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Aliment Pharmacol Ther, 24, 1–17. Tripathi D, et al. (2009). Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology, 50, 825–33. Turon F, et al. (2013). Variceal and other portal hypertension related bleeding. Best Pract Res Clin Gastroenterol, 27, 649–64. Villanueva C, et al. (2013). Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med, 368, 11–21. Wells M, et al. (2012). Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther, 35, 1267–78. Wiese S, et al. (2014). Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. Nat Rev Gastroenterol Hepatol, 11, 177–86. 15.22.4 Hepatic encephalopathy Paul K. Middleton and Debbie L. Shawcross ESSENTIALS Hepatic encephalopathy (HE) is a significant complication of both acute and chronic liver disease, causing much morbidity and mor- tality. It is a complex neuropsychiatric syndrome which displays a wide range of symptoms and is associated with hyperammonaemia and systemic inflammation. The West Haven criteria describe grades of severity from 0 (subclin- ical) and I (changes in awareness, mood, attention, cognition, and sleep pattern) through to IV (coma). It is further classified by the underlying aetiology: type A, due to acute liver failure; type B, secondary to portosystemic shunting; and type C, occurring in chronic liver disease in association with precipitating factors including infections, gastrointes- tinal bleeding, and electrolyte disorders, particularly hyponatraemia. There is no definitive test or set of diagnostic criteria to establish a diagnosis of HE, which remains primarily a clinical diagnosis of ex-clusion in patients with a history or clinical evidence of liver disease. Management depends on the type of HE, but for type C (the com- monest type) typically includes lactulose and rifaximin as well as the identification and management of precipitating factors. Patients with cirrhosis with ongoing overt HE despite optimal medical manage- ment have a poor outlook and should be considered promptly for liver transplantation. Introduction The syndrome of hepatic encephalopathy (HE) was first described in the late 19th century when physiology experiments conducted by Nencki and Pavlov characterized neurobehavioural changes in dogs in which portocaval shunts had been created. The dogs developed symptoms of aggression, irritability, and ataxia postoperatively, pro-gressing to convulsion and eventually coma. These symptoms wors- ened with the ingestion of meat and resulting rise in blood and brain ammonia concentration. HE is a significant complication of both acute and chronic liver disease. Patients who develop HE have significant morbidity, with symptoms affecting their quality of life, ability to work, and ability to live independently. It is also associated with significant mortality, with 3-year survival less than 25% in those with chronic liver disease. HE continues to prove challenging in both diagnosis and man- agement, and further research is required to fully address this clin- ical need. Aetiology The 2014 joint American Association for the Study of Liver Diseases (AASLD)/European Association for the Study of the Liver (EASL) guidelines recommend that HE is characterized by the underlying aetiology. This reflects the significant difference in pathophysiology, management, and prognosis between these groups (Table 15.22.4.1).

15.22.4 Hepatic encephalopathy 3081 Type A hepatic encephalopathy This is secondary to acute liver failure (ALF), which is defined by the time from onset of jaundice to HE. Type B hepatic encephalopathy This is secondary to portosystemic shunting or bypass and not re- lated to underlying chronic liver disease. Most cases are related to the insertion of a transjugular intrahepatic portosystemic shunt (TIPS), which is an important intervention in the management of portal hypertension but limited by the development of HE. Studies estimate the 1-year incidence of HE as between 10 and 50%, with severely disabling encephalopathy affecting 1 to 3% of patients. Encephalopathy risk is considered during assessment for TIPS. Age over 65, history of HE, and

