

Carol Rees Parrish, R.D., M.S., Series Editor

Hepatic Encephalopathy: Are NH₄ Levels and Protein Restriction Obsolete?



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Measurement of plasma ammonia and restriction of dietary protein were once standard practice in the management of hepatic encephalopathy. Recent evidence, however, suggests that ammonia levels have little value in the diagnosis of hepatic encephalopathy. Furthermore, protein restriction may have adverse consequences in cirrhotic patients prone to malnutrition. With a review of the current literature, the following article addresses these controversial issues and discusses current recommendations for the diagnosis and treatment of hepatic encephalopathy.

INTRODUCTION

Hepatic encephalopathy is a major complication of acute and chronic liver disease. This neuropsychiatric syndrome presents clinically with abnormalities in mental status and neuromotor function. Symptoms exist on a spectrum ranging from subtle deficits in attentiveness to severe confusion and even coma. The pathogenesis of this disease is not fully understood, but the accumulation of gut-derived neurotoxins in the setting of hepatic insufficiency remains

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central to current investigations. Over 5.5 million people in the United States have been diagnosed with cirrhosis.¹ Of this population, 30–45% of patients develop overt hepatic encephalopathy during the course of their disease.² This debilitating condition can negatively impact quality of life for patients and their families.¹ Furthermore, admissions for hepatic encephalopathy commonly result in prolonged hospital stays and a costly burden on our health care system.²

Hepatic encephalopathy is usually classified into three groups differentiated by the absence or presence of liver disease: encephalopathy due to acute liver failure (Type A), portosystemic shunting without associated liver disease (Type B), and cirrhosis with portal hypertension (Type C).³ Further subdivisions distin-

guish episodic and persistent hepatic encephalopathy from the clinical entity known as minimal hepatic encephalopathy.

A boom of research has recently occurred in the area of minimal hepatic encephalopathy. This condition is highly prevalent among patients with cirrhosis, affecting up to 80% of this population.⁴ Unlike overt hepatic encephalopathy, patients with minimal hepatic encephalopathy may lack obvious clinical symptoms. Often, the subtle symptoms of minimal hepatic encephalopathy can only be diagnosed through specialized neuropsychiatric testing.³ This condition is best described as a disorder of executive functioning. Patients have deficits in vigilance, response inhibition, working memory, and orientation.⁵ Minimal hepatic encephalopathy has been shown to decrease quality of life and interfere with daily functioning such as the ability to safely operate an automobile.⁴

PATHOPHYSIOLOGY

The specific mechanisms underlying the pathogenesis of hepatic encephalopathy are still under investigation. Episodes are usually precipitated by factors that increase inflammation or ammonia production.⁶ There is agreement that ammonia is a key toxin involved in the disease process. Current research is aimed at characterizing the effects of inflammation, oxidative stress and other factors working in synergy with ammonia to

produce astrocyte swelling as a common pathway towards cerebral dysfunction.⁷

There are many possible precipitants of hepatic encephalopathy including gastrointestinal bleeding, infection, and dehydration secondary to diuretic use, diarrhea, or vomiting. Other causes include hyponatremia, shunting procedures (transjugular intrahepatic portosystemic shunts—TIPS), constipation, etc. (see Table 1). Each of these precipitants has the potential to increase ammonia production/absorption, increase inflammation, or reduce cognitive reserve.⁶ Renal failure can also contribute to increased ammonia levels due to a relative decrease in renal excretion.⁵

The Role of Ammonia

In humans, the colon is a major site of ammonia production. Ammonia is a by-product of intestinal bacterial metabolism of protein and other nitrogenous compounds. Intestinal enterocytes also contribute to ammonia production through the utilization of glutamine.⁸ In healthy individuals, ammonia is converted to urea in the liver, which is then excreted by the kidneys. In patients with liver failure or portosystemic shunting, ammonia bypasses liver metabolism and accumulates in systemic circulation. This ammonia then undergoes metabolism at extrahepatic sites such as skeletal muscle and brain tissue. In the central nervous system, astrocytes are the glial cells that provide nutrients, maintain extracellular ion balance, and express the enzyme glutamine synthetase which converts ammonia to glutamine.⁷ Exposure of astrocytes to toxic levels of ammonia and subsequent accumulation of glutamine causes changes that may explain the neuronal dysfunction seen in hepatic encephalopathy.

