Hepatic Encephalopathy: A Review of Guidelines

**Introduction:** Hepatic encephalopathy is a neuropsychiatric syndrome that most commonly occurs in patients with decompensated liver disease. It affects approximately 30% of patients with liver cirrhosis and is responsible for over 100,000 hospitalisations every year. It is one of the most debilitating complications of liver disease, imposing a huge burden on caregivers and severely affecting patients’ quality of life. With the increasing prevalence of chronic liver disease in the UK, it seems an important priority to recognise and manage these patients effectively.

Due to the limited guidance that has been available, the European Association for the Study of the Liver (EASL), together with the American Association for the Study of Liver Diseases (AASLD), have developed guidelines for the management of hepatic encephalopathy, with medical therapy being the first line choice. These medical treatments are aimed at interrupting the pathological processes underlying hepatic encephalopathy, and have been found to reduce hospital admissions and improve survival.

However, there are still a number of patients who experience recurrent episodes of hepatic encephalopathy despite optimal medical treatment. There is emerging evidence to support the use of radiological therapy for patients who are resistant to medical therapy, however this method is not yet recommended in the EASL-AASLD guidelines.

**Background:** Hepatic encephalopathy can produce a wide range of non-specific, neuropsychiatric symptoms. In its early stages, symptoms may be subtle and can only be detected on psychometric testing. As the condition progresses, patients may experience personality changes, disorientation, acute confusional states and in worst cases, patients can end up in a coma. The severity can be graded using the West Haven Criteria which takes into account some of these clinical features.

It describes hepatic encephalopathy as it progresses through four stages. The stages and their descriptions can be found in Table 1. The classification of hepatic encephalopathy takes into account four factors: the underlying disease, the time course of the condition, the presence of any precipitating factors, and its severity. The underlying disease separates hepatic encephalopathy into Types A, B and C; Type A being due to acute liver failure, Type B due to portosystemic shunting and Type C due to cirrhotic liver disease. In relation to its time course, hepatic encephalopathy can be described as episodic, persistent or recurrent, with recurrent describing bouts of hepatic encephalopathy that occur at intervals of less than 6 months.

Recognising the presence of an underlying precipitant is of particular importance when managing an acute episode of hepatic encephalopathy, as these can be identified and reversed. Common precipitants include gastrointestinal bleeding, infection and diuretic overuse. The pathogenesis of hepatic encephalopathy is complex and is still not fully understood. However, it is believed to be related to an accumulation of nitrogenous waste products in the systemic circulation, particularly ammonia, and the effects they have on the brain.

Non-absorbable Disaccharides: The first line agent recommended in the EASL-AASLD guidelines is lactulose, a non-absorbable disaccharide that lowers the pH within the gut. The resulting effect is an increased excretion of ammonia, as well as an increased utilisation of ammonia by the bacterial gut flora. Despite their frequent use, non-absorbable disaccharides have been found to have variable efficacy in clinical trials. A large meta-analysis conducted in 2004 found that there is no significant effect of non-absorbable disaccharides on acute episodes of hepatic encephalopathy. However, the authors found that there was generally a low methodological quality of the included trials, and this may have influenced the overall result.

As described in the EASL-AASLD guidelines, there is generally a limited amount of high-quality

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By Stephanie Baxter
Evidence surrounding management of hepatic encephalopathy, predominantly due to the lack of consistency in the description and categorisation of hepatic encephalopathy. The main aim of the guidelines were to address this problem and provide a standardised approach to the recognition and management of hepatic encephalopathy with the intention of improving quality of clinical trials in the future.

Currently, the recommendations are based on the existing body of evidence, along with the clinical experience of the authors. Many clinicians speak of the effectiveness of lactulose, and it has been the standard treatment for hepatic encephalopathy since the 1980s. For this reason, it seems reasonable to adhere to the current guidelines until there is emergence of new evidence. Also, lactitol is another non-absorbable disaccharide that can be used as an alternative to lactulose. However, the evidence to support its use is of poor quality, based upon a small meta-analysis of four small trials.

**Rifaximin and Neomycin:** Rifaximin is a semisynthetic antibiotic derived from rifamycin. It is poorly absorbed when taken orally, therefore acts upon bacteria within the gut to reduce production of ammonia. There is currently no evidence to support the use of rifaximin alone, however the National Institute of Health and Care Excellence (NICE) and the EASL-AASLD guidelines recommend the use of rifaximin in combination with lactulose.

The guidelines recommend rifaximin as an add-on to lactulose for the prevention of recurrent episodes of hepatic encephalopathy after a second episode. This has been based upon evidence from a recent, well-conducted randomised control trial in which the use of rifaximin was found to significantly reduce the risk of an episode of hepatic encephalopathy when compared with placebo.

Neomycin is an aminoglycoside antibiotic that, like rifaximin, is poorly absorbed and reaches high concentrations in the gut. It was the first antibiotic used for the treatment of hepatic encephalopathy, with trials dating back to 1977. One of the most recent studies in 1992 found no significant difference between neomycin and placebo in the treatment of episodic hepatic encephalopathy. The evidence for the use of neomycin is generally weak, and its use is complicated by the risk of ototoxicity and nephrotoxicity.

Its use has therefore been overtaken by newer agents.