Child–Pugh score greater than 10 have all been shown to be associated with a higher risk of post-TIPS HE. Type B HE has also been reported in patients, without liver dis- ease, who develop spontaneous portosystemic shunts, including congenital intra- or extrahepatic shunts. Type C hepatic encephalopathy This comprises most cases. The development of type C HE is com- monly associated with a precipitating factor. Precipitating factors include infections, gastrointestinal bleeding, and electrolyte dis- orders particularly hyponatraemia (Box 15.22.4.1). Epidemiology Studies suggest 30 to 40% of patients with cirrhosis will experience an episode of overt HE within their lifetime and between 20 and 80% of patients will develop minimal HE. HE is more likely to occur in those with more severe liver disease, advanced age, and with a history of previous episodes of HE and decompensation (variceal bleeding, ascites, infections). Studies have also shown the presence of diabetes to be an inde- pendent risk factor for developing the first episode of overt HE as well as being associated with more severe episodes. HE is also more commonly seen in malnourished patients. The presence of HE is associated with poorer socioeconomic status, worse unemployment, increased hospitalizations, and higher caregiver burden in comparison to other complications of cirrhosis. Pathogenesis Type A hepatic encephalopathy One of the hallmarks of ALF is the development of HE and cerebral oedema. This is thought to be secondary to hyperammonaemia, oxi- dative stress, and systemic inflammation (Fig. 15.22.4.1). Ammonia ALF reduces hepatic metabolism of bowel-derived ammonia, re- sulting in hyperammonaemia. The ammonia concentration directly correlates with HE severity, the development of cerebral oedema, and progression to intracranial hypertension. Ammonia is also me- tabolized outside the liver in skeletal muscle and in the brain, pri- marily in astrocytes. Numerous studies have associated ammonia exposure to astrocyte swelling in cell culture and animal models. Astrocyte swelling is also a characteristic finding on autopsy in pa- tients who have died of ALF. Two hypotheses are presented to explain this association. Within the brain, ammonia undergoes conversion to glutamine via glu- tamine synthetase within astrocytes. The ‘osmolyte hypothesis’ sug- gests this increase in glutamine causes osmosis of water into the cell resulting in astrocyte swelling. This is supported by studies showing inhibition of glutamine synthetase prevents ammonia-induced astrocyte swelling. However, glutamine levels and astrocyte swelling correlate poorly temporally, and swelling may be absent during peak glutamine levels. Moreover, peak astrocyte swelling is asso- ciated with low levels of glutamine. This led to the ‘Trojan horse’ hypothesis, which suggests glutamine is transported into the mito- chondria where it reverts back to ammonia via phosphate-activated glutaminase. Mitochondrial ammonia accumulation then leads to oxidative stress, mitochondrial dysfunction and astrocyte swelling. Table 15.22.4.1 Categorization of hepatic encephalopathy by aetiology and common associated conditions Type Aetiology Associated conditions Type A Acute liver failure Paracetamol overdose, acute viral hepatitis, drug-induced liver injury, pregnancy related Type B Portosystemic bypass or shunt Post TIPS, spontaneous portosystemic shunt, congenital portosystemic shunt Type C Chronic liver disease Alcohol-related cirrhosis, nonalcoholic fatty liver disease, chronic viral hepatitis, autoimmune hepatitis, metabolic liver disease Box 15.22.4.1 Common causes of precipitating events in type C hepatic encephalopathy in order of frequency • Infections: — Respiratory tract — Gastrointestinal — Spontaneous bacterial peritonitis — Urinary tract • Gastrointestinal bleeding: — Acute — Chronic • Electrolyte derangement: — Hyponatraemia — Hypokalaemia • Dehydration • Constipation • Medication: — Opioid analgesics — Diuretics — Sedatives

 Oxidative stress Ammonia induces oxidative stress through the production of free radicals secondary to N-methyl-d-aspartate receptor activation and

through calcium-dependent processes. Within the mitochondria, it interferes with oxidative phosphorylation leading to mitochondrial dysfunction and further oxidative stress. This may result in opening of the mitochondrial permeability transition pore, destroying the energy potential of the mitochondria and further damaging en- ergy production. This energy failure may result in astrocyte swelling by impairing energy-dependent ion channels, upregulation of aquaporins, and via activation of mitogen-activated protein kin- ases. Oxidative stress and its associated protein phosphorylation/ nitrosylation lead to cellular dysfunction through changes to gene expression, intracellular signalling, and synaptic plasticity. Inflammation/infection There is growing recognition of the synergistic role of systemic in- flammation in the pathogenesis of HE. Patients with systemic in- flammatory response syndrome (SIRS) have been found to have a more rapid progression to more advanced HE with higher mortality. ALF animal models have shown increased cerebral oedema in ani- mals administered with lipopolysaccharide versus control, despite similar levels of ammonia between the groups. In ALF, plasma tu- mour necrosis factor (TNF)-α, interleukin 8, and neutrophil Toll- like receptor-9 expression correlate with severity of HE. SIRS can result from superimposed sepsis or the release of inflammatory me- diators from the necrotic liver. Patients with ALF have neutrophil and monocyte dysfunction contributing to oxidative stress and im- paired immune function, increasing the risk of developing bacterial and fungal infection. SIRS leads to activation of brain endothelium resulting in microglial activation and cerebral production of inflam- matory cytokines. Cerebral and systemic inflammation is associated with increased cerebral blood flow and ammonia delivery which may further contribute to cerebral oedema. Type B hepatic encephalopathy Nitrogen-rich portal blood bypasses the liver either through a TIPS shunt or via spontaneous portosystemic shunts directly into the sys- temic circulation. Symptomatically and pathophysiologically it is similar to type C HE, with absence of cerebral oedema and respon- siveness to ammonia-lowering therapies. Type C hepatic encephalopathy In type C HE, ammonia plays a pivotal role, but there is a growing recognition of the contribution of gut dysbiosis, bacterial transloca- tion, endotoxaemia, systemic inflammation, and immune dysfunc- tion in the pathogenesis (Fig. 15.22.4.2). Ammonia Ammonia has long been associated with the pathogenesis of type C HE since the seminal study examining the role of cation exchange resins for the management of peripheral oedema in patients with cirrhosis. These resins released ammonium ions and led to neuro- logical dysfunction that we now recognize as HE. However, unlike ALF, ammonia levels do not correlate well with symptoms. In type C HE, ammonia is also metabolized within astrocytes, resulting in astrocyte swelling and increased brain water, although significant cerebral oedema is not a feature of the disease. MRI studies have shown evidence of low-grade brain oedema which is reversed with liver transplantation. Ammonia challenge in patients with cirrhosis Fig. 15.22.4.1 Pathophysiology of type A hepatic encephalopathy. H_2O, water; LPS, lipopolysaccharide; NH_3, ammonia.