Astrocytes exposed to ammonia for prolonged periods can undergo a morphologic change to Alzheimer's type 2 astrocytes characterized by large nuclei, prominent nucleoli, and marginated chromatin.⁵ Prolonged exposure to ammonia can also cause a shift in the balance of neurotransmission to result in overall inhibition of post-synaptic potentials. This neuroinhibitory state is characteristic of the hepatic encephalopathy seen in patients with chronic liver disease. Accumulated glutamine acts as an osmolyte within astrocytes, causing cellular swelling

Table 1.
Precipitants of Hepatic Encephalopathy

- Gastrointestinal bleeding
- Infection
- Dehydration secondary to diuretic use
- Diarrhea
- Vomiting
- Hyponatremia
- Shunting procedures (transjugular intrahepatic portosystemic shunts—TIPS)
- Constipation
- Benzodiazepine use
- Narcotic use
- Noncompliance with lactulose therapy

Table 2.
Symptoms Associated with Hepatic Encephalopathy

Cognitive findings include:

- Altered consciousness
- Shortened attention span
- Disorientation
- Memory impairment
- Affective/emotional disturbances

Motor findings can include:

- Asterixis
- Hyperreflexia
- Rigidity

and low-grade cerebral edema disturbing the cerebral oscillatory networks.⁷ Glutamine also increases the oxidative stress within astrocytes causing protein and RNA modifications which impact synaptic plasticity and glioneuronal communication.⁹ Studies suggest the combined effects of astrocyte swelling and oxidative stress cause the decline in brain function seen in hepatic encephalopathy. Researchers are currently trying to define how other factors such as inflammation, infection, hyponatremia, and sedative/narcotic use may work synergistically with ammonia to promote astrocyte changes and symptom progression.

DIAGNOSIS

Overt hepatic encephalopathy is a clinical diagnosis based on the presence of impaired mental status and neuromotor functioning. The West Haven Criteria is a clinical scale used to assess patients' cognitive, behavioral, and motor function. Patients are assigned a grade based on the presence of specific symptoms and their severity (see Table 2).^{9,10} The constellation of symptoms seen in hepatic encephalopathy is not specific to this disease; therefore, the diagnosis is usually established on the basis of exclusion. Laboratory and imaging studies can be helpful in ruling out alternative diagnoses and identifying precipitating causes.³ The diagnosis and grading of hepatic encephalopathy is challenging given the fluctuant course of symptoms, lack of objective clinical markers, and subjective assessment by physicians. Currently, researchers are

investigating the speed of involuntary eye movements (saccadic eye movements) as an objective marker for hepatic encephalopathy.¹¹

Utility of Ammonia Levels

The determination of plasma ammonia (NH_4) levels is often performed in the clinical setting to support the diagnosis of hepatic encephalopathy. However, this practice has been scrutinized over the past decade with poor correlation between NH_4 levels and hepatic encephalopathy.¹² Many conditions unrelated to liver disease can result in elevated NH_4 levels. Compared to controls, plasma NH_4 levels are generally higher in patients with liver disease; however, the use of plasma NH_4 levels as a diagnostic marker for hepatic encephalopathy presents many challenges. Poor phlebotomy technique can artificially elevate NH_4 measurements.¹³ It is also unclear if NH_4 measurements from peripheral circulation truly reflect NH_4 concentrations at the blood-brain barrier.¹⁴ Most convincing are the recent studies that have shown little or no correlation between NH_4 concentration and severity of hepatic encephalopathy.

