HE presents as a terminal event in patients with advanced cancer, and symptoms of HE can mistakenly be attributed to cerebral metastases, drugs, sepsis, or severe constitutional disease.

HE can be encountered after transjugular intrahepatic portosystemic shunt placement to control complications of portal hypertension in patients with hepatic or extrahepatic malignancies.<sup>80,81</sup> HE has also been reported to occur in patients with portal venous thrombosis and transtumoral portosystemic shunting.<sup>9,10</sup>

Various chemotherapeutic agents can cause acute or chronic liver injury leading to HE. There are case reports of fulminant liver injury with gemcitabine and paclitaxel.<sup>7,82</sup> Dacarbazine, 6-thioguanine, actinomycin D, busulfan, and cyclophosphamide have been reported to cause venoocclusive disease, whereas methotrexate has been associated with fibrosis/cirrhosis.<sup>82</sup>

Multiple factors may be associated with liver injury and resultant HE in patients with cancer. These patients are also at risk to develop encephalopathy due to other causes such as cerebral metastases, sepsis, drugs, Wernicke encephalopathy, and hypertensive encephalopathy. Hyperammonemic encephalopathy due to ornithine transcarbamoylase deficiency has been reported in a young patient receiving chemotherapy for hepatocellular carcinoma.<sup>83</sup>

The treatment of HE in cancer patients involves treatment of the primary etiologic factor in addition to the measures to treat HE itself. Although liver injury can occasionally be reversed with appropriate chemotherapy, the prognosis remains dismal if the liver failure is the result of loss of critical mass of hepatocytes due to replacement with malignant cells.

## SUMMARY

HE is a common and serious complication of chronic or acute liver failure. Identification and correction of precipitating factors remain the cornerstone of treatment, and morbidity and mortality can be decreased by timely intervention. The diagnosis and management of HE in ED can be challenging and requires arrangement of care in experienced centers with interaction between ED physicians, hepatologists, and surgeons. HE in cancer patients is multifactorial and requires specific treatment for HE as well as management of the underlying etiology.

## REFERENCES

1. Ference P, Lockwood A, Mullen K, et al. Hepatic encephalopathy definition, nomenclature, diagnosis, and qualification: final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. *Hepatology* 2002; 35:716–21.
2. Poordad FF. Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 2006;25(1):3–9.
3. Smith BC, James OFW. The failing malignant liver. *Gut* 1998;42:454–9.
4. Te HS, Schiano TD, Kahaleh M, et al. Fulminant hepatic failure secondary to malignant melanoma: case report and review of literature. *Am J Gastroenterol* 1999;94:262–6.
5. Alexopoulou A, Koskinas J, Deitsch M, et al. Acute liver failure as the initial manifestation of hepatic infiltration by a solid tumor: report of 5 cases and review of literature. *Tumori* 2006;92(4):354–7.

