

REVIEWS

Hepatic Encephalopathy for the Hospitalist

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The care of patients with advanced liver disease is often complicated by episodes of acute decline in alertness and cognition, termed hepatic encephalopathy (HE). Hospitalists must be familiar with HE, as it is a common reason for hospitalization in this population and is associated with significantly increased mortality. This narrative review addresses common issues related to diagnosis and classification, precipitants, inpatient management, and transitions of care for patients with HE. The initial presentation can be variable, and HE remains a clinical diagnosis. The spectrum of HE manifestations spans from mild, subclinical cognitive deficits to overt coma. The West Haven scoring system is the most widely used classification system for HE. Various metabolic insults may precipitate HE, and providers must specifically seek to rule out infection and bleeding in cirrhotic patients presenting with altered cognition. This is consistent

with the 4-pronged approach of the American Association for the Study of Liver Disease practice guidelines. Patients with HE are typically treated primarily with nonabsorbable disaccharide laxatives, often with adjunctive rifaximin. The evidence for these agents is discussed, and available support for other treatment options is presented. Management issues relevant to general hospitalists include those related to acute pain management, decisional capacity, and HE following transjugular intrahepatic portosystemic shunt placement. These issues are examined individually. Successfully transitioning patients recovering from HE to outpatient care requires open communication with multiple role players including patients, caregivers, and outpatient providers. *Journal of Hospital Medicine* 2016;11:591–594. © 2016 Society of Hospital Medicine

Reversible impairment of brain function in the setting of cirrhosis defines hepatic encephalopathy (HE). HE is associated with significantly decreased survival,¹ and patients with HE have poor outcomes whether HE occurs in isolation or in conjunction with acute-on-chronic liver failure.² A large multicenter study comparing cirrhotics with and without HE also found that those with a history of HE were hospitalized more frequently.²

The presentation of HE is variable, and diagnosis remains clinical. Subtle manifestations of HE persist between episodes, even if gross cognitive function normalizes.³ Retrospective data suggest the effects of serial bouts of HE may be cumulative, because even with appropriate treatment, the severity of impairment correlates with the number of prior episodes.³ Even minimal manifestations of hepatic encephalopathy correlate with reduced quality of life.⁴

The West Haven score is the most validated scoring system.⁵ Higher grades of HE correlate with significantly increased mortality,² but due to difficulties differentiating stages 0 and 1, these criteria remain somewhat controversial. The Spectrum of Neurocog-

nitve Impairment in Cirrhosis (SONIC) has been proposed as an alternate conceptualization of HE as a continuous spectrum rather than discrete stages.⁶ Table 1 shows findings associated with various West Haven and SONIC stages. Both systems include covert and overt encephalopathy. Covert correlates with West Haven grades 0 to 1, and consists mainly of subtle findings that require specialized psychometric testing to detect. The SONIC system terms demonstrable but subclinical manifestations “minimal HE.”⁶ Overt HE includes West Haven grades 2 through 4, and refers to objective findings that can be reliably detected on clinical evaluation.⁷ Whereas specific numeric scores are used largely for research purposes, classifying HE as covert or overt is clinically useful.

Although blood ammonia levels correlate well across populations, they are not diagnostically useful for individuals, because considerable overlap exists between patients with no HE and those with severe encephalopathy.⁸ Ammonia levels also do not predict HE development.⁹ Brain imaging is of limited utility, but may be prudent with abrupt decompensation, focal neurologic findings, or poor response to therapy.¹⁰ A recent single-center review of head computed tomography in cirrhotic patients presenting with altered level of consciousness found a low incidence of intracranial hemorrhage (ICH).¹¹ The number needed to scan was 293 patients to detect a single ICH. Only 1 patient out of 316 had ICH when fever, trauma, and focal neurological findings were excluded. The presence of acute ICH was not associated with platelet count, coagulopathy, creatinine, or Model for End-Stage Liver Disease score.

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TABLE 1. Clinical Findings Associated With West Haven Stages of Hepatic Encephalopathy

West Haven Grade	SONIC Classification	Neurologic Changes	Asterixis
0	Normal	None	None
	Minimal HE	Requires specialized psychometric testing	
1	Overt	Decreased attention span, hypersomnia/insomnia	Detectable
2		Lethargy, disorientation	Obvious
3		Semistupor or stupor	None
4		Coma	None

NOTE: Modified from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines by Vilstrup et al.⁷ Abbreviations: HE, hepatic encephalopathy; SONIC, Spectrum of Neurocognitive Impairment in Cirrhosis.

