EASL CLINICAL PRACTICE GUIDELINES ON THE MANAGEMENT OF HEPATIC ENCEPHALOPATHY

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Classification:

-type a: due to acute liver failure
-type b: due to portosystemic shunt w/o significant liver disease
-type c: due to cirrhosis with or without portosystemic shunt

*covert: minor or no signs/symptoms but abnormalities on neuropsychological and/or neurophysiological tests
*overt: grades II or over

-episodic
- recurrent :more than one episode over a period of 6 months
- persistent :no return to normal/baseline neuropsychiatric performance in between episodes

Precipitating factors:

Recognized precipitating events are constipation, gastrointestinal bleeding , infections, hyponatremia, and dehydration/diuretic overdose. The presence of portosystemic shunts facilitates the occurrence of HE and is associated with more severe forms.

It should be emphasised that HE might occur on top of a pre-existing disease such as, for example, dementia
These causes included infections (urinary infection, pneumonia), perfusion disorders (stroke, myocardial infarction), other neurological causes (subdural haematoma) and several others.

-In patients with cirrhosis, do any brain imaging methods provide results proving HE?
No cerebral imaging proves a diagnosis of HE

Ammonia level in diagnosis and prognosis:

Diagnosis:
Blood ammonia levels correlate with the severity of HE, but patients without manifest HE and even without liver disease can display hyperammonaemia. Moreover, ammonia may remain elevated after clinical HE resolution . However, a normal blood ammonia level has negative predictive value, and normal ammonia in a patient with cirrhosis and delirium should prompt renewed or further differential diagnostic workup for other causes of delirium.
Prognosis:
A recent study in acute-on-chronic liver failure suggested a prognostic role of ammonia in patients with overt HE Hyperammonaemia is associated with decreased transplant-free survival from acute decompensation of cirrhosis.

In patients with overt HE, does the prevention of further decompensation/worsening of the underlying liver disease improve prognosis?

All of the classical signs of decompensation of cirrhosis, including HE, are individually and additively associated with increased mortality, although the association is strongest for HE. Decompensation usually accompanies progression of the underlying liver disease which determines short- and long-term prognosis. Management of non-HE decompensations, e.g. acute variceal bleeding, also improves prognosis even if the liver function remains unchanged. In the case of HE, it has not been studied specifically whether such interventions have the same positive effects on prognosis. However, despite the negative prognostic importance of HE, there is no basis for the assumption that management of other decompensations is without effect. It follows that management of non-HE decompensations and attempts to arrest liver disease progression, e.g. cessation of alcohol misuse in those with alcohol-related cirrhosis, will have a significant impact on the prognosis of patients with HE.

In patients with overt HE, do the identification, prevention, and management of precipitating events, if any, improve treatment outcomes and prognosis?

The primary intervention in patients with overt HE is a search for, and correction of, any precipitating factors. This exercise always precedes specific anti-HE treatment and up to 90% of the patients can be expected to recover from episodic overt HE by correction of one or more precipitating factors. Specific treatment of HE has little prospect of success without management of precipitating factors. However,
several HE-precipitating factors, e.g. infection and bleeding, are associated with increased mortality and effective management of such factors may improve prognosis in patients with overt HE.
Finally, rapid removal of blood from the gastrointestinal tract and rapid resolution of constipation have been shown to improve recovery from an episode of overt HE

In patients who have had a first episode of overt HE, should secondary prophylaxis be initiated to prevent further episodes?
Lactulose is recommended as secondary prophylaxis following a first episode of overt HE, and should be titrated to obtain 2-3 bowel movements per day
Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following>1 additional episodes of overt HE within 6 months of the first one

-In patients presenting with gastrointestinal bleeding, rapid removal of blood from the gastrointestinal tract (lactulose or mannitol by naso-gastric tube or lactulose enemas) can be used to prevent HE

Is vitamin/micronutrient supplementation a treatment option to improve mental status in patients with HE?

Patients with both alcohol- and non-alcohol-related cirrhosis are prone to deficiencies in water-soluble vitamins, particularly thiamine. If Wernicke’s encephalopathy is suspected, high dose parenteral thiamine supplementation is mandatory. Deficiencies in pyridoxine, folate and cobalamin may also develop rapidly in chronic liver disease due to diminished hepatic storage.

In patients with recurrent/persistent HE, is faecal microbiota transplantation (FMT) a treatment option to improve outcome?

Gut microbiome changes have prime importance in the pathogenesis of cirrhosis and HE. FMT is a well-established treatment to
modify the gut microbiome and has been shown to be safe and efficacious in disease states resulting from gut dysbiosis including Clostridium difficile infection. Patients with cirrhosis have an imbalance between healthy and pathogenic gut bacteria with skewed microbiota populations in favour of increased numbers of pro-inflammatory and ammoniagenic species including Enterobacteriaceae, Firmicutes, Archaea and Prevotella. In an open-label randomised phase I safety trial of 10 patients treated with FMT via rectal enema, FMT was shown to be safe and potentially efficacious in treating HE. However, patients were treated with broadspectrum antibiotics prior to FMT and the favourable impact may have been related to the antibiotic administration. The long-term
safety and efficacy of FMT was studied within this population between 12 and 15months. The FMT cohort had no adverse effects on
long-term follow-up. Encapsulated FMT offers a more practically Feasible modality of treatment. Bajaj et al. have recently published a
phase I study demonstrating that oral FMT capsules are safe and well tolerated in 10 patients with cirrhosis and recurrent HE. FMT was
associated with improved duodenal mucosal diversity, antimicrobial peptide expression, lipopolysaccharide-binding protein
and improved cognitive performance. Preliminary data is encouraging,but further validation in larger randomised placebocontrolled
trials focusing on clinical endpoints are warranted before it can be recommended as a treatment option.

In patients with overt HE, which criteria should be used to guide referral to a liver transplantation centre?

Liver transplantation represents the ultimate treatment for HE, but HE is not a transplantation indication in most countries, unless associated with liver failure. Emergency liver transplantation in patients with severe HE in the setting of acute liver failure is commonly indicated and results in rapid resolution of HE together with marked survival improvement. Liver transplantation in patients with overt HE due to cirrhosis may also be considered if associated with other signs of advanced liver failure, as determined by clinical condition and Child-Pugh and MELD scores. Such patients, however, cannot be listed for emergency liver transplantation. Instead, the goal is to stabilise the patient and treat decompensation episodes including an overt HE episode, and then consider liver transplantation following recovery. However, this approach is not possible in all patients. Some patients with HE deteriorate and develop multiorgan failure, requiring treatment in the ICU and ultimately transplantation for survival. In highly selected patients with acute-on-chronic liver failure, liver transplantation results in acceptable outcomes.