 leads to decreased neuropsychological function with MRI changes suggestive of increased brain water. The classic neuropathological feature of type C HE is Alzheimer type II astrocystosis characterized by enlarged nuclei with mar- ginated chromatin. Alzheimer type II astrocytosis develops with exposure to ammonia both in cell culture, animal models, and in patients with congenital abnormalities of the urea cycle resulting in hyperammonaemia. Inflammation/infection SIRS strongly correlates with the presence and severity of HE, in- dependent of ammonia concentration. In one study, an ammonia challenge resulted in altered cognition in patients while infection was present, but not once the infection had resolved. In ammonia- fed animal models, lipopolysaccharide administration increased brain water compared to

controls, implicating synergism between ammonia and inflammation. Positron emission tomography studies have found reduced whole-brain oxygen consumption during episodes of acute HE suggesting reduced brain metabolism or an increase in inhibitory γ-aminobutyric acid tone. Studies have found induction of cerebral inflammation via injection of lipopolysaccharide caused decreased excitatory transmission with deficits in learning and memory, re- versible with glutamatergic antagonists and cyclooxygenase 2 inhibitors. Gut microbiota and endotoxaemia Patients with cirrhosis have increased gut permeability to bacteria and bacterial degradation products, resulting in bacterial transloca- tion and endotoxaemia. This results in hepatic macrophage produc- tion of proinflammatory cytokines such as interleukin 8 and TNFα, which induces systemic inflammation. Additionally, gut dysbiosis has become a well-recognized feature of cirrhosis that has been found to be independently associated with severity of liver disease and development of complications. Manipulation of the microbiome with nonabsorbable antibiotics or probiotics has been shown to re- duce hyperammonaemia, endotoxaemia, and have beneficial effects on cognition. Immune dysfunction Immune dysregulation is an increasingly recognized feature in HE and contributes significantly to systemic inflammation as well as predisposing to the development of infection. Ammonia induces neutrophil dysfunction which contributes to systemic inflammation and the susceptibility to developing infection, and has been shown to be predictive of infection, organ dysfunction, and survival at 90 days and 1 year. Clinical features HE is a complex neuropsychiatric syndrome that encompasses a wide spectrum of symptoms. The West Haven criteria describe four grades of HE increasing in severity from I to IV (Table 15.22.4.2). Grade I encompasses changes in awareness, mood, attention, cognition, and sleep pattern without disorientation or clear clin- ical findings such as asterixis. Changes to sleep pattern include in- creased daytime somnolence and reversal of the sleep–wake cycle. Obtaining collateral history from family members or regular care- givers is vital to identify subtle changes in behaviour or orientation. With grade II, the patient becomes disorientated in time and develops symptoms of lethargy and apathy. There are more obvious personality changes with episodes of inappropriate behaviour. On examination, asterixis is present. This is most clearly identified Hepatic inflammation ↑ IL-8; TNFα Bacterial translocation NH3 Portosystemic shunting Endotoxin TLR4 Systemic inflammation endotoxaemin Bacterial overgrowth Increased gut permeability Fig. 15.22.4.2 Pathophysiology of type C hepatic encephalopathy. TLR, Toll-like receptor.