PRECIPITANTS

Initial evaluation of patients with suspected HE must confirm the presence of HE and identify potentially reversible precipitants. Infection, bleeding, and metabolic derangements (including renal injury, hypovolemia, and hyponatremia) are common precipitants.¹² Searching for precipitants is heavily stressed in the 4-pronged approach recommended by the American Association for the Study of Liver Disease,⁷ as summarized in Table 2. Common precipitants are grouped into “episodic” and “recurrent” causes. Episodic causes are those that represent discrete insults with specific, short-term treatments. Recurrent causes are those that are likely to require active management over time. These distinctions may help inform different approaches for initial or recurrent episodes of HE; in practice, much overlap exists.

Diuretic use has been clearly correlated with incidence of HE.² Although diuretic usage may be an indicator of more advanced liver disease, their use can also contribute to HE via increased risk of hypovolemia and dysnatremia.² Accordingly, caution is necessary when using diuretics to manage patients with HE and refractory ascites. These findings have led some to suggest serial paracentesis may be preferable to diuretics in this population.²

MANAGEMENT

The mainstay of HE treatment is administration of the nonabsorbable disaccharide lactulose. Lactulose is part of nearly all regimens because it is effective, easily titrated, and inexpensive.¹³ It is efficacious orally or as an enema.¹⁴ Lactulose increases both cognitive function and quality of life,¹⁵ and is effective for prophylaxis and treatment of all stages of HE.^{16,17}

Rifaximin is often used as an adjunct to lactulose, particularly in cases of recurrent HE. Small trials have associated rifaximin with increased quality of life¹⁸ and cognitive function.¹⁹ The largest randomized trial of rifaximin was a double-blind, placebo-controlled trial in patients with multiple episodes of overt HE

during the prior 6 months.²⁰ Lactulose was used concomitantly in approximately 91% of patients. At the end of the 6-month study, rifaximin was associated with a 58% relative risk reduction in overt HE recurrence and roughly 50% reduction in HE-related hospitalization. The numbers needed to treat were 4 patients to prevent 1 overt HE episode and 9 to prevent 1 HE-related hospitalization.²⁰

A meta-analysis of 264 patients included in published, high-quality trials found rifaximin monotherapy to be similar to nonabsorbable disaccharides in both efficacy and incidence of diarrhea, but with significantly less abdominal pain.²¹ This analysis was limited by significant heterogeneity among trials. A larger, more recent systematic review and meta-analysis of 19 studies (both published and unpublished) found rifaximin to be effective for treatment, secondary prophylaxis, and possibly decreased mortality.²² Of note, this meta-analysis included placebo studies as well as studies using varying doses of lactulose or other antibiotics as controls. Despite this variability, the authors concluded that the control used in the individual trials did not significantly affect the aggregate results.²² In the largest individual study to show a mortality benefit, improvement seemed to be driven by decreased rates of sepsis when rifaximin was used as an adjunct to lactulose.²³ Cost is a barrier to use, as rifaximin has not proven to be cost-effective as monotherapy instead of lactulose.²⁴ Many insurers will facilitate adjunctive rifaximin with prior authorization, and the manufacturer offers assistance programs.²⁵

Other adjuncts, including laxatives,²⁶ antibiotics,¹² branched-chain amino acids,²⁷ and acarbose²⁸ have far less evidentiary support and require further study prior to incorporation into clinical practice.²⁶ A recent study showed polyethylene glycol to perform similar to lactulose, but the studied volume of 4 L daily may make routine use impractical.²⁹ Dietary protein restriction has been shown in a prospective

TABLE 2. The 4-Pronged Approach to Management of Overt Hepatic Encephalopathy, With Inclusion of Common Identified Precipitants Listed From Most Common to Least Common

1. Initiate care for cirrhotic patients with altered consciousness	
2. Seek and treat alternative causes of altered mental status if present	
3. Identify and treat precipitating factors:	
Episodic	Recurrent
Infection	Electrolyte derangement
Gastrointestinal bleeding	Infection
Hypovolemia	Constipation
Electrolyte derangement	Hypovolemia
Constipation	Gastrointestinal bleeding
4. Commence empiric HE treatment	

NOTE: Modified from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines by Vilstrup et al.⁷ Abbreviations: HE, hepatic encephalopathy.

randomized controlled trial to accelerate body muscle breakdown without affecting HE,³⁰ so is best avoided.