Ong et al. compared four different measurements of NH_4 concentration (arterial and venous total, arterial and venous partial pressure) in 121 patients with cirrhosis and grade 0–4 hepatic encephalopathy.¹⁴ Even though this study showed a moderate correlation between all four measurements and grade of hepatic encephalopathy, there was significant overlap in NH_4 levels between patients with and without hepatic encephalopathy. The researchers concluded that single NH_4 levels have little clinical utility in the diagnosis of hepatic encephalopathy.

In a smaller study of 20 patients with chronic liver failure, Kundra et al. found no statistically significant correlation in the patients with elevated NH_4 levels and the presence of hepatic encephalopathy.¹⁵ Researchers concluded that NH_4 levels were not useful in making the diagnosis of hepatic encephalopathy.

In another study, Nicalao et al. measured NH_4 levels in 27 cirrhotics recovering from hepatic encephalopathy.¹² Ammonia levels were either unchanged or increased in 17 patients after complete clinical resolution

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of their hepatic encephalopathy episode. This study highlighted the minimal utility of sequential NH_4 levels in the management of hepatic encephalopathy.

Plasma NH_4 levels are neither required to make the diagnosis of hepatic encephalopathy, nor helpful in monitoring the effectiveness of NH_4 -lowering therapies. Therefore, the routine determination of NH_4 levels in patients with suspected encephalopathy is not indicated. Current standard of care dictates that patients diagnosed with hepatic encephalopathy are treated with ammonia-lowering therapies regardless of plasma NH_4 levels and monitored clinically for improvement in mental function.

TREATMENT

The approach to patients with suspected hepatic encephalopathy involves identifying and treating precipitating causes, ruling out alternative diagnoses, and initiating ammonia-lowering therapy. The two major therapies used to reduce circulating NH_4 are non-absorbable disaccharides and oral antibiotics. Both therapies are directed at the gut, and reduce intestinal production and absorption of NH_4 .⁴ Lactulose, the primary non-absorbable disaccharide used in the United States, is fermented by colonic bacteria, resulting in the production of organic acids. These organic acids lower colonic pH, favoring the survival of acid resistant, non-urease producing bacteria. Therefore, urea, NH_3 , is converted to ammonium, NH_4 , (the less absorbable form) and trapped in the colon preventing absorption and systemic effects. Lactulose also has a laxative effect, further promoting the elimination of urea through the evacuation of colonic contents.¹⁶

Lactulose possesses a large side effect profile, which presents many challenges to its success in these patients. Many patients find its taste unpalatable, and significant gastrointestinal symptoms are common. Nausea, vomiting, and severe diarrhea are common side effects and can lead to dehydration and noncompliance.⁴ In 2004, a systematic review of randomized trials found insufficient evidence to support or refute the use of non-absorbable disaccharides for the treatment of hepatic encephalopathy.¹⁷ However, a study published in 2009 by Sharma et al. found lactulose to be superior to placebo in the secondary prophylaxis of

hepatic encephalopathy in the outpatient setting. Most clinicians still consider lactulose as their primary agent to prevent hepatic encephalopathy.¹⁶ During periods of severely altered consciousness which prohibits oral intake, lactulose enemas can be used to treat encephalopathy. Often, enema administration is difficult and can be associated with decreased efficacy from oral administration due to large variation in dwell times and medication exposure. Nutrition editors note: given the level of malnutrition often seen in these patients, placing a nasogastric feeding tube (orogastric if mechanically ventilated) would allow both feeding and more efficacious delivery of lactulose until mental status clears or patient able to eat adequately. Further, enemas should also be considered a viable option if patients do not have bowel movements and begin to experience severe bloating and distention. As we improve our understanding of hepatic encephalopathy, the development of other agents with fewer side effects may change our current algorithm for treatment and prevention in the future.

