Refractory Hepatic Encephalopathy

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Key Concepts

• Refractory hepatic encephalopathy results in frequent hospitalizations and the potential for increased morbidity and mortality
• Accelerated liver transplantation has been proposed as a means of treating patients with refractory encephalopathy and a low MELD score
• However, the heterogenous nature of these patients and the myriad of potential factors leading to episodes of encephalopathy, many of which may be reversible, make accelerated transplantation for all patients problematic
• Exceptions may occur, thus, discussion with the Regional Review Board is most appropriate if all avenues have been exhausted

Hepatic encephalopathy is a well known clinical syndrome manifested by a number of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of other known brain disease (1). Manifestations can be as subtle as short term memory loss, hyperirritability, and sleep disturbance, or as severe as hepatic coma (1). Medical management can control symptoms, however, even optimal medical management may be interrupted by episodes precipitated by gastrointestinal bleeding, electrolyte abnormalities, or infection. Furthermore, interventions to control refractory manifestations of portal hypertension, such as a transjugular intrahepatic portosystemic shunt (TIPS), may lead to the new onset of encephalopathy or an increase in frequency or severity of episodes (2). Finally, many episodes occur in the absence of an obvious precipitating factor (3).

Hepatic encephalopathy has a profound effect on survival. One study showed a 42% survival at 1 year following the first episode of overt hepatic encephalopathy and a 23% survival 3 years after the first episode (4). Thus, referral for consideration of liver transplantation is routinely recommended when encephalopathy is first diagnosed. That being said, the presence, severity, and frequency of hepatic encephalopathy are not components of listing for liver transplantation. Prioritization is based on the MELD score, the well known predictor of 90 day survival based on the values of total bilirubin, INR, and serum creatinine (5).

The calculated MELD score does not serve all patients with all disease states awaiting a liver transplant. Multiple exceptions have been identified, based on a disease or syndrome with potential life threatening consequences with a calculated MELD score that would place a patient far down the priority wait list. Hepatocellular carcinoma, hepatopulmonary syndrome, porto-pulmonary hypertension, and polycystic liver disease are a few examples of diseases/syndromes where exception points can be applied above and beyond the calculated MELD score, as long as specific criteria are met (6). Syndromes
without defined exception points can be more problematic and are usually submitted to the appropriate United Network for Organ Sharing (UNOS) Regional Review Board in the United States, made up of a representative of each transplant center in the region. These exceptions may be approved, though many are not. For example, patients with severe pruritus caused by cholestatic liver disease or frequent episodes of bacterial cholangitis/sepsis with biliary obstruction may not be approved, depending on the circumstances and the region.

Refractory hepatic encephalopathy in a patient with a low MELD score as an indication for accelerated liver transplantation? Most, if not all, liver transplant centers have dealt with this complicated scenario. Patients nowhere near the top of the wait list enter the proverbial “revolving door” of hospital admission and discharge. Due to the increased morbidity and mortality associated with episodes of hepatic encephalopathy, specifically aspiration, infection, and procedure related complications, an accelerated path to a transplant would appear to make sense. Before UNOS allocation criteria are changed, however, it is important to understand the potential reasons behind these episodes and correct all factors that could be contributing to the problem.

Identification of the precipitating factor(s) of an episode of hepatic encephalopathy is crucial in its management. Correction of the factor is as important as appropriate medical management. An obvious example is gastrointestinal bleeding. Failure to control the bleed will likely lead to ongoing encephalopathy, regardless of medical management. Control of the bleed may require placement of a TIPS, potentially increasing portosystemic shunting and the potential for hepatic encephalopathy. Finally, the presence of an occult infection that is not eradicated will potentially lead to additional episodes.

Most transplant hepatologists recognize, however, that the identification of these factors is not always easy, in spite of a careful physical examination and exhaustive testing. In fact, many episodes of encephalopathy have no obvious precipitating factor, i.e., bleeding, infection, and constipation are absent (3). However, the “spontaneous” episode should make one pause. A recent episode at our institution with a patient readmitted within 3 days lead to additional history from the patient’s wife. In order to maintain their health insurance and the patient’s eligibility for a transplant, she continued to work. Although she laid out all of his medications each morning and they were always gone when she returned home, the patient made no secret of his dislike for all preparations of lactulose and the resultant fecal urgency. Was non-compliance ever verified?

No, but these questions will always arise in patients who come into the hospital with regularity.

Another frequently discussed and debated issue is the presence of a TIPS and its effect on encephalopathy. Refractory post-TIPS encephalopathy usually leads to discussion of down-sizing or thrombosis of the TIPS to decrease shunting and, theoretically, improve encephalopathy (7,8). My personal concern is the potential for recurrence of the portal hypertensive complication leading to TIPS placement initially. Anecdotally, I have seen a number of cases of what appeared to be refractory post-TIPS encephalopathy, characterized by multiple hospitalizations, with sudden improvement without TIPS revision. Whether this represents “stabilization” or simply a patient/family understanding the need for compliance is unclear. But this is exactly the issue that makes refractory encephalopathy with a low MELD score an indication for an accelerated pathway to transplantation problematic.

Exception points are well accepted for a number of disease states/syndromes, ALL of which have a reasonably well defined natural history and a poor prognosis without transplantation. The addition of serum sodium to the MELD score has been debated for years, with exhaustive discussion, study, and modeling. Hepatologists are well acquainted with the difficult management problem hyponatremia presents in the patient with cirrhosis (9). Even with this well recognized complication, approval has been slow to occur. Although one could certainly argue that elimination of episodes of hepatic encephalopathy could be associated with improved morbidity and mortality, it is difficult to justify an accelerated pathway to liver transplantation for a patient with a syndrome that may be related to non-compliance or could respond to optimal medical management or other intervention, such as TIPS revision. Although the presence of increased intracranial pressure in a patient with cirrhosis, a rare complication (10), was proposed as a potential exception (11), this has not been mandated by UNOS. Of course, exceptions do occur and should be discussed with the appropriate Regional Review Board. However, due to the heterogeneous population and myriad of clinical circumstances, coming up with well defined criteria that could be reliably applied to all patients with refractory hepatic encephalopathy is unlikely, if not impossible.

Management of hepatic encephalopathy can be challenging for a number of reasons. However, liver transplantation, in an accelerated fashion, is not the answer for all patients with poorly controlled symptoms.
References