6. Salmon JS, Thompson MA, Arildsen RC, et al. Non-Hodgkin's lymphoma involving the liver: clinical and therapeutic considerations. *Clin Lymphoma Myeloma* 2006; 6(4):273–80.
7. Nieto Y, Cagnoni PJ, Bearman SI, et al. Acute encephalopathy: a new toxicity associated with high dose paclitaxel. *Clin Cancer Res* 1999;5(3):481–6.
8. Tanvetyanon T, Choudhury AM. Fatal acute tumor lysis syndrome, hepatic encephalopathy and flare phenomenon following combined androgen blockade. *J Urol* 2004;171:1627.
9. Yamamoto T, Kuyama Y, Takeuchi K, et al. Hepatic encephalopathy due to portal venous thrombosis in a patient with pancreatic tumor. *Pancreas* 2003;26(3):313–4.
10. Kapoor BS, Hunter DW, Greeno E, et al. Hepatic encephalopathy secondary to transtumoral portal venous shunting. *Hepatogastroenterology* 2003;50(49):4–7.
11. Kondo H, Kasahara Y. Prevention of severe hepatic injury by interferon-alfa in chronic active hepatitis lacking HBeAg (mutant strain) in a patient with malignant lymphoma. *Cancer* 1998;125:171–5.
12. Shawcross D, Jalan R. The pathophysiologic basis of hepatic encephalopathy: central role for ammonia and inflammation. *Cell Mol Life Sci* 2005;62: 2295–304.
13. Wright G, Jalan R. Management of hepatic encephalopathy in patients with cirrhosis. *Best Pract Res Clin Gastroenterol* 2007;21:95–110.
14. Cordoba J, Blei A. Hepatic encephalopathy. In: Schiff ER, Sorell MF, Maddrey WC, editors. *Diseases of liver*. 10th edition. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 569–99.
15. Keiding S, Sorensen M, Bender D, et al. Brain metabolism of 13N-ammonia during acute hepatic encephalopathy in cirrhosis measured by positron emission tomography. *Hepatology* 2006;43:42–50.
16. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. *Gut* 2006;55:98–104.
17. Kundra A, Jain A, Banga A, et al. Evaluation of plasma ammonia levels in patients with acute liver failure and chronic liver disease and its correlation with the severity of hepatic encephalopathy and clinical features of raised intracranial tension. *Clin Biochem* 2005;38:696–9.
18. Shawcross DL, Davies NA, Williams R, et al. Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis. *J Hepatol* 2004;40:247–54.
19. Amodio P, Montagnese S, Gatta A, et al. Characteristics of minimal hepatic encephalopathy. *Metab Brain Dis* 2004;19:253–67.
20. Mattarozzi K, Campi C, Guarino M, et al. Distinguishing between clinical and minimal hepatic encephalopathy on the basis of specific cognitive impairment. *Metab Brain Dis* 2005;20:359–67.
21. Weissenborn K, Giewekemeyer K, Heidenreich S, et al. Attention, memory, and cognitive function in hepatic encephalopathy. *Metab Brain Dis* 2005;20:359–67.
22. Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. *Metab Brain Dis* 2001;16:37–41.
23. Prasad S, Dhiman RK, Duseja A, et al. Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy. *Hepatology* 2007;45:549–59.
24. Mullen KD. Pathogenesis, clinical manifestation, and diagnosis of hepatic encephalopathy. *Semin Liver Dis* 2007;27(Suppl 2):3–9.
25. Ferenci P. Treatment options for hepatic encephalopathy: a review. *Semin Liver Dis* 2007;27(Suppl 2):10–7.

