i An update to this article is included at the end

Clinical Practice Guidelines

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EASL Clinical Practice Guidelines on the management of hepatic encephalopathy☆

European Association for the Study of the Liver*

Summary

The EASL Clinical Practice Guidelines (CPGs) on the management of hepatic encephalopathy (HE) present evidence-based answers to a set of relevant questions (where possible, formulated in PICO [patient/population, intervention, comparison and outcomes] format) on the definition, diagnosis, differential diagnosis and treatment of HE. The document does not cover the pathophysiology of HE and does not cover all available treatment options. The methods through which it was developed and any information relevant to its interpretation are also provided.

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Introduction and methods

The Governing Board of the European Association for the Study of the Liver (EASL) selected a panel of experts to prepare these Clinical Practice Guideline (CPGs) with the purpose of providing the best available evidence on diagnosis and management of hepatic encephalopathy (HE). The EASL Governing Board and the CPG panel went on to identify a Delphi panel of 36 reviewers including 24 hepatologists/gastroenterologists/internists, 5 nurses, 2 methodologists, 1 neurologist, 1 neurophysiologist, 1 neuropsychologist, 1 neuroradiologist, 1 neuroscientist and 1 patient with a background in psychology, all with an interest in HE; 24 participated in all review steps. The CPG panel was first assigned the task of identifying the most relevant topics, in the form of PICO [P Patient, Population, or Problem; I Intervention, Prognostic Factor, or Exposure; C Comparison or Intervention (if appropriate), O Outcome] questions, which resulted in 29 questions; on first Delphi panel review, some of these questions were modified/removed and some added, resulting in the 31 final questions which are presented in the current document. While the panel agreed to the PICO format, for a number of topics the format was not applicable and/or the evidence insufficient. Therefore, intermediate format questions were accepted and treated as such.

An extensive literature search of publications in English was performed by an experienced research librarian (Helene Sognstrup, Royal Danish Library Aarhus) using PubMed, Embase and the Cochrane Library.

Features and limits: Language: English (not possible in Cochrane); Publication year: All years; Publication type: Clinical, trials, Randomized controlled trials.

((“Hepatic Encephalopathy”[MeSH Terms] OR “Hepatic Encephalopathy”[Text Word] OR neuropsycholog*[Text Word] OR “Psychometrics”[Mesh] OR “Cognition Disorders”[MeSH Terms] OR “Cognition”[MeSH Terms]) AND (((“Liver Diseases”[MeSH Terms] OR “liver diseas*”[Text Word]) AND (“Chronic Disease"[MeSH Terms] OR "chronic disease*"[Text Word])) OR ("Liver Cirrhosis"[MeSH Terms] OR "Liver Cirrhosis"[Text Word])) AND (“clinical trial”[Title] OR “randomi*”[Title])) OR ((“Hepatic Encephalopathy”[MeSH Terms] OR "Hepatic Encephalopathy"[-Text Word] OR neuropsycholog*[Text Word] OR “Psychometrics”[Mesh] OR “Cognition Disorders”[MeSH Terms] OR "Cognition"[MeSH Terms]) AND (((“Liver Diseases"[MeSH Terms] OR "liver diseas*"[Text Word]) AND ("Chronic Disease"[MeSH Terms] OR "chronic disease*"[Text Word])) OR ("Liver Cirrhosis"[MeSH Terms] OR "Liver Cirrhosis"[Text Word])) AND ("clinical trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH Terms] OR "Clinical Trials as Topic"[MeSH Terms]))

Four hundred and sixteen references were retrieved from PubMed, 326 from Embase and 257 from the Cochrane Library, for a total of 999 references, which were then reduced to 726 after deduplication. All panellists read the retrieved literature and searched for further literature, where appropriate. Each panellist chose a number of PICO questions based on their specific expertise; where overlap/disparities were present agreement was sought and easily reached.

The evidence was evaluated and scored, and the recommendations produced following EASL’s methodological recommendations for CPGs (Tables 1 and 2)[1]; definitions and statements were not graded. After a first in-person meeting, due to the COVID-19 pandemic, all subsequent meetings were held by teleconference. All recommendations were discussed and approved by all panellists. The Delphi panel examined the recommendations. Returning scores were graded as follows: less than 50% approval: re-write recommendation and resubmit to the Delphi panel; 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; 75-90% approval: no need to re-write the recommendation but the document will take into account the comments; ≥90% approval: assumed as consensus, no change needed but small corrections possible. To consider a question approved, an

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° Clinical Practice Guideline Panel: Chair: Sara Montagnese; EASL Governing Board representative: Pierre-Emmanuel Rautou; Panel members: Manuel Romero-Gómez, Fin Stolze Larsen, Debbie L. Shawcross, Dominique Thabut, Hendrik Vilstrup, Karin Weissenborn.

* Corresponding author. Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 22 807 03 60; fax: +41 (0) 22 328 07 24.
E-mail address: easloffice@easloffice.eu.

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Table 1. Level of evidence based on the Oxford Centre for Evidence-based Medicine.

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic Reviews (SR) (with homogeneity) of Randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Systematic Reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (Mechanism-based Reasoning)	Any estimate of effect is uncertain

Table 2. Grades of recommendation.

Grade	Wording	Criteria
Strong	Must, shall, should, is recommended Shall not, should not, is not recommended	Evidence, consistency of studies, risk-benefit ratio, patient preferences, ethical obligations, feasibility
Weak or open	Can, may, is suggested May not, is not suggested	

agreement from at least 75% of Delphi panel members was required.

When neutral answers were excluded, all questions received a score above 75%, thus there was no formal need for revision. However, several specific comments on the recommendations and the free comments provided by the Delphi panel were extremely useful and important, so the recommendations and the overall document were modified accordingly, and 2 further Delphi reviews performed, together with a review by the EASL Governing Board.

Despite constant debate on HE classification, the panel felt that there were no grounds nor any actual need to revise the classification previously proposed in the joint 2014 EASL-AASLD guideline,[2] with particular reference to the indication that HE should be described by type, grade, time course and precipitant (when identified). As for grade and, again, despite ongoing discussions on the semantics and appropriateness of the term Covert as raised by Jalan and Rose,[3] this was maintained for 3 main reasons: i) continuous changes in HE nomenclature seem to have been more damaging than useful in the past, making it difficult for the community at large to become familiar with the meaning/use of the different terms proposed over time[4]; ii) the 2014 definition of overt as ≥ West Haven grade II (thus excluding the vague and operator-dependent grade I)[5] was undoubtedly a step forward for the purposes of both clinical research and multicentre trials; iii) as the diagnosis of grade I HE is vague and operator-dependent, the border between minimal HE and covert HE has always, by definition, been difficult to trace, making the literature on minimal HE largely relevant to both terms.[6] Hence our decision to use the term covert also with reference to evidence and literature produced in years where the most commonly used terms were minimal and/or subclinical HE. Finally, as several of the Delphi panel experts highlighted in their free comments, some more specific topics (for example sedation recommendations during endoscopy in patients with HE) and, more importantly, a number of drugs which have shown promise in HE are not covered by this guideline, as they were not the subject of specific PICO questions. A short, pragmatic review on these drugs has recently been published.[7]

Questions and recommendations

In patients with HE, can pre-defined classification criteria improve diagnostic accuracy and the effects of treatment?