section 15 Gastroenterological disorders 3084 with the patient positioned with their arms out straight with their wrists fully extended and fingers spread. Asterixis is a flapping tremor due to negative myoclonus with arrhythmic loss of posture. Subtle asterixis can be better detected through palpation. Grade III HE is associated with worsening confusion and dis- orientation to place, with reduction in consciousness from somno- lence to semistupor. The patient remains responsive to stimuli but may no longer be able to maintain their own airway. As the condi- tion deteriorates to grade IV encephalopathy, the patient becomes unresponsive to stimuli and falls into coma. There can be a rapid progression through stages of encephalop- athy, especially in patients suffering ALF. The Glasgow Coma Score (GCS) is valuable to use alongside the West Haven criteria in order to identify when intervention to manage conscious level is appro- priate, and for its ease in interdisciplinary communication. A grade of subclinical HE is also described, termed minimal HE. This condition has no clinical features of encephalopathy, but im- paired cognitive function can be elicited with neuropsychometric function testing. These tests should be conducted by experienced examiners on patients who are most likely to benefit from diagnosis, such as those with impaired quality of life or those in whom impair- ment may affect their work or public safety such as driving.

These tests examine different components of cognitive functioning and it is advised that at least two are performed. Minimal and grade I HE both lack clear and reliable clinical fea- tures and have poor interobserver reliability. As a result, these grades can also be described as covert HE. Conversely, West Haven cri- teria grade II and above have more reliable clinical features and are termed overt HE. Clinical presentations of HE can fluctuate in their time course and can be further characterized as episodic, recurrent, or per- sistent (Fig. 15.22.4.3). Recurrent HE is defined as episodes of HE that occur within 6 months or less. Persistent HE describes the continuous presence of HE symptoms. There can often be milder persistent symptoms interspersed with episodes of more severe overt HE. Some clinical syndromes often associated with extensive port osystemic shunting have been described relating to HE. These in- clude HE-related parkinsonism and hepatic myelopathy. About 25% of patients with HE have extrapyramidal symptoms including tremor, cog-wheel rigidity, bradykinesia, shuffling gait, and loss of facial expression. Hepatic myelopathy is characterized by slowly progressive spastic paresis with hyper-reflexia most commonly af- fecting the lower limbs and extensor plantar responses. Upper limb and sensory/sphincter involvement have been rarely reported. Improvement of these syndromes has been reported with closure of portosystemic shunts and liver transplantation. Differential diagnosis Due to the wide spectrum of presentation of HE, there are many possible differential diagnoses to consider. In patients presenting with features of overt HE, the differential diagnosis should include causes of delirium or altered conscious- ness (Table 15.22.4.3). Conditions that occur commonly in patients with cirrhosis include sepsis and severe hyponatraemia. Other con- siderations unrelated to underlying liver disease include central nervous system infections, uraemia, lactic acidosis, and intracra- nial bleed or stroke. Alcohol-related liver disease remains the most prevalent cause of cirrhosis in the United Kingdom. Alcohol intoxication, withdrawal, or Wernicke’s encephalopathy may present with symptoms of altered consciousness, personality change, or abnormal behaviour that may be consistent with HE. Neuroactive drugs such as opiates, benzodi- azepines, and neuroleptics should be considered. Several case reports also describe patients suffering nonconvulsive epilepsy who were initially misdiagnosed with HE, highlighting the important role of electroencephalography (EEG) in the investigation of encephalopathy. Table 15.22.4.2 Explanation of West Haven criteria for hepatic encephalopathy with comparable Glasgow Coma Scores Grade using West Haven criteria Clinical features Glasgow Coma Score 0 No abnormality apparent on clinical examination 15 I Short-term memory loss, difficulty in concentrating, and reverse of sleep–wake cycle 15 II Lethargy, apathy, drowsiness, flapping tremor (asterixis), disorientation, confusion, inappropriate behaviour 12–15 (Verbal response or obeying command typically impaired) III Stuporose but easily rousable, marked confusion, incoherent speech 6–12 IV Coma, unresponsive 3–6 (May respond to painful stimuli) IV III II I MHE 0 0 2 4 6 Time (months) Hepatic encephalopathy Grade of HE 8 10 12 Episodic Recurrent Persistant Fig. 15.22.4.3 Representation of the fluctuant clinical course over time for patients with episodic, recurrent, and persistent hepatic encephalopathy (HE). Minimal HE and grade I represent covert HE. Grades II to IV represent overt HE.