Other agents for the treatment of hepatic encephalopathy include several oral antibiotics. These medications work by reducing the number of ammonia-producing bacteria present in the gut. Neomycin and metronidazole have been used successfully for this purpose. However, the concerns of nephrotoxicity and ototoxicity with neomycin and peripheral neuropathy with metronidazole have justifiably limited the use of these agents.⁵ Rifaximin, a gut-selective antibiotic with low systemic bioavailability, was recently approved for use in chronic hepatic encephalopathy. A study published by Bass et al. in 2010 showed that rifaximin plus lactulose is more effective than lactulose alone in the secondary prophylaxis of hepatic encephalopathy.¹ Recent studies have examined the role of rifaximin in the treatment of minimal hepatic encephalopathy.^{18,19} Sidhu et al. evaluated the efficacy of rifaximin in improving neuropsychometric test (NP) performance and health-related quality of life (HRQOL) in patients with minimal hepatic encephalopathy.¹⁹ This trial demonstrated that rifaximin significantly improved NP performance and HRQOL after 8 weeks compared to placebo. Researchers concluded that rifaximin is a safe and effective treatment for minimal hepatic encephalopathy (MHE), and suggested that all patients

Table 3.
Factors Associated with Malnutrition in Cirrhotic Patients

Decreased Intake

- Anorexia
- Early satiety
- Ascites
- Altered mental status/encephalopathy
- Frequent hospitalizations

Decreased Absorption

- Inadequate bile flow
- Bacterial overgrowth
- Pancreatic insufficiency

Metabolic alterations

- Increased or decreased metabolic rate
- Increased protein requirements
- Glucose intolerance/insulin resistance
- Rapid postprandial gluconeogenesis
- Reduced glycogen stores
- Elevated leptin
- Elevated TNF- α
- Decreased insulin-like growth factor-1

Iatrogenic Factors

- Excessive dietary restrictions
- Intolerance of hospital food
- Frequent Paracentesis
- Diuresis (micronutrient losses)
- Lactulose therapy

with cirrhosis be screened for minimal hepatic encephalopathy. In a related study, Bajaj et al. assessed the efficacy of rifaximin in improving driving simulator performance in patients with MHE.¹⁸ The researchers found that patients receiving rifaximin group showed significant improvement in total driving errors after 8 weeks compared to placebo.

Rifaximin lacks the side effect profile of neomycin and metronidazole and is well tolerated. Insurance coverage and cost have been limiting factors in its use, but with its recent FDA approval this may mitigate those issues for patients and increase its accessibility. With any long-term antibiotic therapy there is always a potential for developing drug resistance or *Clostridium difficile* infection. If more patients are

placed on antibiotics for hepatic encephalopathy in the coming years, these adverse events may become more apparent.

Utility of Protein Restriction

Malnutrition is well documented in cirrhotic patients, with higher rates found in patients with liver disease secondary to excessive alcohol consumption.²⁰ The need for increased caloric needs is often evident and widely agreed upon. However, proper levels of protein replacement in cirrhotic patients is controversial. Dietary protein restriction has been suggested in the treatment of hepatic encephalopathy as a means to reduce the nitrogenous load entering the gut, thereby reducing NH₄ production and absorption. Conversely, accelerated protein catabolism in liver disease patients may require higher levels of protein loads for maintenance.¹⁰ Cirrhotic patients require on average 0.8–1.3 g protein/kg/day to maintain their nitrogen balance as compared to 0.6 g protein/kg/day in healthy patients.²¹

Cordoba et al. performed a randomized controlled trial in 20 cirrhotic patients with hepatic encephalopathy comparing protein-restricted diets to normal protein diets.²² There was no difference in the course of the disease between the two groups; however, higher protein breakdown was documented in the protein-restricted group. Researchers concluded that there are no benefits to restricting protein intake. Rather, significant adverse nutritional consequences may result when protein is limited. In cirrhotic patients, poor nutritional status is a major risk factor for mortality.⁶ Malnutrition in these patients is multifactorial (see Table 3). When protein requirements are not achieved due to limitations with restricted diets, increased skeletal muscle breakdown releases nitrogen-containing amino acids that contribute to NH₄ production, prolonging the course of encephalopathy. For these reasons, protein restriction is no longer recommended for the treatment of hepatic encephalopathy and possibly could be harmful. Patients should be started on a normal protein diet and treated with the proper medical therapies for encephalopathy episodes.