Recommendation

- HE should be qualified as type A in patients with acute liver failure, type B in those with portosystemic shunt, and type C in those with cirrhosis. Overt HE should be qualified as recurrent if ≥2 bouts occur within 6 months and persistent if the patient does not return to her/his baseline performance between bouts. The severity of mental alterations, any identified precipitants and the presence of portosystemic shunts should also be recorded as these factors impact upon both diagnostic accuracy and treatment **(LoE 5, strong recommendation, 96% consensus).**

The currently recommended classification of HE is based on the severity of the underlying liver disease and/or presence of portosystemic shunting, the severity and time course of mental alterations and any identified precipitating events. Thus “type A” HE is due to acute liver failure, “type B” to portosystemic shunt without significant liver disease and “type C” to cirrhosis with or without portosystemic shunt.[2] In terms of its severity, HE is qualified as covert (minor or no signs/symptoms but abnormalities on neuropsychological and/or neurophysiological tests) or overt (grades II or over according to the West Haven criteria[2]). Finally, in terms of its time course, overt HE is classified as episodic, recurrent (more than one episode over a period of 6 months) or persistent (no return to normal/baseline neuropsychiatric performance in between episodes).[2] Recognised precipitating events are constipation, gastrointestinal bleeding, infections, hyponatremia, and dehydration/diuretic overdose.[8] The presence of portosystemic shunts facilitates the occurrence of HE and is associated with more severe forms.[9] All such information should be recorded when an episode of HE occurs, as it has both therapeutic and prognostic implications. It is reasonable to assume that a classification based on the above

criteria may improve diagnostic accuracy and treatment outcome.

In patients with HE, are the West Haven criteria and Glasgow coma scale appropriate for grading?

Recommendation

- The West Haven criteria should be used for HE grading when at least temporal disorientation is present (*i.e.* from West Haven grades ≥2). In patients with no or mild neuropsychiatric abnormalities (*i.e.* not meeting the criteria for the diagnosis of HE grades ≥2 based on the West Haven criteria), a neuropsychological/neurophysiological or therapeutic test should be used to diagnose covert HE. In patients with grades III-IV West Haven criteria, the Glasgow coma scale should be added **(LoE 5, strong recommendation, 96% consensus).**

The diagnosis of overt HE is usually straightforward in clinical practice. However, grading and staging is mandatory, mainly for monitoring. West Haven and Glasgow coma scales have been utilised for many years.[5,10] No comparative analysis has been published yet. The West Haven scale is easy to use in clinical practice, at least from grade II upwards and especially with its semi-quantitative equivalents.[2,11] However, in the clinical setting, it has often been used in an intuitive way, leading to discrepancies in grading between observers. In patients with HE and impaired consciousness, including those managed in an intensive care unit, the Glasgow coma scale should be added.

How does the term "brain failure" in patients with acute-on-chronic liver failure relate to HE?

Recommendation

- The term "Brain Failure" should be replaced with the term "acute encephalopathy", in accordance with international guidelines on delirium. Acute encephalopathy should not be used as a synonym for HE in patients with acute-on-chronic liver failure because while it may be accounted for by HE, there may be alternative or concomitant causes for its development **(LoE 4, strong recommendation, 91% consensus).**

The term "brain failure" first appeared in hepatology in 2014 as one of the organ failures defining patients with acute-on-chronic liver failure.[12] The term is descriptive, it has no pathophysiological connotation, it does not exist in standard neurological terminology, and it may be considered an equivalent of the more correct and more commonly utilised term *acute encephalopathy*.[13] Acute encephalopathy refers to a pathophysiological process, and can translate clinically speaking into subdelirium, delirium or coma, depending on the severity of symptoms. Since the current definition of HE implies that HE is *caused by* and not only *associated with* liver failure,[2] the terms HE and acute encephalopathy are not interchangeable. Acute encephalopathy may be accounted for by HE, either on its own or in association with other forms of encephalopathy.[14–16] It remains important for management purposes that each form of acute encephalopathy is treated according to its underlying cause.[17] By contrast, taking a simplistic approach to the neuropsychiatric alterations exhibited by patients with liver failure[14] may stand in the way of validating the results of clinical trials of novel drugs, because no drug can be expected to target a large number of pathophysiological processes and/or to be tested reliably within a context of unclear diagnoses.

In patients with cirrhosis, do the features and prognosis of HE depend on aetiology of cirrhosis?

Recommendation

- Patients with HE should not be classified based on the aetiology of their underlying liver disease **(LoE 4, strong recommendation, 93% consensus).**

The definition of HE does not consider the underlying cause of liver failure. However, aetiologies such as alcohol, viral hepatitis, and metabolic dysfunction-associated fatty liver disease (MAFLD) can impact brain function through mechanisms different from those directly linked to liver failure.[18–20] Furthermore, conditions such as diabetes and age could influence the risk of HE. Alcohol is neurotoxic in itself, making it difficult to distinguish the contribution of aetiology *vs.* liver dysfunction. Likewise, MAFLD is becoming the most common cause of cirrhosis and such patients may show impaired neurocognitive function and lower brain volume even in non-cirrhotic stages.[21] Some patients with MAFLD can exhibit hyperammonaemia and astrocytic and microglial activation in the absence of cirrhosis.[21–25] In viral hepatitis, neuropsychiatric patient-reported outcomes, such as depression or loss of attention, are independent of disease severity. The abnormalities on brain imaging differ from other aetiologies, possibly relating to viral replication in endothelial cells, astroglia and microglia, causing neuroinflammation.[26] Lastly, patients with porto-sinusoidal hypertension can suffer from HE in the absence of liver dysfunction, mainly owing to large portosystemic shunts. In conclusion, aetiology probably does have an impact on brain function together with medications, ageing and comorbidities, and formulating a differential diagnosis is challenging. Nevertheless, in multivariate analysis, aetiology has not emerged as an independent variable predicting risk of overt HE in the majority of studies.[27]

In patients with suspected HE, can the exclusion or identification of alternative or additional causes of neuropsychiatric impairment improve prognostic accuracy and the results of treatment?