 In patients presenting with symptoms of covert HE, other causes of impaired cognition should be considered (Table 15.22.4.4). In the elderly, primary dementias are possible differentials. Chronic alcohol excess is associated with several possible causes of cognitive impair- ment such as secondary dementia due to vitamin B12 deficiency, Korsakoff’s syndrome, or directly related to alcohol excess. These patients are also at greater risk of chronic subdural haematomas and a history of trauma should be elicited. Hypothyroidism should be considered as an important revers- ible cause of cognitive impairment. Depression is common in

pa- tients with chronic disease and severe depression can present as a pseudodementia, especially in the elderly. Obstructive sleep apnoea should be considered in those presenting with increased daytime somnolence that have risk factors such as obesity and diabetes. Clinical investigation There is no definitive test or set of diagnostic criteria to establish a diagnosis of HE, which remains primarily a clinical diagnosis of ex- clusion in patients with a history or clinical evidence of liver disease. History and examination Symptoms of changes to short-term memory, mood, cognition, sleep pattern, and personality should be elicited. In overt HE, these should be forthcoming, but may require direct questioning in covert HE. Collateral history from family members or long-term carers is recommended. A past medical history of liver disease or risk factors for liver disease should be obtained, along with a full drug history. In the acute scenario, initial examination should take an 'ABCDE' approach with prompt management of the airway if compromised. An assessment of the patient's conscious level should be performed using the GCS. On examination, stigmata of chronic liver disease may be found. The development of asterixis or hyper-reflexia would suggest overt HE. Patients with grade II-IV HE may exhibit clonus. The presence of focal neurological deficits would suggest an alterna- tive diagnosis. Laboratory tests A full set of blood tests including full blood count, renal function, liver biochemistry, lactate, and coagulation screen should be per- formed to assess underlying liver function and screen for precipi- tants such as infection or gastrointestinal bleeding. Blood and urine cultures should be taken as part of a septic screen. In patients with ascites, an ascitic tap should be performed to assess for the presence of spontaneous bacterial peritonitis. Elevated blood ammonia has a strong association with HE in ALF, but has not been found to correlate well with symptoms in type C HE, hence although an elevated blood ammonia supports the diag- nosis of HE, a normal ammonia concentration does not exclude it. Imaging A plain chest X-ray should be performed as part of the septic screen. A CT head should be performed in patients presenting with acute HE, especially if there is evidence of focal neurology or the GCS is reduced to rule out intracranial bleeds, stroke, and space- occupying lesions. A contrast abdominal CT may be able to identify portosystemic shunts. In the outpatient setting, a magnetic resonance brain scan is re- commended when patients present with chronic neurocognitive dysfunction. This helps to rules out other neurodegenerative path- ology such as Alzheimer's, where hippocampal atrophy may be ob- served, and small vessel ischaemia. The finding of bilateral increased signal intensity in the lentiform nucleus and substantia nigra on MRI T1-weighted imaging is suggestive of chronic portosystemic shunting. This was previously referred to as hepatocerebral degener- ation and is believed to result from chronic manganese deposition. Although this can be seen in welders and following hyperalimenta- tion therapy, it is often considered pathognomonic of HE. Neuropsychological tests Clinical tests such as the abbreviated mental test score can be used to quickly assess cognitive function. For the diagnosis of minimal HE,

Table 15.22.4.3 Differential diagnosis for overt hepatic encephalopathy

Infective	Sepsis
	Meningitis
	Encephalitis
Metabolic	Hyponatraemia
	Hypothyroidism
	Lactic acidosis
Alcohol related	Alcohol intoxication
	Alcohol withdrawal
	Wernicke's encephalopathy
Medication	Opiates
	Benzodiazepines
	Neuroleptics
Diabetes related	Hypoglycaemia
	Diabetic ketoacidosis
	Hyperglycaemic hyperosmolar state
Neurological	Intracranial bleed/stroke
	Nonconvulsive epilepsy
	Space-occupying lesion

Table 15.22.4.4 Examples of differential diagnosis for covert hepatic encephalopathy

Primary dementia	Alzheimer's disease
	Meningitis
	Encephalitis
Secondary dementia	Alcohol related
	Vitamin B12 deficiency
	Korsakoff's syndrome
Metabolic	Hypothyroidism
	Hyponatraemia
Other	Chronic subdural haematoma
	Obstructive sleep apnoea
	Pseudodementia
	Space-occupying lesion

