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REVIEW

Management of Hepatic Encephalopathy in the Hospital

Michael D. Leise, MD; John J. Poterucha, MD; Patrick S. Kamath, MD; and W. Ray Kim, MD

Abstract

Hepatic encephalopathy (HE) develops in up to 50% of patients with cirrhosis and is a feature of decompensated cirrhosis. With the goal of reviewing the evidence for treatment and prevention of overt hepatic encephalopathy, pubmed was searched using search terms *hepatic encephalopathy* AND *treatment*, limited to human studies from January 1, 2003, through December 1, 2013, and supplemented by key references. The inpatient incidence of HE is approximately 23,000 annually, and management of these patients is common for internists and subspecialists. Treatment of the hospitalized patient with HE has changed in recent years. Treatment entails 2 phases: induction and maintenance of remission. Most cases of significant HE are precipitated by infection, gastrointestinal bleeding, medications, or other culprits. All patients should be evaluated for secondary triggers of HE, and treatment should be initiated with a nonabsorbable disaccharide (ie, lactulose) in most patients. Rifaximin (off label) can be added in patients not responding to lactulose. Neomycin is a less preferred alternative to rifaximin owing to its adverse effect profile. Other therapies, including zinc, L-ornithine–L-aspartate, and branched-chain amino acids, can be considered for patients not responding to disaccharides and nonabsorbable antibiotics. Large portosystemic shunts may be embolized in patients with medically refractory recurrent or severe HE with otherwise well-compensated cirrhosis. Molecular Adsorbent Recirculating System is now available for patients with severe HE who do not respond to medical therapy. It is critically important that patients hospitalized with significant HE continue maintenance therapy at the time of dismissal to prevent further episodes. Patients with a first-time episode of HE can be administered lactulose, and careful instructions should be provided to patients and caregivers about dose titration to achieve 3 bowel movements daily. Patients with recurrent HE episodes despite lactulose use benefit from the addition of rifaximin, which decreases the frequency of recurrent HE episodes and related hospitalizations. Last, patients and their families should be counseled about the risk of motor vehicle accidents, which require mandatory reporting to the Department of Motor Vehicles in some states.

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Hepatic encephalopathy (HE) is a significant neuropsychiatric syndrome that most commonly occurs in decompensated cirrhosis. Clinical features range from clinically imperceptible symptoms in minimal HE (MHE), which require neuropsychometric testing to identify, to a comatose state in the worst cases.[1] The Working Party for Hepatic Encephalopathy established nomenclature for HE in 1998.[2] Type A HE refers to HE secondary to acute liver failure, type B refers to enteric hyperammonemia (without liver disease), and type C is associated with chronic liver disease. The severity of HE is graded using the WestHaven criteria (grades 1-4), but alternative terminology has been suggested and has gained some traction. In the new lexicon, called SONIC (spectrum of neurocognitive impairment in cirrhosis), covert HE (CHE) includes MHE and grade 1 HE and overt HE (OHE) encompasses grades 2 to 4 HE (Table 1). Episodic HE develops over a short time frame and can fluctuate, whereas persistent HE impairs day-to-day executive function. Most patients with episodic OHE (grade 2 or higher) will require management in the hospital, which is the focus of this review.

Hepatic encephalopathy eventually occurs in up to 50% of patients with cirrhosis.[3,4] Hepatic encephalopathy portends a worse survival for patients compared with similar patients without HE, even after accounting for the Model for End-Stage Liver Disease (MELD) score.[5] The development of HE merits consideration of liver transplantation. Whether treatment of HE alters survival is unknown. Treatment of HE continues to be a significant area of investigation. Currently,

From the Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN.

ARTICLE HIGHLIGHTS

- Episodic overt hepatic encephalopathy (OHE) is responsible for an increasing number of hospital admissions and readmissions.
- New terminology has been suggested and is gaining traction in which West Haven grades 0 and 1 are covert HE and grades 2 to 4 are OHE.
- Most patients with OHE require hospital-based care during the induction treatment phase, followed by a maintenance treatment strategy in the outpatient setting.
- Lactulose is the mainstay of induction and maintenance treatment.
- Rifaximin, when added to lactulose, has been found to prevent episodes of OHE and hospitalization compared with lactulose alone.
- Rifaximin and neomycin are acceptable adjunctive therapies for patients with OHE who are not responsive to lactulose or who have severe OHE, although rifaximin may be preferable owing to a better adverse effect profile.
- Evidence for the use of zinc, L-ornithine–L-aspartate, and branched-chain amino acids is less compelling, whereas there is increasing data to suggest a benefit of portosystemic shunt embolization in carefully selected patients.

nonabsorbed disaccharides (eg, lactulose and lactitol) and nonabsorbable antibiotics (eg, neomycin and rifaximin) represent the mainstay of treatment (Table 2).

Hospitalization for episodic OHE, or the development of OHE during hospitalization, is common. In the US Nationwide Inpatient Sample, the inpatient incidence of HE ranged from 20,918 (in 2005) to 22,931 (in 2009).[6] Up to 80% of OHE episodes are precipitated by an event such as infection or gastrointestinal bleeding. Management of the hospitalized patient with episodic OHE, common for internists and subspecialists, is directed at correcting the underlying precipitant and providing pharmacologic treatment that reduces ammoniagenesis.

Most patients require maintenance medications at the time of hospital dismissal as secondary prophylaxis for episodic OHE. Data suggest that many patients do not receive maintenance medication at or after dismissal. An abstract presented at the American Association of the Study for Liver Disease annual meeting in 2012 characterized a subset of insurance claims for patients by *International Classification of Diseases, Ninth Revision* code for HE (code 572.2) and compared this to prescriptions filled between January 1, 2009, and December 31, 2011. For 2009 (n=13,623), 2010 (n=15,529), and 2011 (n=16,328), 89.2%, 87.8%, and 86.4% of patients with HE had inpatient claims for HE, respectively, and 60.3%, 62.3%, and 63.9% did not receive ongoing treatment.[7,8] Volk et al[9] also described a high readmission rate (69%) in a cohort of patients with decompensated cirrhosis (n=402) where one of the most common reasons for preventable readmission was recurrent HE due to lack of education on or inappropriate use of lactulose. Thus, more attention should be focused on ensuring that patients are prescribed and educated about maintenance medication therapy for secondary prevention of OHE at the time of hospital dismissal.[10] In this review, we summarize the evidence on the optimal medical treatments for patients who have been hospitalized for episodic OHE and suggest treatment algorithms

TABLE 1. Hepatic Encephalopathy Grades

Grade	Impairment		SONIC criteria
	Intellectual	Neuromuscular	
0	Normal	Normal	Normal
MHE	Normal examination findings; subtle changes in work or driving	Minor abnormalities of visual perception or on psychometric or number tests	Covert
1	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination	Covert
2	Changes in sleep-wake cycle, lethargy, mood and behavioral changes, cognitive dysfunction	Asterixis, ataxic gait, speech abnormalities (slow and slurred)	Overt
3	Altered level of consciousness (somnolence), confusion, disorientation, amnesia	Muscular rigidity, nystagmus, clonus, Babinski sign, hyporeflexia	Overt
4	Stupor and coma	Oculocephalic reflex, unresponsiveness to noxious stimuli	Overt

MHE = minimal hepatic encephalopathy; SONIC = spectrum of neurocognitive impairment in cirrhosis.

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