Recommendation

- In patients with suspected HE, alternative or additional causes of neuropsychiatric impairment should be identified to improve prognostic accuracy and the results of treatment **(LoE 4, strong recommendation, 100% consensus).**

There is no clinical study to answer this question. However, a correct diagnosis is the precondition for rational therapeutic and prognostic evaluation. It should be emphasised that HE might occur on top of a pre-existing disease such as, for example, dementia. Patients with suspected HE should therefore undergo the same standardised diagnostic evaluation as any other patient with altered consciousness. This is emphasised by the finding of extrahepatic causes for acute encephalopathy in 22% of patients with liver disease suspected of HE.[28] These causes included infections (urinary infection, pneumonia), perfusion disorders (stroke, myocardial infarction), other neurological causes (subdural haematoma) and several others. The diagnostic work-up might include blood tests for glucose, electrolytes, inflammatory markers (*e.g.* C-reactive protein), full blood count, blood alcohol level and ammonia, thyroid-stimulating hormone, brain imaging, as well as screening for psychoactive drugs, lumbar puncture to rule out meningitis or encephalitis, and an electroencephalogram (EEG) to exclude non-convulsive seizures. Concomitant disorders that may present with HE-like symptoms must be considered, as well as HE precipitating factors. Concomitant disorders that must be considered are infections, hyponatremia, renal dysfunction, hypo- or hyperglycaemia, alcohol or drug abuse, intracranial bleeding, thiamine deficiency, malnutrition or hypothyroidism, as reported.[29–31] Differential diagnosis is even more important within the context of a poor or partial response to anti-HE treatment.

Does mild cognitive impairment (MCI) of an aetiology other than liver dysfunction show features that are different from those of covert HE in patients with cirrhosis?

Statement

- Features of covert HE and MCI of an aetiology other than liver dysfunction show significant overlap **(LoE 2, 90% consensus).**

MCI is an intermediate state between normal ageing and dementia.[32] The differential diagnosis of covert HE is especially relevant in patients with liver disease over the age of 60 years. The prevalence of MCI in this age group is up to 20%[33] but daily functioning in the presence of MCI is largely preserved,[34] in stark contrast to the severe daily functional impairment of patients with covert HE. MCI may present with memory dysfunction or alterations of complex attention, executive function, learning, language, perceptual–motor function, or social cognition and has usually been noticeable for at least 6 months, in contrast to the cognitive impairment of covert HE which is often fluctuating. Considering the features of covert HE – deficits in attention, concentration, visuo-spatial orientation and coordination, motor speed and accuracy –[35] there is an obvious overlap in symptomatology with MCI, but there are also some differences. Language, for example, is preserved in patients with covert HE as is memory, while an alteration of motor speed and accuracy is not typical of MCI.[32] Since comorbidities are frequent in patients with cirrhosis, especially the elderly, abnormal psychometric test results cannot be interpreted solely as an indication of covert HE. A possible overlap of comorbidities has to be considered, and finally a diagnosis of covert HE should be reconsidered in the context of response to HE therapy.

In patients with delirium, is ammonia measurement useful for purposes of diagnosis, differential diagnosis, treatment and prognosis?

Recommendation

- In patients with delirium/encephalopathy and liver disease, plasma ammonia measurement should be performed, as a normal value brings the diagnosis of HE into question **(LoE 4, strong recommendation, 95% consensus).**

Ammonia plays a central role in the pathophysiology of HE. In principle, if a patient is normoammonaemic, they do not have a sufficient degree of hepatic failure and/or portosystemic shunting to justify a working diagnosis of HE. However, there has been much debate on the use of ammonia measurement in clinical practice.

Diagnosis. Blood ammonia levels correlate with the severity of HE, but patients without manifest HE and even without liver disease can display hyperammonaemia.[36,37] Moreover, ammonia may remain elevated after clinical HE resolution.[38,39] However, a normal blood ammonia level has negative predictive value,[36,40] and normal ammonia in a patient with cirrhosis and delirium should prompt renewed or further differential diagnostic work-up for other causes of delirium. Hence, plasma ammonia measurement, when measured correctly, should be performed in patients with acute encephalopathy and liver disease and is considered to have a high negative predictive value in relation to a working diagnosis of HE.

Treatment. The role of ammonia measurement in guiding HE treatment has not been well studied. In clinical trials, patients are often not categorised by hyperammonaemia, and ammonia analyses are often not systematically performed or timed.[39] This is debatable if one is using drugs which are expected to lower ammonia levels. Ammonia lowering is inconsistently associated with clinical treatment response, and ammonia levels are not used to monitor therapy. A *post hoc* analysis of patients with cirrhosis and 2 episodes of overt HE showed that the level of ammonia after recovery was predictive of the onset of new episodes of HE, even with mild hyperammonaemia. Hospitalisation rates were shown to increase in patients with ammonia 1.5x the

upper limit of normal.[41] However, these findings were not confirmed in a recent study.[42] Hence, tailoring HE therapy using ammonia monitoring cannot be routinely recommended.

Prognosis. Hyperammonaemia is associated with decreased transplant-free survival from acute decompensation of cirrhosis, although the prognostic value of ammonia in patients with cirrhosis and acute encephalopathy remains unclear. A recent study in acute-on-chronic liver failure suggested a prognostic role of ammonia in patients with overt HE.[37]

Should patients with cirrhosis and delirium undergo cerebral imaging for the purposes of diagnosis, differential diagnosis and treatment?

Recommendation

- In patients with delirium/encephalopathy and liver disease, brain imaging by CT scan or MRI should be performed in case of diagnostic doubts or non-response to treatment **(LoE 5, strong recommendation, 96% consensus).**

Diagnosis. There is no specific radiological diagnostic sign of HE on a cerebral CT scan in patients with delirium. However, the technique may provide other relevant information, especially of the low-grade diffuse brain oedema related to hyperammonaemia. The CT scan can measure the gravity of cerebrospinal fluid and thus contribute towards differential diagnosis.[43,44] A CT scan can also reveal brain atrophy, which participates in deteriorating neurological status in patients with liver disease,[45,46] although atrophy is more closely related to the cause of liver disease – alcohol and metabolic syndrome – than to HE. Multimodal brain magnetic resonance imaging (MRI), including at least magnetic resonance spectroscopy, can identify a metabolic profile with relatively high specificity for HE (see below). However, accessibility to the modality is restricted to large units. Moreover, the examination usually requires general anaesthesia in patients with delirium. Hence, brain MRI is not recommended for the diagnosis of HE in patients with delirium.

Differential diagnostics. Brain imaging is always warranted if there is clinical suspicion of a cerebral lesion or haemorrhage as is often the case in alcohol-related cirrhosis (relative risk for intracerebral bleeding at alcohol overuse above 5).[47]

Treatment. Brain CT or MRI have not been evaluated for guiding or monitoring treatment of HE. This may change with the emergence of improved techniques and software that may serve as surrogate markers in the future.

In patients with cirrhosis, do any brain imaging methods provide results proving HE?

Statement

- No cerebral imaging proves a diagnosis of HE **(LoE 4, 96% consensus).**

CT scan. There are no specific features of HE on brain CT scan.