section 15 Gastroenterological disorders 3086 guidelines recommend the use of two psychometric or neurophysio- logical tests (Table 15.22.4.5). There is no consensus on which tests are best. They require trained staff and specialist equipment that limit their use and availability, especially in resource-poor settings. The Psychometric Hepatic Encephalopathy Score (PHES) likely represents the most accessible test in view of the lack of specialist equipment required.
Electroencephalography EEG may be useful to support a diagnosis of metabolic encephalop- athy as well as to rule out alternative diagnoses such as nonconvulsive epilepsy. In overt HE, the characteristic finding is of triphasic waves on a background of generalized slowed activity. Its role in covert HE is less clear, and studies so far recommend its use alongside other neuropsychological tests. EEG requires trained and experienced staff and may not be available in all centres.
Management Acute liver failure Patients presenting with HE in ALF are critically unwell and have the potential to deteriorate rapidly. Early discussion with a trans- plant centre is recommended, with prompt transfer of the patient if appropriate. Airway management Close monitoring of the GCS and airway is vital as patients may not be able to protect their airway and are at risk of aspiration. In patients presenting with grade III and IV HE, their airway is un- safe and they should undergo prompt endotracheal intubation and transfer to intensive care. HE and cerebral oedema The likelihood of progression to cerebral oedema and intracranial hypertension increases with grade of HE; patients with grade III have a 25 to 35% risk and patients with grade IV a 65 to 75% risk. In the intensive care environment, several neuroprotective strategies are undertaken, as detailed in Table 15.22.4.6. Management of hyperammonaemia High-volume haemofiltration is the mainstay therapy in re- ducing hyperammonaemia in ALF. There is no evidence that lactulose, rifaximin, or l-ornithine l-arginine (LOLA) has any role in ALF. Management of infection Patients should be closely monitored for signs of infection and treated promptly with empirical broad-spectrum antibiotics and antifungals to avoid development of intracranial hypertension. Management of hyponatraemia Hyponatraemia may promote the progression of HE and should be corrected. A randomized controlled clinical trial investigating the role of hypertonic saline in patients with ALF and advanced HE showed a reduction in the incidence and severity of intracra- nial hypertension. AASLD guidelines recommend maintaining a serum sodium concentration of 145 to 155 mmol/L in patients at high risk of cerebral oedema, such as those with hyperammonaemia and grade III/IV HE. Liver transplantation The definitive management of cerebral oedema with intracranial hypertension in ALF is with emergency liver transplantation, when HE resolves rapidly after transplantation.
Table 15.22.4.5 Examples of psychometric or neurophysiological tests used in the diagnosis of minimal hepatic encephalopathy Test Explanation of procedure Psychometric Hepatic Encephalopathy
Score (PHES) This is a paper and pencil-based test comprising the sum score of five subtests assessing attention, motor speed and accuracy, visual orientation, and visuospatial construction Critical flicker frequency (CFF) The patient is presented with a pulsing light that decreases in frequency (60 Hz downwards). The patient must press a button once they perceive the light pulses to have fused. The frequency when the lights fuse is measured Continuous reaction time test (CRT) The patient is presented with a series of 500-Hz tones played at random intervals of 2–6 s via headphones. The patient must press a button when they are heard. Reaction time is measured Inhibitory control test (ICT) Computer-based test where the patient is shown a series of letters and must press a button when an X is followed by a Y. Pairs of XX and YY occur to lure the patient to hit the button. The rate of response to XY pairs and lure pairs is measured Stroop test Patients are shown words describing a colour printed in a different colour. The test measures the interference between recognition reaction time to a coloured field and a written colour name SCAN test

Computerized test measuring speed and accuracy of performing increasingly complex digit recognition memory tasks Table 15.22.4.6 Neuroprotective measures that can be applied in an intensive care setting. Oxygen concentration and partial pressure of carbon dioxide is titrated through manipulation of mechanical respiration. Mean arterial pressure is achieved through titration of inotropes and fluid management. Temperature can be controlled using external heating devices Position Positioned 20–30° with minimal movement Temperature ~36°C Oxygen saturations