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Table 4.
Comparison of Standard Enteral Products with Hepatic Formulas

<i>Product</i>	<i>Calories/mL</i>	<i>Protein g/1000 Kcal</i>	<i>% Fat (%MCT)</i>	<i>% Fat 1000 Kcal*</i>
Hepatic Formulas				
Hepatic-Aid II (Hormel Healthlabs)	1.17	35	28 (0)	\$51.98
NutriHep (Nestle)	1.5	40 g (26 BCAA)	12 (70)	\$44.50
Standard Formulas				
Isosource 1.5 (Nestle)	1.5	45	38 (30)	\$6.78
Jevity 1.5 (Ross)	1.5	43	29 (19)	\$4.40
Osmolite 1.5 (Ross)	1.5	42	29 (20)	\$4.47
Nutren 1.5 (Nestle)	1.5	40	40 (50)	\$6.00

*Cost information obtained from company toll-free # (March 2011); does not include tax and shipping.

- Nestle Nutrition: (888) 240-2713; www.nestlenutritionstore.com
- Abbott Nutrition: (800) 258-7677; www.abbottnutrition.com
- www.4webmed.com: (877) 493-2633

*Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus²³

Branched Chain Amino Acids (BCAA)

The possibility of dietary modifications with branched chain amino acids (BCAA) to avoid complications of encephalopathy are often considered. However, trials of specialized BCAA formulas are limited by the small number of patients enrolled, the lack of adequate feeding in the “control” group, or the failure to provide standard “anti-encephalopathic” agents (such as lactulose) during the study. Branched chain amino acid formulas should be rarely used due to their expense and questionable efficacy, and reserved only for those patients who appear intolerant of adequate protein from standard formulas and after all other efforts have failed. See Table 4 for a comparison of hepatic and standard formulas available.

CONCLUSION

Hepatic encephalopathy often affects end stage liver disease patients. As minimal hepatic encephalopathy is more widely recognized, its treatment may drastically improve the quality of life for many cirrhotic patients. Episodes may be precipitated by GI bleeding, infection, non-compliance with medications, or even dehydration. Ammonia has a central role in the pathophysiology of hepatic encephalopathy as it affects cerebral edema and neurotransmitter function. However, we are recognizing that NH₄ levels do not accurately reflect patients’ clinical status and protein restriction may have potentially harmful effects. Proper nourishment with an adequate diet and treatment with agents such as lactulose, and recently

Table 5.
Summary Points

- Do not use serial NH₄ levels to assess patients for hepatic encephalopathy
- Do not restrict protein in diet
- Minimal hepatic encephalopathy can affect patient's quality of life and is often under-recognized
- Diagnosing precipitating factors should be a focus during episodes of encephalopathy
- Use primary agents, lactulose and rifaximin are essential to treat encephalopathy
- Ensure patient compliance with medication
- Avoid constipation

approved Rifaximin, may help us control further exacerbations and nutritional demise of our patients in the future. See Table 5 for a summary of suggested interventions. ■

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As of April 28, 2010, all pancreatic enzymes on the market were required to obtain FDA approval or be removed from the market. Table 1 provides those pancreatic enzymes that obtained, or have pending FDA approval as of April 21, 2011.

Notes:

- All are oral, delayed release capsules.
- Capsules cannot be chewed or crushed. Capsules can be opened and contents sprinkled. (www.epocrates.com) (www.rx-list.com)
- Resource: www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204745.htm

<i>Name</i>	<i>Amylase Units</i>	<i>Lipase Units</i>	<i>Protease Units</i>	<i>Contact</i>
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Creon 12,000	60,000	12,000	38,000	Abbott (Solvay); (800) 241-1643 www.abbottgrowth-us.com
Creon 24, 000	120,000	24,000	76,000	Abbott (Solvay); (800) 241-1643 www.abbottgrowth-us.com
Pancreaze	n/a	1000	n/a	Ortho-McNeil; (800) 526-7736 www.mcneilpediatrics.net
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