Structural MRI. Most patients with cirrhosis or portosystemic shunts present with bilateral symmetric pallidal hyperintensities in the T1-weighted MR spin echo sequence, while the T2-weighted images are normal[48,49]. The signal intensity is probably related to manganese accumulation resulting from the shunt, which does not seem to have a pathophysiological role in HE itself.[48] Hyperintensities may increase after transjugular intrahepatic portosystemic shunt (TIPS) placement and reverse following improvement of liver function, occlusion of congenital portosystemic shunts, or liver transplantation. This suggests that pallidal intensity may be related to portal hypertension rather than HE. Conventional brain MRI techniques do not show T2-weighted signal-intensity abnormalities representing the slight cerebral oedema that may be present in patients with type C HE. 1H-magnetic resonance spectroscopy[50–53] has been shown to be useful in the differential diagnosis of HE. Low levels of myoinositol and choline with high glutamine content have been associated with HE.[54]

In patients with cirrhosis, should covert HE be screened for in the clinic and/or ward, and how?

Recommendation

- In patients with cirrhosis and no history of overt HE, screening for covert HE should be performed with tests for which experience/tools and local norms are available. As the only bedside test available to date, the Animal Naming Test is worthy of further study and validation **(LoE 4, strong recommendation, 83% consensus).**

The diagnosis of covert HE is relevant because the condition occurs in 30-70% of patients with cirrhosis (to some extent depending on test methods and cut-off values), is associated with poor quality of life,[55–57] reduced socio-economic potential,[58] and, most importantly, with an increased risk of developing overt HE over time.[55,59–61] Patients with covert HE have been shown not to drive as safely as unimpaired patients with cirrhosis,[62] although driving ability is difficult to establish at a single patient level. Lastly, covert HE could impact on cirrhosis progression[63] and overall survival.[64]

In patients without previous overt HE episodes, covert HE may predict overt HE, while in those with previous overt HE episodes, subsequent overt HE episodes depend more on the severity of liver dysfunction and/or portosystemic shunting.[65] A genetic risk score combining previous bouts of overt HE, genetic profile and liver dysfunction has been used to calculate the risk of HE during follow-up.[27]

How to screen covert HE? Covert HE affects multiple facets of mental functioning, which may or may not be impaired to the same degree at any given time. Thus, the diagnosis is often better based on more than one test, to be chosen depending on available local norms/expertise.[66] However, there is no gold standard, and very little data on how to combine and interpret different tests and their outcomes. Concordance between tests is low because they assess different pathways.[64] Tests can be neuropsychological (paper & pencil or computerised) or neurophysiological.[67] Neuropsychological tests have the advantage of being closer to the disability one is attempting to measure. However, they are prone to learning effects and affected by both age and educational attainment; thus, the availability of pertinent local

norms is crucial. The neuropsychological Animal Naming Test (*i.e.* the number of animals listed in 60 seconds, no equipment required) has recently been shown to compare favourably with more established covert HE measures,[35] and to predict overt HE.[68]

In patients with cirrhosis, does screening for covert HE enable treatment initiation and overt HE prevention?

Recommendation

- Patients with covert HE should be treated with non-absorbable disaccharides **(LoE 3, strong recommendation, 92% consensus).**

Covert HE is a strong risk factor for overt HE and responds well to anti-HE interventions.[69] It is therefore expected, but not yet proven in randomised-controlled trials (RCTs), that treatment will result in a reduction of overt HE episodes, which would add to the arguments for screening. The pathophysiology of any degree of HE is believed to be the same; covert HE is a risk factor for overt HE and, by and large, there is a progression in neuropsychological and neurophysiological abnormalities when moving from covert to overt HE. The difference between clinically detectable minor cognitive abnormalities (grade I) and abnormalities that require tests to detect (minimal) is often difficult to establish. This may speak in favour of considering both conditions as one entity (covert HE), including for the purposes of treatment initiation. There is evidence of beneficial effects of anti-HE strategies on neuropsychological and neurophysiological performance in several studies[69–77] and some network meta-analyses.[78–81] However, there are no robust data to confirm that treatment of covert HE also results in a reduction of overt HE risk. On the other hand, in a situation where covert HE is suspected, even if not confirmed, treatment with non-absorbable disaccharides (and/or rifaximin) could be initiated and, if beneficial, also used as confirmation of the diagnosis (*ex juvantibus*).

In patients with liver failure and HE, are liver-support systems of proven benefit for HE?

Statement

- In patients with liver failure and overt HE, albumin dialysis ameliorates HE and can be considered. The impact on prognosis is, however, uncertain and further study is warranted **(LoE 2, 77% consensus).**

An artificial liver assist device would be valuable to resolve HE by removing neurotoxins when liver function is impaired, especially if it also improves the prospects of survival. Several studies show that high-volume plasma exchange improves the grade of HE and confers a survival benefit in patients with acute liver failure, but this is not demonstrated in patients with cirrhosis.[82] The removal of both water-soluble and lipophilic substances from the blood by albumin dialysis, *i.e.* the molecular adsorbent recirculating system (MARS) device, has been shown in 3 RCTs and a meta-analysis (on raw data of these trials) to result in a faster reduction in the grade of HE in cirrhosis[83,84] but with only a modest impact on survival.[85]

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

Recommendation

- In patients with HE, all measures to control progression of the underlying liver disease should be undertaken **(LoE 4, strong recommendation, 100% consensus).**

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.[86] Decompensation usually accompanies progression of the underlying liver disease which determines short- and long-term prognosis.[87,88] 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?

Recommendation

- In patients with HE, precipitating factors should be sought and managed **(LoE 2, strong recommendation, 100% consensus).**

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.[89] Specific treatment of HE has little prospect of success without management of precipitating factors. It remains uncertain if successful treatment of an episode of HE in itself improves prognosis. 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[90] and rapid resolution of constipation[91,92] have been shown to improve recovery from an episode of overt HE.

In patients with overt HE, which criteria should be used to guide admission to an intensive care unit (ICU) to improve outcome?

Recommendation

- Patients with overt HE grade 3 and 4 are at risk of aspiration and should be treated in the ICU. No single marker can identify patients who will benefit from ICU admission, and referral relies on clinical judgement **(LoE 4, strong recommendation, 96% consensus).**

The clinical course of patients with HE stage 3-4 is unpredictable and often calls for a rapid decision regarding escalating monitoring and treatment, a clinical setting that speaks in favour of care in a high dependency or intensive care environment.[93] Relatively old studies showed a reluctance towards admitting such patients to the ICU.[94,95] However, several prognostic scores, *i.e.* model for end-stage liver disease (MELD), APACHE II (Acute Physiology and Chronic Health Evaluation II) and CLIF-C (Chronic Liver Failure consortium) organ failure, are now available and can help identify patients with an unacceptably high predicted mortality, in whom ICU care is not warranted due to futility.[96–99] Thus, overt HE in a patient with cirrhosis is not an absolute contraindication for admission to the ICU as it is potentially fully reversible. In patients with HE grade 3-4, and a Glasgow coma score less than 7, respiratory function is endangered as the patient is unable to protect their airways. In such cases, management in the ICU is recommended unless other factors speak against it.

