University Hospitals of Derby and Burton NHS Foundation Trust

Hepatic Encephalopathy – Full Clinical Guideline

Reference no.:CG-HEP/2021/200

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/ or portosystemic shunts. It manifests as a wide spectrum of neurological and psychiatric abnormalities, ranging from subclinical alternations to coma. It confers a prognostic significance with regards to the underlying liver disease. The probability of transplant free survival is reported as 42% at 1 year and 23% at 3 years.

Assessment

- Initiation of care for patient with altered consciousness – assess GCS/ West Haven stage.
  In patients with West-Haven grade 3/4 HE or GCS < 10/15 consider the need for ICU review.

- Consider alternative diagnoses - HE is in part a diagnosis of exclusion
  - Alcohol (intoxication, withdrawal, Wernickes encephalopathy*)
  - Drugs - e.g Benzodiazepines, opiods, neuroleptics
  - Intracerebral haemorrhage (risk increased 5-fold in patients with CLD)
  - Diabetes (Hypoglycaemia, DKA, HHS, lactic acidosis)
  - Other electrolyte abnormalities e.g Hyponatraemia, Hypercalcaemia
  - Sepsis with delirium or neuroinfection
  - Non convulsive Epilepsy

  * All patients with evidence of liver disease and confusion should receive high dose iv pabrinex (i.e 2 pairs tds for 3 days then od for 5 days)

- Assess for a reversible trigger (present in 90% of cases). In order of frequency:
  - Sepsis
  - GI bleeding
  - Diuretics - overdiuresis
  - Electrolyte abnormalities/ Metabolic alkalosis (e.g hypokalaemia may precipitate HE)
  - Constipation

West-Haven criteria for Hepatic encephalopathy

Stage	Consciousness	Intellect and behaviour	Neurological findings
0	Normal	Normal	Normal examination; if impaired psychomotor testing, then MHE
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behaviour	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behaviour	Muscular rigidity and clonus; Hyper-reflexia
4	Coma	Coma	Decerebrate posturing

Note that HE may be associated with pyramidal and or extrapyramidal signs, particularly when persistent. Cirrhosis associated parkinsonism (previously known as hepatolenticular degeneration) is unresponsive to NH3 lowering treatments

Investigations

- FBC, UEs, LFTs, INR, NH3 (needs to be performed in working hours and taken to lab on ice). A raised NH3 alone is not diagnostic of HE and does not add prognostic value. A normal value, however, calls for the diagnosis of HE to be reconsidered
- Microbiology - blood and urine culture ± ascitic WCC/ Culture
- ± CT brain (if first episode or if clinical suspicion dictates)
- ± EEG - may support diagnosis of HE (though similar finding seen in metabolic disturbance e.g hyponatraemia, renal dysfunction and sepsis) and helpful in excluding non-convulsive epilepsy

- Number connection test (see appendix) - can provide support to the diagnosis of Hepatic encephalopathy, though main role is in evaluating improvement

Management of overt HE

- **Volume expansion**: STOP diuretics and if there is concern regarding intra-vascular volume depletion then volume expand with 1L of IV 0.9% saline over 1-2 hours. There is evidence to suggest that volume expansion reduces plasma ammonia concentration by increasing ammonia excretion and reducing ammoniagenesis.
- **PO4 enema**
- **Lactulose**: initially 15-30mls up to every 1-2hrs (usually qds dosing) until 2 soft stools. The dose should then be titrated to achieve two to three soft stools per day (usually bd dosing). The main effect of Lactulose is likely to be the purgative effect, but it also a prebiotic and lowers colonic pH to about 5.0. The reduction in pH favours the formation of the nonabsorbable NH4+ from NH3, and effectively reducing plasma ammonia concentrations.
- **Oral antibiotics:** consider starting Neomycin 1000mg PO qds or Metronidazole 400mg tds for 7/7. Ototoxicity, nephrotoxicity and neurotoxicity prohibit their long-term use. Norfloxacin is no longer available.
- **Diet: Do NOT restrict dietary protein but ensure the protein load is spread through the day**: Protein restriction may actually aggravate hepatic decompensation as ammonia concentration will actually increase due to muscle breakdown. Aim to avoid long fasting periods by encouraging meals, snacks (+/-supplements) every 2-4 hours. Inclusion of a 50g carbohydrate snack immediately before bedtime may help to minimise muscle breakdown overnight. If unable to meet nutritional requirements orally, consider artificial feeding. In severe cases of HE, enteral feeding over 24 hours should be considered.
- **Zinc sulphate:** Zinc deficiency is common in patients with cirrhosis and in those with hepatic encephalopathy. There is limited data to suggest that long term zinc supplementation (Zinc sulphate 220mg tds for 1 month, then once daily) may improve severe recurrent refractory HE but no large trials have been conducted.