26. Conn HO. Quantifying the severity of hepatic encephalopathy. In: Conn HO, Bircher J, editors. *Hepatic encephalopathy: syndromes and therapies*. Bloomington (IL): Medi-ed Press; 1994. p. 13–26.
27. Groeneweg M, Quero JC, De Bruijn I, et al. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998;28:45–9.
28. Morgan MY. Cerebral magnetic resonance imaging in patients with chronic liver disease. *Metab Brain Dis* 1998;13:273–90.
29. Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med* 2003;114:188–93.
30. Nicolao F, Efrati C, Masini A, et al. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. *J Hepatol* 2003;38:441–6.
31. Kramer L, Tribl B, Gendo A, et al. Partial pressure of ammonia versus ammonia in hepatic encephalopathy. *Hepatology* 2003;31:30–4.
32. Mortensen PB. The effect of oral-administered lactulose on colonic nitrogen metabolism and excretion. *Hepatology* 1992;16:1350–6.
33. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ* 2004;328:1046.
34. Strauss E, Tramote R, Silva EP, et al. Double-blind randomized clinical trial comparing neomycin and placebo in the treatment of exogenous hepatic encephalopathy. *Hepatogastroenterology* 1992;39:542–5.
35. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. *Gastroenterology* 1977;72:573–83.
36. Atterbury CE, Maddrey WC, Conn HO. Neomycin-sorbitol and lactulose in the treatment of acute portal-systemic encephalopathy. A controlled, double-blind clinical trial. *Am J Dig Dis* 1978;23:398–406.
37. Blanc P, Daures JP, Liautard J, et al. Lactulose-neomycin combination versus placebo in the treatment of acute hepatic encephalopathy. Results of a randomized controlled trial. *Gastroenterol Clin Biol* 1994;18:1063–8.
38. Lizardi-Cervera J, Almeda P, Guevara L, et al. Hepatic encephalopathy: a review. *Ann Hepatol* 2003;2(3):122–30.
39. Williams R, Bass N. Rifaximin, a nonabsorbed oral antibiotic, in the treatment of hepatic encephalopathy: antimicrobial activity, efficacy, safety. *Rev Gastroenterol Disord* 2005;5(Suppl 1):S10–8.
40. Jaing ZD, Ke S, Palazzini E, et al. In vitro activity and fecal concentration of rifaximin after oral administration. *Antimicrobial Agents Chemother* 2000;44(8):2205–6.
41. Pedretti G, Calzetti C, Missale G, et al. Rifaximin versus neomycin on hyperammonemia in chronic portal systemic encephalopathy of cirrhotics: a double-blind, randomized trial. *Ital J Gastroenterol* 1991;23:175–8.
42. Bucci L, Palmieri GC. Double blind, double dummy comparison between treatment with rifaximin and lactulose in patients with medium to severe degree hepatic encephalopathy. *Curr Med Res Opin* 1993;13:109–18.
43. Leevy C, Phillips J. Hospitalizations during the use of rifaximin versus lactulose for the treatment of hepatic encephalopathy. *Dig Dis Sci* 2007;52:737–41.
44. Neff G, Kemmer N, Zacharias V, et al. Analysis of hospitalizations comparing rifaximin versus lactulose in the management of hepatic encephalopathy. *Transplant Proc* 2006;38:3552–5.
45. Huang E, Esrailian E, Spiegel BMR. The cost effectiveness and budget impact of competing therapies in hepatic encephalopathy - a decision analysis. *Aliment Pharmacol Ther* 2007;26:1147–61.

46. Bass NM, Ahmed A, Johnson L, et al. Rifaximin treatment is beneficial for mild hepatic encephalopathy. *Hepatology* 2004;40(suppl 4):646A [abstract 1116].
47. Sushma S, Dasarathy S, Tandon RK, et al. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double blind randomized trial. *Hepatology* 1992;16:138–44.
48. Efrati C, Masini A, Merli M, et al. Effect of sodium benzoate on blood ammonia response to oral glutamine challenge in cirrhotic patients: a note of caution. *Am J Gastroenterol* 2004;95(12):3574–8.
49. Barbaro G, Di Lorenzo G, Soldini M, et al. Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicenter double-blind, placebo controlled, cross-over study. *Hepatology* 1998;28:374–8.
50. Als-Nielsen B, Kjaergard LL, Gluud C. Benzodiazepine receptor antagonists for acute and chronic hepatic encephalopathy. *Cochrane Database Syst Rev* 2001;(4). CD002798.
51. Goulenok C, Bernard B, Cadranet JF, et al. Flumezanil vs placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. *Aliment Pharmacol Ther* 2002;16:361–72.
52. Kircheis G, Wettstein M, Dahl S, et al. Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002;17:453–62.
53. Stauch S, Kircheis G, Adler G, et al. Oral L-ornithine-L-aspartate therapy of chronic hepatic encephalopathy: results of a placebo-controlled double-blind study. *J Hepatol* 1998;28:856–64.
54. Stange J, Mitzner SR, Klammt S, et al. Liver support by extracorporeal blood purification: a clinical observation. *Liver Transpl* 2000;6:603–13.
55. Heeman U, Treichel U, Looock J, et al. Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. *Hepatology* 2002;36:949–58.
56. Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of randomized study. *J Hepatol* 2004;41:38–43.
57. Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology* 2003;125:755–64.
58. Bernal W, Hall C, Karvellas CJ, et al. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology* 2007;46(6):1844–52.
59. Munoz SJ. Difficult management problems in fulminant hepatic failure. *Semin Liver Dis* 1993;13:395–413.
60. Clemmesen JO, Larsen FS, Kondrup J, et al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. *Hepatology* 1999;29:648–53.
61. Rolando N, Wade J, Davalos M, et al. The systemic inflammatory response syndrome in acute liver failure. *Hepatology* 2000;32:734–9.
62. Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. *Hepatology* 2005;41:422–33.
63. Blei AT, Olafsson S, Webster S, et al. Complications of intracranial pressure monitoring in fulminant hepatic failure. *Lancet* 1993;341:157–8.
64. Vaquero J, Fontana RJ, Larson AM, et al. Complications of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. *Liver Transpl* 2005;11:1581–9.
65. Alba L, Hay JE, Angulo P, et al. Lactulose therapy in acute liver failures. *J Hepatol* 2002;36:33A.
66. Hoofnagle JH, Carithers RL, Sapiro C, et al. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995;21:240–52.