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

Recommendation

- Patients with recurrent or persistent HE should be considered for liver transplantation and a first episode of overt HE should prompt referral to a transplant centre for evaluation **(LoE 5, strong recommendation, 85% consensus).**

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.[100] 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.[101,102] 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.[103–105] However, this approach is not widely used in Europe because of the limited availability of donor livers and strict allocation policies. The development of overt HE has been associated with poor transplant-free survival[86,106]; thus, a first episode of overt HE should prompt referral to a transplant centre for an initial evaluation.

In patients who have had a first episode of overt HE, should secondary prophylaxis be initiated to prevent further episodes?

Recommendations

- 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 **(LoE 1, strong recommendation, 96% consensus).**
- 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 **(LoE 2, strong recommendation, 92% consensus).**

An open-label RCT showed that patients who had recovered from an episode of overt HE and were receiving lactulose had a 14-month HE recurrence risk of 20% *vs.* 47% among those who did not receive lactulose.[107] A recent systematic review and network meta-analysis of a total of 1,828 participants demonstrated that lactulose was effective at preventing overt episodes of HE with only mild gastrointestinal adverse effects.[79] An updated Cochrane review,[80] evaluating 38 trials, demonstrated a beneficial effect of lactulose on preventing overt episodes of HE (risk ratio [RR] 0.58, 95% CI 0.50 to 0.69; 1,415 participants; 22 RCTs) but only 2 of these RCTs specifically addressed the effectiveness of lactulose in the secondary prophylaxis of overt HE.[107,108]

Rifaximin compared to placebo decreased the risk of recurrence of overt HE in patients with cirrhosis and ≥2 episodes of overt HE within the previous 6 months, with HE episodes occurring in 22.1% of patients in the rifaximin group *vs.* 45.9% in the placebo group (number needed to treat 4) (hazard ratio 0.42; 95% CI 0.28 to 0.64; p <0.001). Rifaximin also decreased the risk of hospitalisation (13.6%) *vs.* placebo (22.6%), with a number needed to treat of 9; of these patients, 91% were on concurrent lactulose therapy, supporting the use of rifaximin in addition to lactulose for the prevention of HE after a second overt HE episode.[109] In a systematic review and meta-analysis including this trial and one further smaller RCT which did not show benefit,[110] overall, rifaximin had a beneficial effect on the secondary prevention of overt HE (RR 1.32; 95% CI 1.06 to 1.65).[111]

Due to the very low overall quality of published trials, there is no evidence for the use of probiotics compared with lactulose

and no RCT has examined probiotics in the secondary prevention of overt HE.[112]

Branched-chain amino acids have a beneficial effect on HE (RR 0.73, 95% CI 0.61 to 0.88; 827 participants; 16 trials; high quality of evidence)[113] but, in the only high quality RCT to date, they did not prevent recurrence in patients with a previous episode of overt HE.[114]

Should prophylaxis of HE be used in an acute bleeding episode in patients with cirrhosis?

Recommendation

- 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 **(LoE 1, strong recommendation, 85% consensus).**

Gastrointestinal bleeding often precipitates HE, and HE is generally multifactorial in nature (liver failure, hyperammonaemia, systemic inflammation and infection). The relationship between gastrointestinal bleeding and increase in blood ammonia is well established.[115,116] A recent open-label single-centre randomised study showed that lactulose treatment significantly reduced the incidence of HE in patients with gastrointestinal bleeding (14% *vs.* 40 %, p <0.03), without any effect on survival (8.5% *vs.* 14%, p = n.s.).[117] Another single-centre open-label randomised study also suggested that lactulose significantly reduced HE incidence (3.2% *vs.* 16.9 %, p <0.02); the factors independently associated with the occurrence of HE were Child-Pugh score and lactulose treatment.[118] The meta-analysis of those 2 trials confirmed the beneficial effect of lactulose on the prevention of HE during gastrointestinal bleeding (7% *vs.* 28%, p <0.01), though it was not associated with any survival benefit.[119] Mannitol by mouth has also been shown to work in this context, also by comparison with paromomycin plus lactulose.[120,121] In patients with gastrointestinal bleeding, broad-spectrum antibiotic prophylaxis also had a beneficial effect on survival, especially in patients with Child-Pugh C cirrhosis. However, the efficacy of antibiotic prophylaxis on HE occurrence has not been studied.

Should prophylaxis of HE be used before TIPS placement in patients with cirrhosis?

Recommendation

- In patients with cirrhosis and previous episodes of overt HE, rifaximin can be considered for prophylaxis of HE prior to non-urgent TIPS placement. Non-absorbable disaccharides, as a stand-alone or in combination, are worthy of further study in this context **(LoE 2, strong recommendation, 82% consensus).**

One of the main drawbacks of TIPS for the treatment of portal hypertension-related complications is the increased risk of HE. On average, an episode of overt HE occurs in 35% to 50% of patients after TIPS.[122–124] Mortality is more than doubled in patients with early overt HE (hazard ratio 2.75; 95% CI 1.75-4.32; p <0.001),[123] which was confirmed in a meta-analysis.[124]

This risk of HE after TIPS may be nearly halved using a smaller diameter covered stent.[125] HE developed in significantly more of those with a stent >8 mm compared to 6-7 mm (54% *vs.* 27%; p = 0.015),[126] but the benefit of placing smaller stents has not been confirmed in all studies.[127]

Whilst a previous RCT comparing lactitol 60 g/day with rifaximin 1,200 mg/day and no treatment did not show pharmacological therapy to be effective for prophylaxis during the first month after TIPS placement,[128] a large double-blind placebo-controlled RCT supports the use of rifaximin to prevent post-TIPS HE[129]: in 197 patients with cirrhosis undergoing TIPS for intractable ascites or prevention of variceal rebleeding, rifaximin 600 mg twice daily significantly reduced the incidence of an overt HE episode over the following 168 days (53% *vs.* 34%) (*post hoc* RCT analysis). In this trial, rifaximin was started 14 days prior to TIPS placement and continued for approximately 6 months. The potential benefit of rifaximin 6 months after TIPS and beyond remains to be investigated. Human albumin solution has no impact on HE occurrence after TIPS.[130]

When should prophylactic therapy for HE be discontinued in patients with cirrhosis?

Recommendation

- In patients with a history of overt HE with improvement of liver function and nutritional status and in whom precipitant factors have been controlled, discontinuation of anti-HE therapy should be considered on an individual basis **(LoE 5, weak recommendation, 77% consensus).**

No RCT is available to demonstrate the beneficial impact of stopping prophylactic therapy. In patients with a history of overt HE whose liver function[131] and/or nutritional status[132] has improved, or in those patients whose history of overt HE was due to a precipitant factor which will not recur (for example a patient with a history of overt HE precipitated by gastrointestinal bleeding whose varices have been obliterated) discontinuation of therapy can be considered on a case-by-case basis.