> 95% Mean arterial pressure 75 mmHg Pco2 4–4.5 kPa

15.22.4 Hepatic encephalopathy 3087 Type B hepatic encephalopathy Management of type B HE follows the same considerations as type C HE, detailed in the following 'Type C hepatic encephalopathy' subsection. Post-TIPS HE In patients with post-TIPS HE who do not respond to standard med- ical management, resizing or occlusion of the TIPS stent is a possible management option. This intervention, however, may worsen portal hypertension and increase their risk of variceal bleeding. The deci- sion to proceed with TIPS resizing should be made in cases with a clear diagnosis of type B HE because HE secondary to worsening liver function will not benefit from manipulation of the shunt. Spontaneous portosystemic shunt In cases of type B HE secondary to spontaneous portosystemic shunting, there are several studies describing resolution of symp- toms with embolization or endovascular closure of shunts. Type C hepatic encephalopathy General aspects Current AASLD/EASL guidelines only recommend routine inter- vention for patients with overt HE. These guidelines outline a four- pronged management approach (Box 15.22.4.2). As in ALF, patients with type C overt HE have the potential to deteriorate to coma, hence regular monitoring of their GCS and airway is required. Patients who are unable to maintain their airway should be intubated and managed in an intensive care environment. Consideration should be made to possible alternative diagnoses explaining the patient's symptoms. Reversible causes such as hypo- glycaemia should be investigated for and managed urgently. Identification and management of precipitating factors re- mains one of the most valuable interventions in the management of overt HE. In particular, patients should be investigated for signs of underlying infection. A full septic screen is appropriate, with a low threshold for initiating empirical broad-spectrum antibiotics. Electrolyte abnormalities, particularly hyponatraemia, should be corrected. Gastrointestinal bleeding should be ruled out. Patients with a history of constipation should be initiated on laxatives. The use of enemas is valuable in patients with faecal loading and in those with grade III/IV HE. Specific treatments Lactulose Lactulose is a nonabsorbable disaccharide which has historically formed the mainstay of HE management. It is metabolized by gut flora to produce lactic and acetic acid, resulting in acidification of the bowel. This promotes the conversion of absorbable gut-produced ammonia to inabsorbable ammonium and is thought to change the gut flora to nonurease bacteria, further reducing ammonia produc- tion. Its effect as an osmotic laxative is thought to be independently beneficial and has an important role in managing or preventing constipation, a recognized precipitant of HE. Lactitol is another nonabsorbable disaccharide used as an alternative in some centres. A Cochrane meta-analysis of randomized controlled trials found insufficient evidence to support the use of nonabsorbable disaccharides in acute HE. This was due to the lack of high-quality trials. With the inclusion of lower-quality trials, nonabsorbable di- saccharides were found to reduce the risk of no improvement com- pared to placebo or no

intervention. No large multicentre trials of lactulose versus placebo have been conducted, but the use of lactulose is supported by decades of clinical experience and AASLD/EASL guidelines recommend lactulose as the first-choice treatment for episodic overt HE. Rifaximin Rifaximin is a semisynthetic antibiotic based on rifamycin that is poorly absorbed by the gastrointestinal tract. A few studies have examined its use as monotherapy compared to lactulose. Although showing similar benefit, there is currently not enough evidence to recommend it for use alone.
A randomized controlled trial showed significant benefits to resolution of HE and hospital stay with rifaximin and lactulose compared to rifaximin alone. Alternative treatments Oral branched-chain amino acids (BCAAs) are thought to have a beneficial effect on HE by improving skeletal muscle metabolism of ammonia by providing a source of glutamate. A Cochrane re- view showed a beneficial effect of BCAAs, but highlighted the lack of evidence compared with established treatments. Another thera- peutic option is L-ornithine L-aspartate, (LOLA): supplied by Hepa Merz, this is available in Europe but not the United States. Given intravenously, it stimulates the urea cycle and glutamine synthesis, which are key metabolic pathways in ammonia detoxification.
A meta-analysis found LOLA to be associated with improvement in HE with reduction in ammonia levels. AASLD/EASL guidelines recommend the use of these treatments as alternative or additional agents in patients nonresponsive to conventional therapy. Secondary prevention After a first episode of overt HE, initiation of treatment to maintain remission should be considered, especially in those who are at high risk of recurrence such as those who have poor liver function, are malnourished, or have uncontrolled precipitants. Lactulose AASLD/EASL guidelines recommend lactulose for the prevention of recurrent episodes of overt HE. A randomized controlled trial showed a significant benefit with lactulose versus placebo for pre- vention of recurrence of HE in patients with cirrhosis who had re- covered from an episode of overt HE. There is some evidence that lactulose has a role in primary prophylaxis in HE, but guidelines currently only recommend considering primary prophylaxis in pa- tients who are high risk of developing the condition. Box 15.22.4.2 The AASLD/EASL recommended a
four-pronged approach to the management of type C overt hepatic encephalopathy • Management of altered consciousness • Investigate and manage alternate diagnoses • Identification and management of precipitating factors • Commencement of empirical hepatic encephalopathy treatment