ISSUES PERTINENT TO HOSPITAL MANAGEMENT

Concurrent HE frequently complicates inpatient management of acute pain. Acetaminophen below 3 g daily for short-term use is safe,³¹ but may be insufficient. Non-steroidal anti-inflammatory agents are best avoided given risks for renal dysfunction and bleeding.³² Although a direct connection between opiate use and HE remains unproven, these agents are problematic because they can cause both sedation and constipation. Nonetheless, they are often needed for pain control. Oxycodone has a more desirable side effect profile than other narcotics. We often prescribe doses every 6 hours initially to account for decreased hepatic metabolism. Morphine has active metabolites that can accumulate in cirrhotics, so morphine use is best avoided.³² Fluctuations in cognition may help distinguish narcosis from HE; specifically, narcosis causes chronic somnolence worst shortly after an opiate dose, whereas HE causes alterations in sleep-wake cycles including insomnia.³² Frequent adjustment of opiate dose and frequency may be required to balance analgesia with unwanted sedation and constipation.

Decisional capacity frequently complicates care of patients with cirrhosis. Patients may decline therapy because of dissatisfaction with bowel frequency, but such lapses in adherence likely contribute to HE recurrence. Patients with overt HE are often incapable of making decisions based on informed consent. If such patients have inadequate social support to ensure medical attention if symptoms progress, then mandatory treatment is reasonable. This may include involuntary administration of medications via rectal or nasogastric tube. Once cognition improves enough that he or she can reliably articulate risks, benefits, and alternatives of declining therapy, then it is reasonable to allow them to do. Subspecialty consultation with psychiatry or ethics may be useful in such situations.

For cirrhotics admitted for management of nonhepatic issues (particularly operations or invasive procedures), vigilance is needed to monitor for HE during hospitalization. Patients with HE have increased risk of falls and impaired driving, which may lead to admission onto surgical services.⁴ Changes in diet, medications, bowel function, and environment may all contribute to encephalopathy. HE occurring during admission for other diagnoses still requires prompt titration of lactulose. Routine inquiry about bowel function and sleep quality are likely to help identify trouble early.

Placement of transvenous intrahepatic portosystemic shunt (TIPS) increases the risk for HE via introduction of neurotoxins directly into the systemic circulation. These patients can typically be treated medically,³³

TABLE 3. Example of a Lactulose Titration Plan

Your dose of lactulose is 30 mL (1 tbsp) 3 times daily with meals.
 If you have fewer than 3 BMs in any day, take an additional dose of lactulose at bedtime.
 If you begin to experience difficulty sleeping at night, excessive drowsiness during the day, or confusion, take 2 doses of lactulose with each meal to ensure 3 or more BMs daily.
 If you have more than 4 BMs in any 24 hour period and are not having any of the symptoms mentioned above, skip a single dose of lactulose then resume your usual schedule.

NOTE: Abbreviations: BMs, bowel movements.

but are likely to require increased lactulose dosage. TIPS revision may be necessary for patients with treatment-refractory HE, but retrospective evidence suggests this is rarely necessary.³³ In that study, only a single patient out of 81 with post-TIPS HE required TIPS closure.

Under the *International Classification of Disease, 10th Revision*, a diagnosis of HE is often most consistent with “metabolic encephalopathy” (G93.41).³⁴ It may also be coded as “chronic hepatic failure without coma” (K7210) or “chronic hepatic failure with coma” (K7211).³⁵ Whenever possible, specifying the underlying liver disease (eg, hepatitis C virus, alcohol) is preferable.

TRANSITIONING TO OUTPATIENT CARE

HE patients are usually ready for community living once their cognition has improved enough to reliably take medications. Key aspects of HE management need to be communicated clearly to patients and caregivers. Barriers to optimal outpatient care mostly relate to lactulose adherence. Stressing the direct correlation between insufficient bowel movements and HE progression may enhance adherence. All patients need a lactulose titration plan including when doses can be skipped and when additional doses are needed. Even minimal symptoms of HE need to be addressed,³⁶ and specific vigilance for alterations in sleep-wake cycles needs to be adopted. Table 3 is an example of a lactulose titration plan that can be used at discharge. These plans should be included in discharge documents and within communication to outpatient healthcare providers. Close follow-up with a hepatology specialist is ideal to ensure appropriate lactulose use, answer questions that arise upon return home, and address other concerns related to cirrhosis.

Although specific interventions to decrease readmission have not been studied in this population, best practices from other populations (such as medication self-management, follow-up plans, and red flags to be on watch for³⁷) likely apply. Defining optimal strategies to decrease readmission is an opportunity for hospitalists to contribute to standardization of care for these patients.

CONCLUSIONS

HE is a common but very treatable complication of cirrhosis. Various metabolic insults may precipitate HE, and hospitalists should seek to reverse contributing factors whenever possible. Lactulose titrated to ensure adequate bowel output is the cornerstone of both therapy and prevention for HE. Adjunctive use of rifaximin improves many outcomes. Patient education about manifestations of HE and medication titration is crucial to achieving smooth transition to the outpatient setting.