In patients with HE, is zinc supplementation a treatment option to improve mental status?

Recommendation

- In patients with HE, routine zinc supplementation is not recommended **(LoE 2, strong recommendation, 95% consensus).**

Tissue zinc concentrations have been shown to be reduced in patients with cirrhosis and zinc has been implicated in the

pathogenesis of HE.[133,134] However, data on the effects of zinc supplementation on mental performance are conflicting[133,135–140] and supplementation, as a rule, cannot be recommended as part of HE management.

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

Recommendation

- In patients with HE, demonstrated or suspected vitamin/micronutrient deficiencies should be treated, as they can compound HE **(LoE 4, weak recommendation, 88% consensus).**

Patients with both alcohol- and non-alcohol-related cirrhosis are prone to deficiencies in water-soluble vitamins, particularly thiamine. Post-mortem evidence of Wernicke's encephalopathy is often observed, even in the absence of a history/clinical signs during life.[141] 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.[142] However, good-quality data on their prevalence and/or need for correction are limited, as routine vitamin/micronutrient status is not easily assessed in patients with cirrhosis. Nevertheless, a course of oral multivitamin supplementation could be justified in patients with decompensated liver disease.[143] Finally, one should always be reminded that vitamin/micronutrient deficiencies may cause a metabolic encephalopathy which can accompany but should not be confused with HE.

In patients with recurrent/persistent HE, is the identification and, where possible, the obliteration of portal-systemic shunts a treatment option to improve outcome?

Recommendation

- Obliteration of accessible portal-systemic shunts in patients with cirrhosis with recurrent or persistent HE (despite adequate medical treatment) can be considered in stable patients with a MELD score <11 **(LoE 4, weak recommendation, 100% consensus).**

Large spontaneous portal-systemic shunts are associated with recurrent or persistent HE in cirrhosis. Up to one-third of patients with cirrhosis have large (>8 mm) or smaller portal-systemic shunts on imaging. Almost 50% of these are splenorenal shunts. HE was reported in 48% of patients with large portal-systemic shunts and 34% of patients with small portal-systemic shunts.[144] Portal-systemic shunts with a total surface area >83 mm^2 increase the risk of overt HE and mortality in patients with cirrhosis.[145] Only 2 small retrospective cohort studies including a total of 58 patients have examined the utility of shunt obliteration.[146,147] Shunt embolisation in patients with recurrent or persistent HE who were diagnosed with a single large portal-systemic shunt resulted in almost 60% of patients being free of HE at 100 days and almost 50% remaining free of HE for 2 years in a European multicentre cohort study.[146] Hospitalisation rate and HE severity were also decreased. MELD score was the strongest positive predictive factor of HE recurrence, with a cut-off of 11 used for patient selection to ensure safe embolisation without an increase in *de novo* development or aggravation of pre-existing varices, portal hypertensive gastropathy, or ascites. The success of this intervention therefore seems to be dependent on whether there is sufficient functional liver mass to accommodate redirected portal flow.[146,147] A trial of shunt obliteration by coil-assisted retrograde transvenous obliteration has also shown extremely promising results and limited side-effects in patients with highly recurrent or persistent HE.[148] In conclusion, obliteration of accessible portal-systemic shunts in patients with cirrhosis with recurrent or persistent HE can be considered in stable patients with a low MELD score and no obvious contraindications.

In patients with recurrent/persistent HE, is the replacement of animal protein with vegetable and dairy protein a treatment option to improve outcome?

Recommendation

- In patients with recurrent/persistent HE, replacement of animal protein with vegetable and dairy protein can be considered, provided that overall protein intake is not compromised and that patient's tolerance is considered **(LoE 4, weak recommendation, 83% consensus).**

While the rationale for the replacement of animal protein with vegetarian and dairy protein in patients with HE is compelling, the evidence base to support it is scarce and controversial.[143,149] In short-term analysis in patients with chronic HE shifting from animal to vegetable proteins was associated with slight improvements in psychometric tests and ammonia balance.[150,151] However, changes in dietary habits are not easy to implement, and tolerance and adherence to vegetarian proteins could be reduced, impacting on overall nutritional status. Furthermore, unmonitored use of vegetarian and dairy diets can lead to decreased overall protein and calorie intake and should therefore: i) be confined to patients in whom standard treatment has failed and who seem truly intolerant to animal protein[152]; and ii) performed by expert centres under very close dietary monitoring to avoid inducing weight loss and sarcopenia.[143,153]

In patients with recurrent/persistent HE, is liver transplantation a treatment option to improve outcome?

Recommendation

- Patients with end-stage liver disease and recurrent or persistent HE not responding to other treatments should be assessed for liver transplantation **(LoE 4, strong recommendation, 100% consensus).**

The development of HE in patients with cirrhosis is associated with reduced quality of life and a poor prognosis.[106] Recurrent or persistent HE is frequently driven by spontaneous portosystemic shunting; dominant shunts should be identified, and obliteration considered in those with MELD scores <11. Post-TIPS HE can be treated by shunt reduction or closure. If no shunts can be identified or the patient does not respond to occlusion or if liver function is poor, liver transplantation is the last treatment option. In patients with HE as the primary driver for transplantation, it can be difficult to determine the right time to consider transplantation as the allocation of donor organs in many transplantation centres relies on the MELD score, which does not include HE.[154] A pragmatic solution is to consider liver transplantation i) once the patient has experienced an index complication, including HE, with a MELD score above 15, and ii) when a patient has a history of recurrent hospitalisation for overt HE.[101] Patients with chronic persistent HE with only a mild degree of hepatic insufficiency may be considered for liver transplantation if all other treatments have failed. This requires careful work-up and the patient, family and other health professionals should be aware that the manifestations of HE are not always resolved as quickly as expected after liver transplantation.[155,156] Great attention should be paid to closure of all shunts during the transplantation procedure.

In patients with hepatic myelopathy, is liver transplantation a treatment option to improve outcome?

Recommendation

- In patients with hepatic myelopathy, liver transplantation should be considered as soon as possible since there is no other therapeutic option **(LoE 4, strong recommendation, 94% consensus).**

Hepatic myelopathy is a rare complication of cirrhosis that is most often (>80%) accompanied by extensive portosystemic shunts.[157,158] It is characterised by rapidly progressing spastic paraparesis without sensory deficit or sphincter dysfunction and does not respond to standard therapies for HE. After months of progression patients either depend on walking aids or become wheelchair-dependent.[159] For differential diagnosis spinal MRI should be performed to exclude other possible causes of a myelopathy including vitamin B12-, thiamine, and copper deficiency. In a short case series,[160,161] patients with clinical signs of hepatic myelopathy who underwent liver transplantation had similar outcomes as patients transplanted due to other forms of HE.[162–164]

In patients with cirrhosis-related Parkinsonism, are dopaminergic drugs a treatment option to improve outcome?