**Interventional Radiology:** The medical management of hepatic encephalopathy, as discussed above, is aimed at reducing the overall amount of ammonia within the systemic circulation. In patients with liver cirrhosis, this accumulation of ammonia is a consequence of hepatocellular dysfunction and portosystemic shunting. In many cases of hepatic encephalopathy, symptoms are initiated abruptly by an identifiable precipitating event, such as acute infection, or gastrointestinal bleeding. However, a number of patients will experience recurrent episodes of encephalopathy, without any obvious trigger. These patients will usually not respond to the optimal medical treatment, and will have frequent hospitalisations as a result.

Several reports have suggested that up to 70% of patients with refractory hepatic encephalopathy will have large spontaneous portosystemic shunts (SPSS) collateral blood vessels that develop to bypass the liver. The association between portosystemic shunts and the development of hepatic encephalopathy is well known from the experience with surgical shunts and transjugular intrahepatic portosystemic shunts (TIPS).

In many cases, the shunts are large enough to divert a significant proportion of the portal blood flow. This can result in portal flow steal, a mechanism that is critical in the development of hepatic encephalopathy. With this in mind, it seems that the occlusion of such SPSSs could represent a therapeutic target for patients with recurrent hepatic encephalopathy.

Percutaneous embolization of portosystemic shunts is a method that has been used for the treatment of recurrent hepatic encephalopathy. Several cases have been reported in which embolization of large shunts have been found to improve neurological symptoms in patients with recurrent hepatic encephalopathy. However, a literature search carried out using PubMed revealed the evidence.
available is limited, and that it is represented mostly by single case reports, or small case series 42-53. The nature of such evidence makes it difficult to draw firm conclusions about the efficacy and safety of shunt embolization.

More recently, two retrospective studies have been published that reviewed the efficacy and safety of this method for the treatment of recurrent hepatic encephalopathy 54,55. In 2013, Laleman et al. carried out a multicentre study across six European liver units 54. A total of 37 patients were included, the largest cohort to have been reported, all of whom had known liver cirrhosis and recurrent hepatic encephalopathy with large portosystemic shunts.

All 37 of these patients underwent embolization of the shunts and their outcome was assessed. 18 of the 37 patients remained free of hepatic encephalopathy over an average follow-up of 697 days. There was also a significant decrease in hepatic encephalopathy-related hospital admissions found post-embolisation, and an improvement in patient autonomy. These results are in accordance with the retrospective study carried out by An et al. 55.

Here, the authors reviewed a total of 34 patients with known liver cirrhosis and recurrent hepatic encephalopathy. 17 underwent successful embolization of their portosystemic shunts, while the remaining 17 served as a control group. Both groups received best medical treatment throughout. This study assessed the recurrence of hepatic encephalopathy over a follow-up period of 2 years, as well as patient survival and liver function. Overall, embolization was found to significantly reduce the recurrence rate of hepatic encephalopathy, and improve patient survival in those with modestly preserved liver function.

The significance of preserved liver function has been described in both of these recent studies, as the Model for End-Stage Liver Disease (MELD) score appears to be a strong positive predictor of recurrence of hepatic encephalopathy 54-55. The MELD score can be used to predict survival in patients with advanced liver disease and incorporates INR, serum creatinine and serum bilirubin 56. An et al. found that survival in patients with a MELD ≥15 tended to be worse in the embolised patients than in the control group of patients. Additionally, patients with a MELD score ≥11 were more likely to experience recurrence of hepatic encephalopathy post-embolization, as identified in the European multicentre study 54. This should perhaps provide guidance as to who may benefit from this procedure in the future.

Conclusion: The approach to managing hepatic encephalopathy can be summarised as follows. Initially, any precipitating factors should be identified and managed, including infections, gastrointestinal bleeding and diuretic overuse. Lactulose therapy should then be commenced, which should be taken as 25ml twice daily, aiming for 3 soft bowel motions per day. Lactulose should then be continued as prophylaxis.

If a patient goes on to have a further episode of hepatic encephalopathy, rifaximin is recommended as an add-on therapy. If at this point there is no resolution of symptoms, further treatment is available. Oral branched-chain amino acids and intravenous L-ornithine L-aspartate are among the options, and have been recommended in the EASLAASLD guidelines 7.

Alternatively, patients with recurrent episodes of hepatic encephalopathy who are receiving the maximal treatment regime should be investigated for the presence of portosystemic shunts using contrast-enhanced CT. The presence of a large shunt may then be considered for percutaneous embolization.

As for radiological intervention, there seems to be an increasing amount evidence to support the use of percutaneous embolization of portosystemic shunts in patients with recurrent hepatic encephalopathy. This method seems to be of particular benefit to patients with a MELD score ≤11, which should be taken into account in future studies 54. An important point to consider is the safety of such a procedure on the long-term outcome of the patients. In order to assess this further, it would be beneficial to carry out a large scale trial with a longer follow up period. The problem with this may be that the diagnosis of large portosystemic shunts is often delayed, so few patients end up getting referred 38,54.
The routine use of embolization may, therefore, not be adopted for the time being. However, it may be useful to incorporate investigation for portosystemic shunts much earlier in the management of patients presenting with hepatic encephalopathy.

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<th>Table 1: Stages of hepatic encephalopathy</th>
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<td><strong>Minimal hepatic encephalopathy (MHE)</strong></td>
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<td><strong>Grade 1</strong></td>
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<td><strong>Overt hepatic encephalopathy</strong></td>
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References