67. Donovan JP, Shaw BW Jr, Langnas AN, et al. Brain water and acute liver failure: the emerging role of intracranial pressure monitoring. *Hepatology* 1992;16:267–8.
68. Nath F, Galbraith S. The effect of mannitol on cerebral white matter water content. *J Neurosurg* 1986;65:41–3.
69. Canalese J, Gimson AES, Davis C, et al. Controlled trial of dexamethasone and mannitol for the cerebral edema of fulminant hepatic failure. *Gut* 1982;23:625–9.
70. Simma B, Burger R, Falk M, et al. A prospective, randomized, and controlled study of fluid management in children with severe head injury: lactated Ringer's solution versus hypertonic saline. *Crit Care Med* 1998;26:1265–70.
71. Khanna S, Davis D, Peterson B, et al. Use of hypertonic saline in the treatment of severe refractory posttraumatic intracranial hypertension in pediatric patients. *Crit Care Med* 2000;28:1144–51.
72. Murphy N, Auzinger G, Bernel W, et al. The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure. *Hepatology* 2004;29(2):464–70.
73. Bernel W, Auzinger G, Sizer E, et al. Intensive care management of acute liver failure. *Semin Liver Dis* 2008;28:188–200.
74. Blei AT. Brain edema in acute liver failure. *Crit Care Clin* 2008;24:99–114.
75. Lee WM, Rossaro L, Fontana R, et al. Intravenous N-acetylcysteine improves spontaneous survival in early stage non-acetaminophen acute liver failure. *Hepatology* 2007;46:71A.
76. Polson J, Lee WM. AASLD position paper: the management of acute liver failure. *Hepatology* 2005;41(5):1179–97.
77. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: a single centre experience of 18 cases. *Gut* 1998;42:576–80.
78. Mas MR, Sinsek IC, Can C, et al. Fulminant hepatic failure as the initial presentation of primary hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 2000;12(5):575–8.
79. Kohrt HE, Ouyang DL, Keeffe EB. Antiviral prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Clin Liver Dis* 2007;11(4):965–91.
80. Wallace MJ, Madoff DC, Ahrar K, et al. Transjugular intrahepatic portosystemic shunts: experience in the oncology setting. *Cancer* 2004;101(2):337–45.
81. Chung WJ, Jang BK, Park KS, et al. Effect of transjugular portosystemic shunt for variceal bleeding in hepatocellular carcinoma patients with portal vein thrombosis. *Korean J Hepatol* 2005;11(2):157–63.
82. DeLeve LD. Cancer chemotherapy. In: Kaplowitz N, DeLeve LD, editors. *Drug-induced liver disease*. New York: Marcel Dekker; 2003. p. 593–632.
83. Chan JS, Harding CO, Blanke CD. Postchemotherapy hyperammonemic encephalopathy emulating ornithine transcarboxylase (OTC) deficiency. *Southampton Med J* 2008;101(5):543–5.