Recommendation

- In patients with cirrhosis-related Parkinsonism, dopaminergic treatment should be tested **(LoE 2, strong recommendation, 95% consensus).**

There are a few case reports on the effect of dopaminergic drugs in cirrhosis-related Parkinsonism, but only 2 controlled studies. In contrast to the case reports and case series which showed contradictory results, the 2 controlled studies point to a possible benefit of dopaminergic treatment for patients with cirrhosis-related Parkinsonism. A RCT included 6 patients treated for 8-12 weeks with 15 mg bromocriptine/day after increasing the daily dose from 2.5 mg to 15 mg over a time period of 16 days. The patients were assessed by physicians unaware of the trial drug. All patients showed an improvement in their mental state and speech, impaired gait was improved in 2 of 4, as was tremor in 4 of 4. After the initial phase, 5 of the patients were further treated in a double-blind cross-over design for 16 weeks. Those patients who received placebo during the first 8 weeks of this cross-over trial rapidly deteriorated to their former functional status but improved again when bromocriptine was re-started. Those who crossed to placebo after another 8 weeks of bromocriptine therapy deteriorated as well, but only after about 1 week of placebo therapy.[165] In 2018, another double-blind, randomised, placebo-controlled study to assess the efficacy of bromocriptine in patients with cirrhosis-related Parkinsonism was reported. Twenty-two were randomised to receive placebo, 24 to receive bromocriptine. The bromocriptine dose was increased from 2.5 mg to 15 mg within 4 weeks. The primary endpoint was response to treatment at 12 weeks. Response to treatment was defined as a >30% reduction in the baseline UPDRS motor score at 12 weeks of therapy. Partial response was defined as reduction in the score of 10%-30% at 12 weeks of therapy and non-response was defined as a reduction in Unified Parkinson Disease Rating Scale (UPDRS) motor score of <10% at 12 weeks of therapy. Response was seen in 7 patients (29%) in the bromocriptine group compared to none in the placebo group. Twelve patients in the treatment group (50%) compared to 1 in the placebo group (4.5%) showed partial response. No major adverse events occurred in either treatment group. Of note, non-responders were more severely affected, had significant postural instability and a longer history of Parkinsonian clinical symptoms, indicating that treatment should be started early in the development of the disease.[166] In conclusion, there is evidence for a benefit of bromocriptine treatment in patients with cirrhosis-related Parkinsonism.

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

Recommendation

- In patients with recurrent/persistent HE, FMT is not routinely recommended as a treatment option but its validation in large randomised placebo-controlled trials powered for clinical outcomes is warranted **(LoE 2, weak recommendation, 93% consensus).**

Gut microbiome changes have prime importance in the pathogenesis of cirrhosis and HE.[167] 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.[168] 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*.[169] 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.[170] However, patients were treated with broad-spectrum antibiotics prior to FMT and the favourable impact may have been related to the antibiotic administration (not given to the standard of care arm). This would still support FMT as having possible utility in restoring antibiotic-induced disruption in microbial diversity and function in the context of HE.[171] The long-term safety and efficacy of FMT was studied within this population between 12 and 15 months. The FMT cohort had no adverse effects on long-term follow-up.[172] 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.[173] 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 placebo-controlled trials focusing on clinical endpoints are warranted before it can be recommended as a treatment option.

In patients with cirrhosis and covert HE, is it useful to institute treatment for the purposes of differential diagnosis and to reduce the likelihood of developing overt HE?

Recommendation

- In patients with covert HE, anti-HE treatment should be considered for the purposes of differential diagnosis and to prevent overt HE **(LoE 5, strong recommendation, 89% consensus).**

While there is evidence of varying strengths that show treatment can reverse covert HE, improve quality of life and reduce the likelihood of overt HE,[174] there are no RCTs to show that treatment of covert HE prevents overt HE; these studies need to be performed. It is however true that covert and overt HE share the same pathophysiology, and therefore it can be argued that treatment of covert HE should be considered. Similarly, a course of anti-HE treatment for the purposes of differential diagnosis is also reasonable.[29]

Should patients with a history of, or with, overt HE be provided with advice in relation to driving for the purposes of their own and public safety?

Recommendation

- Patients who have had an episode of overt HE should be provided with information on the risks associated with driving and on the appropriateness of formal driving assessment with the relevant authorities **(LoE 5, strong recommendation, 100% consensus).**

During driving simulation studies and on-road driving tests, patients with cirrhosis and HE have been shown to exhibit problems with vehicle handling, adaptation, cautiousness, lane-keeping, brake usage, and are more likely to need intervention from an instructor to avoid accidents.[175–178] Patients with cirrhosis and cognitive impairment have more documented traffic accidents and violations compared to unimpaired patients with cirrhosis[179] and may overestimate their driving competence.[176,180] Two studies found no increased rate of accidents in patients with cirrhosis and covert HE[181,182] and patients with covert HE may not be unsafe drivers in reality.[183] Nevertheless, treatment with rifaximin in a randomised trial has been shown to improve driving simulator performance in patients with covert HE.[184,185] There are no clear published guidelines on driving for patients with covert HE with or without recent overt HE. Expert consensus recommends avoidance of driving after an episode of overt HE[176] as most patients with HE experience significant "lapses of consciousness" following a recent or current episode.[186] Verbal and written advice to avoid driving following an episode of overt HE should be given to patients and caregivers. If patients want to resume driving, they should schedule a formal driving re-assessment with the local authorities based on local regulations.

Attempts to draw up international guidelines on whether patients with cirrhosis and HE can continue to drive have been fraught, owing to different regulatory and legal approaches with respect to HE in different jurisdictions, both within and between countries. Clinicians should be aware of their local responsibilities and be mindful that they are not trained to assess fitness to drive. No single psychometric test has the ability to reliably divide patients into safe and unsafe drivers.[187]

In patients with cirrhosis who are considered for TIPS, which neurologic work-up should take place to assess risk of post-TIPS HE?