 Rifaximin The use of rifaximin to prevent HE has been well examined. A ran- domized controlled trial showed in a large number of patients over a 6-month period that rifaximin maintained remission and reduced the risk of hospitalization from HE better than placebo. A systemic review and meta-analysis confirmed rifaximin to have a benefi- cial effect on HE with a possible associated reduction in mortality. AASLD/EASL recommends rifaximin as an add-on to lactulose for prevention of recurrent episodes of HE after the second episode. The National Institute for Health and Care Excellence (Guideline TA337) has authorized the use of rifaximin for reducing the recur- rence of episodes of overt HE in patients over 18 years old. Liver transplantation Patients with cirrhosis with ongoing overt HE despite optimal med- ical management have a poor prognosis and should be considered promptly for liver transplantation. Management of covert HE Several trials have examined the role of lactulose, rifaximin, and probiotics on the management of covert HE, but these studies are limited by the variations in methods to diagnose and assess im- provement in the condition. However, covert HE has been found to adversely impact patients' quality of life and driving ability. In pa- tients who have found their work compromised by covert HE symp- toms, or when there is a concern for public safety, treatment may be indicated on a case-by-case basis. Guidelines do not recommend the routine

treatment of minimal HE and covert HE. Other management considerations Nutrition Traditionally, patients suffering from HE were managed with low- protein diets on the premise that this would reduce gut-derived ammonia. However, a randomized controlled trial comparing low- protein diet with increasing increments of protein to a diet normal in protein in patients presenting with overt HE found no significant difference in HE outcome between the groups, but found higher rates of protein breakdown in the low-protein group. Patients with HE are more likely to be malnourished and have reduced muscle mass. Skeletal muscle is a site of extrahepatic am- monia metabolism and hence sarcopenia is a risk factor for HE. It has also been shown to be a poor prognostic factor in patients with cirrhosis. In view of this AASLD/EASL guidelines recommend strict energy and protein intake goals for patients with HE (Box 15.22.4.3) contained within small frequent meals throughout the day. Driving Both overt HE and covert HE have a significant impact on the patient's cognitive abilities and safety to drive. Studies have shown patients with covert HE have reduced performance in driving simulators compared to controls. There are no published guidelines, but doctors have a duty to discuss the risks of driving with any patient with HE and should ad- vise them to stop driving until they can be assessed by the Driver and Vehicle Licensing Agency in the United Kingdom. Prognosis Acute liver failure In ALF, HE is a strong independent predictor of poor outcome, with a reported odds ratio for mortality between 12 and 20. HE grade also has a significant impact on prognosis, with one study showing that patients presenting with grade I/II HE had a 52% 3-week transplant-free survival rate in comparison with only a 33% rate in patients with grade III/IV HE. Indeed, despite similar trans- plant rates, overall survival was higher in the grade I/II group, 77%, compared with the grade III/IV group, 56%. Type B hepatic encephalopathy Prognosis in patients with type B HE is primarily related to the severity of underlying liver disease. Higher mortality is associated with higher- grade HE (III/IV), which may indicate worse underlying liver function. Type C hepatic encephalopathy In patients with cirrhosis, HE is a cardinal sign of decompensa- tion and is associated with poor outcome. One follow-up study from the first episode of HE reported 42% survival after 1 year and only 23% survival at 3 years. Patients who develop episodic overt HE have an estimated 50% risk of recurrence within the first year. Factors associated with recurrence include poor liver function, the presence of minimal HE, and renal dysfunction. Grade of HE at the time of listing for liver transplant is an independent risk factor for waiting list mortality. Patients with grade III/IV HE have significantly increased 90-day mortality in comparison to patients with grade I/II HE or in the absence of HE (24.4%, 6.8%, and 3.5% respectively). Detection of covert HE is independently associated with in- creased mortality and risk of hospitalization and is associated with an increased risk of developing future overt HE. Historically, HE was thought to fully resolve following liver trans- plantation, but more recent studies have disputed this and have shown evidence of persistent cognitive impairment and demyelin- ation despite resolution of extracellular brain oedema. However, studies are difficult to interpret as many patients will have com- peting risk factors for persistent cognitive impairment such as cere- brovascular disease or chronic alcohol excess. Future developments HE remains a clinical diagnosis based on exclusion of alternative diagnoses and a holistic appreciation of the clinical features and in- vestigations suggestive of the condition. Diagnosis of minimal HE is even more complex due to the lack of solid clinical features and the variety of neurophysiological and psychometric tests available and the uncertainty associated with their interpretation. This diagnostic uncertainty hinders clinical management and research, and in the case of covert HE precludes routine intervention. To address this, fu- ture research should aim to develop highly sensitive screening tests, Box 15.22.4.3 Recommended dietary intake per kg of ideal body weight in patients with hepatic encephalopathy • Energy intake 35 to 40 kcal/kg/day • Protein intake 1.2 to 1.5 g/kg/day

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