If not improving – First reconsider alternative diagnoses; then:

- **Rifaxamin (550mg bd) –** a minimally absorbed oral antibiotic with broad-spectrum coverage for gram-positive and gram-negative aerobes and anaerobes. Its main use is preventing recurrent episodes of HE and is associated with improved health-related quality of life.

Management of episodic HE (40% cumulative risk of recurring overt HE at 1 year)

- **Lactulose**: The dose should then be titrated to achieve two to three soft stools per day
- **Rifaxamin (550mg bd)**; Add to lactulose to prevent recurrent HE after 2nd episode

Minimal HE (MHE)

Minimal HE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with CLD who are not disoriented or display asterixis. Prevalence may be up to 50%, but treatment is not required unless leading to impairment of quality of life or implications on employment or public safety. Various testing strategies have been proposed, but there is no agreed gold standard. Routine testing for minimal HE in the liver clinic is not recommended. If testing is performed then AASLD/ EASL recommend the portosystemic encephalopathy (PSE) syndrome test (a battery of 5

paper-pencil tests) + a computerised test (continuous reaction time, inhibitory control test, stroop test or scan test) or neurophysiological test (critical flicker frequency or EEG).

Driving/ DVLA

Hepatic cirrhosis with chronic encephalopathy is listed under Alcohol-related disorders by the DVLA. The advice is that the patient must not drive and must notify the DVLA. Their licence will be revoked until recovery is satisfactory. In law it is the duty of the licence holder to notify the DVLA of any relevant condition. Healthcare professionals should advise the individual on the impact of their medical condition for safe driving ability, advise the individual of their legal requirement to notify DVLA of any relevant condition and notify the DVLA directly of an individual's medical condition or fitness to drive, where they cannot or will not notify the DVLA themselves. In practice we cannot be certain a patient will inform the DVLA and the default position should be to inform the patient that you will be writing to the DVLA, but that we recommend they also inform the DVLA themselves.

Further reading:
Hepatic encephalopathy in Chronic liver disease: 2014 Practice guideline by AASLD/ EASL

Documentation Controls (these go at the end of the document but before any appendices)

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3</td><td>Status

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<tr><td colspan="6">Intended Recipients: All clinicians managing patients with liver disease</td></tr>
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Appendix: **Number Connection test**

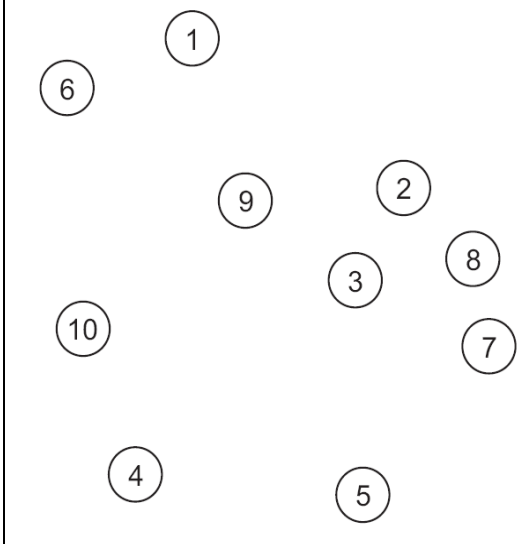
The number connection test can provide support to the diagnosis of Hepatic encephalopathy. A healthy person should be able to complete the task in less than 30 seconds.

- Where possible carry out the test at the same time of day
- Explain the task to the patient by using the practice sheet - numbered 1-10. "*Your task is to order the numbers by drawing a line between them with a pencil, starting with the smallest number first. You do this as fast as you can"*
- If the patient makes a mistake on the practice sheet, correct them until you are sure they understand the task at hand
- Now move to the test sheet, numbered 1 to 25 (there are 4 test sheets and a different sheet should be used if this is a repeat test). Have the patient place the pencil on number 1 and start the stopwatch as you give the signal to begin.
- If the patient skips a number draw his/her attention to the error and continue from the number before the error, e.g *"You forgot 7! Place your pencil on 6 and the connect it with 7 and then onto 8"*
- If the patient requires more than 120 secs, stop the test and record the last number he or she arrived at

Evaluating the test

Time required	**HE Stage**
≤ 30 secs	None
31-50 secs	0-1
51-80 secs	1-2
81-120 secs	2-3
Forced termination	3

Practice sheet



Test sheet 1