Treatment of Overt Hepatic Encephalopathy

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KEYWORDS

• Hepatic encephalopathy • Cirrhosis • Portal hypertension • Portosystemic shunt • Ammonia

KEY POINTS

- Hepatic encephalopathy (HE) is caused by a combination of liver failure and portosystemic shunting.
- Any episode of HE may signal an important precipitating event; always consider infection, gastrointestinal bleeding, constipation, and metabolic derangements.
- HE is associated with an elevated blood ammonia concentration.
  - Factors other than ammonia may contribute to HE, but remain to be defined.
  - The actual blood ammonia concentration correlates poorly with clinical findings – serial monitoring is rarely useful.
  - All current medical therapies are thought to work by reducing blood ammonia.
  - Current drugs approved for managing HE are non-absorbable disaccharides and non-absorbable antibiotics.
- HE is associated with excess mortality beyond the Model for End-Stage Liver Disease score.
- Patients with HE should be considered for orthotopic liver transplantation.
- Investigational agents increase flux through the urea cycle or increase urinary excretion of other ammonia-containing compounds.

INTRODUCTION

Hepatic encephalopathy (HE) is a reversible impairment of neuropsychiatric function, usually caused by a combination of portosystemic shunting and impaired hepatic function. Cases of HE caused by a large shunt in the absence of cirrhosis are known as type B, and are considerably less common. The consequences and cost of HE are substantial; a recent study of patients in the United States reported 22,931 hospitalizations in 2009 with an average length of stay of 8.5 days at a cost of $63,108 per case and a mortality rate of about 15%.[1] A 10-year study of patients who were listed for orthotopic liver transplantation reported a significantly higher mortality among patients

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with HE; the 90-day wait-list mortality was significantly higher among patients with advanced HE compared with those with low-grade or no HE (24.4% vs 6.8% vs 3.5%, respectively; $P<.001$). When stratified by Model for End-Stage Liver Disease (MELD) score, patients with severe HE had a 90-day wait-list mortality similar to that of nonencephalopathic patients with MELD scores 6 to 7 points higher (Fig. 1).[2]

The individual contributions of liver dysfunction and portosystemic shunting are not easily separated, and the basis of HE is incompletely understood. HE is frequently ascribed to excess activity of γ-aminobutyric acid-ergic (inhibitory) neurons in the brain in response to nitrogenous overload. The basis of treatment has therefore centered on reducing blood ammonia concentrations. This empiric approach works fairly well, but the role of blood ammonia concentration as a single agent is frequently overemphasized in clinical practice. Although beyond the scope of this review, other factors such as cerebral blood flow and oxygen extraction may be affected in patients with HE, and do not seem to be related to blood ammonia or the cerebral metabolic rate of blood ammonia.[3]

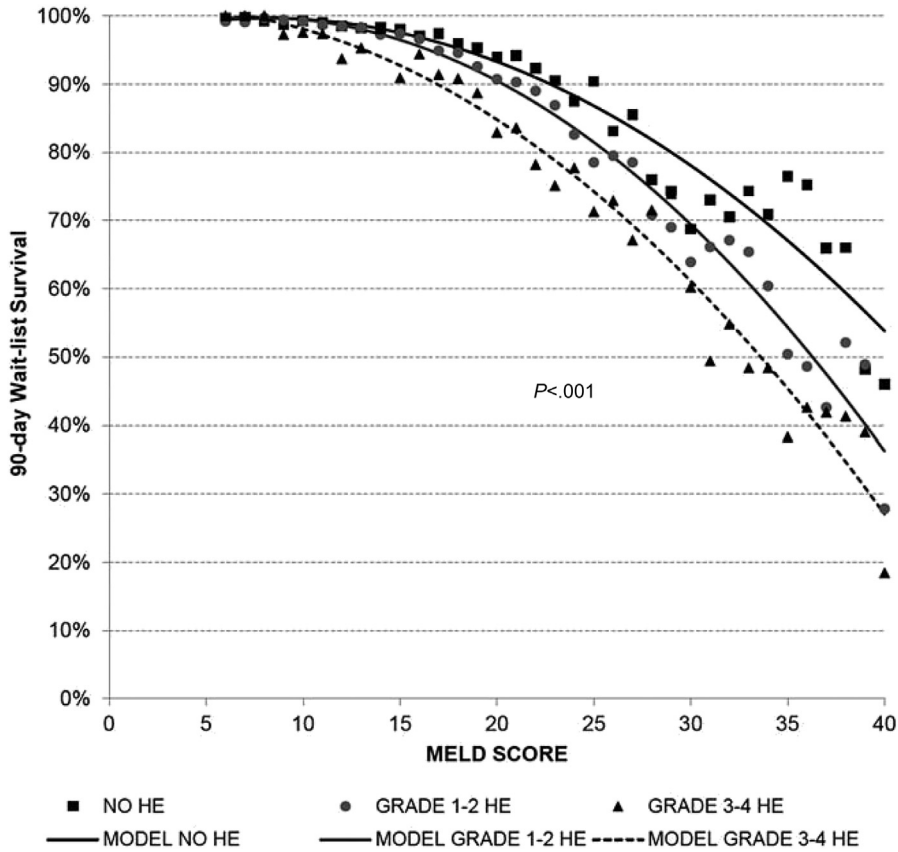

Fig. 1. Ninety-day wait-list survival stratified by Model for End-Stage Liver Disease (MELD) score and severity of hepatic encephalopathy (HE). The presence of advanced (grade 3–4) HE increases mortality by the equivalent of 6 to 7 points when compared with patients without HE. (*From* Wong RJ, Gish RG, Ahmed A. Hepatic encephalopathy is associated with significantly increased mortality among patients awaiting liver transplantation. Liver Transpl 2014;20:1459; with permission.)