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References

- Bustamante J, Rimola A, Ventura PJ, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol*. 1999;30(5):890–895.
- 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):275–281.
- Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology*. 2010;138(7):2332–2340.
- Agrawal S, Umapathy S, Dhiman RK. Minimal hepatic encephalopathy impairs quality of life. *J Clin Exp Hepatol*. 2015;5(suppl 1):S4–S48.
- Blei AT1, Córdoba J; Practice Parameters Committee of the American College of Gastroenterology. Hepatic encephalopathy. *Am J Gastroenterol*. 2001;96(7):1968–1976.
- Bajaj JS, Wade JB, Sanyal AJ. Spectrum of neurocognitive impairment in cirrhosis: Implications for the assessment of hepatic encephalopathy. *Hepatology*. 2009;50(6):2014–2021.
- Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715–735.
- Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. *Am J Med*. 2003;114(3):188–193.
- Ge PS, Runyon BA. Serum ammonia level for the evaluation of hepatic encephalopathy. *JAMA*. 2014;312(6):643–644.
- 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):437–447.
- Donovan LM, Kress WL, Strnad LC, et al. Low Likelihood of intracranial hemorrhage in patients with cirrhosis and altered mental status. *Clin Gastroenterol Hepatol*. 2015;13(1):165–169.
- Perumalswami PV, Schiano TD. The management of hospitalized patients with cirrhosis: the Mount Sinai experience and a guide for hospitalists. *Dig Dis Sci*. 2011;56(5):1266–1281.
- Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database Syst Rev*. 2004(2):CD003044.
- Uribe M, Campollo O, Vargas F, et al. 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):639–643.
- Sharma P, Sharma BC. Disaccharides in the treatment of hepatic encephalopathy. *Metab Brain Dis*. 2013;28(2):313–320.
- Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology*. 2009;137(3):885–891, 91.e1.
- Dhiman RK, Sawhney MS, Chawla YK, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. *Dig Dis Sci*. 2000;45(8):1549–1552.
- Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy—a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2011;34(8):853–861.
- Sidhu SS, Goyal O, Mishra BP, Sood A, Chhina RS, Soni RK. Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy (the RIME Trial). *Am J Gastroenterol*. 2011;106(2):307–316.
- Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362(12):1071–1081.
- Jiang Q, Jiang XH, Zheng MH, Jiang LM, Chen YP, Wang L. Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol*. 2008;20(11):1064–1070.
- Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther*. 2014;40(2):123–132.
- Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol*. 2013;108(9):1458–1463.
- Huang E, Esrailian E, Spiegel BM. The cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy—a decision analysis. *Aliment Pharmacol Ther*. 2007;26(8):1147–1161.
- Salix Pharmaceuticals. Patient assistance program. Available at: <http://www.salix.com/about-us/corporate-responsibility/patient-medication-assistance>. Accessed October 24, 2015.
- Sharma P, Sharma BC. Management of overt hepatic encephalopathy. *J Clin Exp Hepatol*. 2015;5(suppl 1):S82–S87.
- Naylor CD, O'Rourke K, Detsky AS, Baker JP. Parenteral nutrition with branched-chain amino acids in hepatic encephalopathy. A meta-analysis. *Gastroenterology*. 1989;97(4):1033–1042.
- Gentile S, Guarino G, Romano M, et al. A randomized controlled trial of acarbose in hepatic encephalopathy. *Clin Gastroenterol Hepatol*. 2005;3(2):184–191.
- Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350–electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. *JAMA Intern Med*. 2014;174(11):1727–1733.
- Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol*. 2004;41(1):38–43.
- Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther*. 2005;12(2):133–141.
- Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. *Mayo Clin Proc*. 2010;85(5):451–458.
- Casadaban LC, Parvinian A, Minocha J, et al. Clearing the confusion over hepatic encephalopathy after TIPS creation: incidence, prognostic factors, and clinical outcomes. *Dig Dis Sci*. 2015;60(4):1059–66.
- Centers for Medicare and Medicaid Services. ICD-10 code lookup: encephalopathy&bc=AAAAAAAAAAACAA%3d%3d&. Accessed January 26, 2016.
- Centers for Medicare and Medicaid Services. ICD-10 code lookup: hepatic failure. Available at: <https://www.cms.gov/medicare-coverage-database/staticpages/icd-10-code-lookup.aspx?Keyword=hepatic%20failure&bc=AAAAAAAAAAACAA%3d%3d&>. Accessed January 26, 2016.
- Waghray A, Waghay N, Mullen K. Management of overt hepatic encephalopathy. *J Clin Exp Hepatol*. 2015;5(suppl 1):S75–S81.
- Coleman EA, Parry C, Chalmers S, Min S. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med*. 2006;166:1822–1828.