



[Print](#) :: [Close](#)

FAST FACTS AND CONCEPTS #188

Author(s): Julie Wilson Childers MD and Robert Arnold MD

Background Hepatic encephalopathy (HE) is a neuropsychiatric syndrome with a fluctuating course associated with end stage liver disease (ESLD). HE symptoms, which are graded from 0 to IV, range from subtle personality or sleep disturbances to confusion and coma. Severe HE (grade III or IV) is manifested by gross disorientation, bizarre behavior, stupor, or coma (1). Without transplantation, severe HE signifies a poor prognosis (58% 1 year and 77% 3 year mortality in one case series) (2). In addition, 15% of patients awaiting liver transplantation die before receiving an organ (3).

Etiology The cause of HE is uncertain, but may be related to the accumulation of neurotoxic substances normally metabolized by the liver; these include ammonia and endogenous benzodiazepine-like substances that activate GABA-receptors to cause neurotoxicity.

Evaluation HE is a diagnosis of exclusion, and in one study 80% of cases were associated with an identifiable secondary cause such as gastrointestinal bleeding, infection (including spontaneous bacterial peritonitis), renal failure, alcohol withdrawal, excessive dietary protein, volume depletion, or drugs (particularly benzodiazepines) (4). Serum ammonia levels are usually elevated in patients with HE, although the utility of following these has not been established.

Therapy begins with correction of the underlying causes if this is consistent with the goals of care. Specific therapy of HE is aimed at limiting production of and increasing excretion of intestinally derived toxins, particularly ammonia.

- **Non-absorbable disaccharides** such as *lactulose* and *lactitol* are the mainstay of treatment though there is a lack of controlled evidence supporting their use (5). These agents not only cause increased transit time through the gut and less absorption of toxins, but also promote bacterial fermentation, leading to a hostile environment for ammonia-producing bacteria. The daily dose of lactulose should be titrated to result in two to four soft stools daily. For most patients the daily dose is between 30 and 60 grams. Side effects include gastrointestinal cramping, diarrhea, and flatulence.
- **Non-absorbable antibiotics** such as *neomycin* and *vancomycin* were the first treatments for HE. They lower ammonia by combating urea-producing bacteria in the gut. Neomycin likely produces more rapid improvement than lactulose but its use is limited by its nephro- and oto-toxic effects (5). *Rifaximin* is a nonabsorbable derivative of rifampin which received orphan drug status from the FDA in 2005 for treatment of HE. Rifaximin, given at 400 mg orally three times a day, is as effective as neomycin or lactitol and better tolerated than other nonabsorbable antibiotics (6). Rifaximin costs \$4.00 a pill (average wholesale price). Because of this and its lack of clear superiority to disaccharides rifaximin is considered a second-line agent for patients who cannot tolerate or who are not responding to disaccharide therapy.
- **Other therapies** have limited efficacy in treating HE and play no clear role in its management. These include branched chain amino acids (7), the benzodiazepine antagonist flumazenil (8, 9), and limitation of dietary protein (10).

Advance care planning The patient's values, goals of care, and treatment options should be discussed in the context of HE's poor prognosis. A health care proxy should be established before cognitive impairment prevents this.

Supportive care The patient and family must be educated to recognize HE's symptoms and understand its

fluctuating course, avoiding precipitating factors when possible. Patients who are confused should be reoriented and measures should be taken to prevent falls, skin breakdown, and aspiration. Intravenous fluids, nasogastric feeding, and airway protection are sometimes appropriate. Dose-adjusted acetaminophen (<2 gm/day) is the first line analgesic. Opioids can worsen HE but are sometimes necessary to adequately treat pain; their use should be closely monitored and balanced with the patient's degree of suffering and goals of care (11). Dying patients should receive attentive comfort care. Besides pain – dyspnea, restlessness, edema, and secretion management are common challenges in dying ESLD patients.

References

1. Blei AT, Cordoba J. Practice guidelines: Hepatic encephalopathy. *Am J Gastroenterology*. 2001; 96(7):1968-1976.
2. Bustamante J, Rimola A, Ventura PJ, Navasa M, Cirera I, Reggiardo V, et al. Prognostic significance of hepatic encephalopathy in patients with cirrhosis. *J Hepatol*. 1999; 30:890-895.
3. Russo MW, LaPointe-Rudow D, Kinkhabwaa M, Emond J, Brown RS. Impact of adult living donor liver transplantation on waiting time survival in candidates listed for liver transplantation. *Am J Transplantation*. 2004; 4(3):427-431.
4. Fessel JM, Conn HO. An analysis of the causes and prevention of hepatic coma. *Gastroenterology*. 1972; 62:191.
5. Als-Nielsen B, Gluud LL, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD003044. DOI: 10.1002/14651858.CD003044.pub2.
6. Mas A, Rodes J, Sunyer L, et al. Comparison of rifaximin and lactitol in the treatment of acute hepatic encephalopathy: results of a randomized, double-blinded, double-dummy, controlled clinical trial. *J Hepatol*. 2003; 38(1):51-8.
7. Als-Nielsen B, Koretz RL, Kjaergard LL, Gluud C. Branched-chain amino acids for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001939. DOI: 10.1002/14651858.CD001939.
8. 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(2):374-8.
9. Als-Nielsen B, Gluud LL, Gluud C. Benzodiazepine receptor antagonists for hepatic encephalopathy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD002798. DOI: 10.1002/14651858.CD002798.pub2.
10. Cordoba J, Lopez-Hellin J and Planas M, et al. Normal protein diet for episodic hepatic encephalopathy. *J Hepatol*. 2004; 41:38-43.
11. Larson AM and Curtis JR. Integrating palliative care for liver transplant candidates: "Too well for transplant, too sick for life". *JAMA*. 2006; 295(18):2168-76.

Fast Facts and Concepts are edited by Drew A Rosielle MD, Palliative Care Center, Medical College of Wisconsin. For more information write to: drosiell@mcw.edu. More information, as well as the complete set of Fast Facts, are available at EPERC: www.eperc.mcw.edu.

Version History: Originally published September 2007. Current version re-copy-edited in May 2009.

Copyright/Referencing Information: Users are free to download and distribute Fast Facts for educational purposes only. Childers JW, Arnold R. Hepatic Encephalopathy in ESLD. Fast Facts and Concepts. September 2007; 188. Available at: http://www.eperc.mcw.edu/fastfact/ff_188.htm.

Disclaimer: Fast Facts and Concepts provide educational information. This information is not medical advice. Health care providers should exercise their own independent clinical judgment. Some Fast Facts cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.

ACGME Competencies: Patient Care, Medical Knowledge

Keyword(s): Prognosis, Pain - Evaluation

© 2008 Medical College of Wisconsin

Medical College of Wisconsin

8701 Watertown Plank Road, Milwaukee, WI 53226

www.mcw.edu | 414.456.8296

[Print](#) :: [Close](#)