Recommendation

- In patients scheduled for non-urgent TIPS, the presence and/or history of overt and covert HE should be thoroughly assessed. One single episode of HE is not an absolute contraindication, especially if precipitated by bleeding **(LoE 5, strong recommendation, 89% consensus).**

To date, no method is available to reliably identify patients who will go on to develop HE after TIPS. The psychometric hepatic encephalopathy score[188–190] studied before TIPS placement could not indicate cut-offs that predicted a high risk for post-TIPS HE. Ammonia determination, and its time course after amino acid challenge, have recently been studied as predictive factors of post-TIPS HE. Low ammonia levels before TIPS placement, higher increases in blood ammonia, as well as increased response regarding neuropsychiatric indices (sleepiness and psychometric tests after amino acid challenge) were associated with more frequent HE occurrence after TIPS.[189] If confirmed, these results could help to improve the stratification of patients at risk of post-TIPS HE. Brain MRI, and especially diffusion tensor imaging, are recommended only for research purposes.[191] In summary, we recommend, in the context of non-urgent TIPS, a careful assessment of medical history,

with particular reference to overt HE history[192]; liver and kidney function, focusing on bilirubin levels, international normalised ratio and urea levels[193]; a neurological and neuropsychological examination to detect HE, to rule out and manage large spontaneous porto-systemic shunts[194]; and, finally, microbiome analysis could also help with decision-making in patients with TIPS at risk of overt HE.[195] In summary, new bouts of post-TIPS HE could be modulated by using covered stents[196] and promoting early placement of TIPS.[197,198]

Abbreviations

APACHE II, acute physiology and chronic health evaluation II; CLIF-C, chronic liver failure consortium; CPGs, clinical practice guidelines; EASL, European Association for the Study of the Liver; FMT, faecal microbiota transplantation; HE, hepatic encephalopathy; ICU, intensive care unit; MAFLD, metabolic dysfunction-associated fatty liver disease; MARS, molecular adsorbent recirculating system; MCI, mild cognitive impairment; MELD, model for end-stage liver disease; MRI, magnetic resonance imaging; PICO, P Patient, Population, or Problem; I Intervention, Prognostic Factor, or Exposure; C Comparison or Intervention (if appropriate), O Outcome; RCTs, randomised-controlled trials; RR, risk ratio; TIPS, transjugular intrahepatic portosystemic shunt; UPDRS, Unified Parkinson Disease Rating Scale.

Conflict of interest

Please refer to the accompanying EASL disclosure forms for details.

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Appendix. Delphi round agreement on the statements and recommendations of the present CPGs.

Recommendation/statement	Consensus
HE should be qualified as type A in patients with acute liver failure, type B in those with portosystemic shunt, and type C in those with cirrhosis. Overt HE should be qualified as recurrent if ≥2 bouts occur within 6 months and persistent if the patient does not return to her/his baseline performance between bouts. The severity of mental alterations, any identified precipitants and the presence of portosystemic shunts should also be recorded as these factors impact upon both diagnostic accuracy and treatment **(LoE 5, strong recommendation).**	96%
The West Haven criteria should be used for HE grading when at least temporal disorientation is present (*i.e.* from West Haven grades ≥2). In patients with no or mild neuropsychiatric abnormalities (*i.e.* not meeting the criteria for the diagnosis of HE grades ≥2 based on the West Haven criteria), a neuropsychological/neurophysiological or therapeutic test should be used to diagnose covert HE. In patients with grades III-IV West Haven criteria, the Glasgow coma scale should be added **(LoE 5, strong recommendation).**	96%
The term "Brain Failure" should be replaced with the term "acute encephalopathy", in accordance with international guidelines on delirium. Acute encephalopathy should not be used as a synonym for hepatic encephalopathy in patients with acute-on-chronic liver failure because while it may be accounted for by HE, there may be alternative or concomitant causes for its development **(LoE 4, strong recommendation).**	91%
Patients with HE should not be classified based on the aetiology of their underlying liver disease **(LoE 4, strong recommendation).**	93%
In patients with suspected HE, alternative or additional causes of neuropsychiatric impairment should be identified to improve prognostic accuracy and the results of treatment **(LoE 4, strong recommendation).**	100%
Features of covert HE and MCI of an aetiology other than liver dysfunction show significant overlap **(LoE 2).**	90%
In patients with delirium/encephalopathy and liver disease, plasma ammonia measurement should be performed, as a normal value brings the diagnosis of HE into question **(LoE 4, strong recommendation).**	95%
In patients with delirium/encephalopathy and liver disease, brain imaging by CT scan or MRI should be performed in case of diagnostic doubts or non-response to treatment **(LoE 5, strong recommendation).**	96%
No cerebral imaging proves a diagnosis of HE **(LoE 4).**	96%
In patients with cirrhosis and no history of overt HE, screening for covert HE should be performed with tests for which experience/tools and local norms are available. As the only bedside test available to date, the Animal Naming Test is worthy of further study and validation **(LoE 4, strong recommendation).**	83%
Patients with covert HE should be treated with non-absorbable disaccharides **(LoE 3, strong recommendation).**	92%
In patients with liver failure and overt HE, albumin dialysis ameliorates HE and can be considered. The impact on prognosis is, however, uncertain and further study is warranted **(LoE 2).**	77%
In patients with HE, all measures to control progression of the underlying liver disease should be undertaken **(LoE 4, strong recommendation).**	100%
In patients with HE, precipitating factors should be sought and managed **(LoE 2, strong recommendation).**	100%
Patients with overt HE grade 3 and 4 are at risk of aspiration and should be treated in the ICU. No single marker can identify patients who will benefit from ICU admission, and referral relies on clinical judgement **(LoE 4, strong recommendation).**	96%
Patients with recurrent or persistent HE should be considered for liver transplantation and a first episode of overt HE should prompt referral to a transplant centre for evaluation **(LoE 5, strong recommendation).**	85%
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 **(LoE 1, strong recommendation).**	96%
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 **(LoE 2, strong recommendation).**	92%
In patients presenting with gastrointestinal bleeding, rapid removal of blood from the gastrointestinal tract (lactulose or mannitol by nasogastric tube or lactulose enemas) can be used to prevent HE **(LoE 1, strong recommendation).**	85%
In patients with cirrhosis and previous episodes of overt HE, rifaximin can be considered for prophylaxis of HE prior to non-urgent TIPS placement. Non-absorbable disaccharides, as a stand-alone or in combination, are worthy of further study in this context **(LoE 2, strong recommendation).**	82%

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Recommendation/statement	Consensus
In patients with a history of overt HE with improvement of liver function and nutritional status and in whom precipitant factors have been controlled, discontinuation of anti-HE therapy should be considered on an individual basis **(LoE 5, weak recommendation).**	77%
In patients with HE, routine zinc supplementation is not recommended **(LoE 2, strong recommendation).**	95%
In patients with HE, demonstrated or suspected vitamin/micronutrient deficiencies should be treated, as they can compound HE **(LoE 4, weak recommendation).**	88%
Obliteration of accessible portal-systemic shunts in patients with cirrhosis with recurrent or persistent HE (despite adequate medical treatment) can be considered in stable patients with a MELD score <11 **(LoE 4, weak recommendation).**	100%
In patients with recurrent/persistent HE, replacement of animal protein with vegetable and dairy protein can be considered, provided that overall protein intake is not compromised and that patient's tolerance is considered **(LoE 4, weak recommendation).**	83%
Patients with end-stage liver disease and recurrent or persistent HE not responding to other treatments should be assessed for liver transplantation **(LoE 4, strong recommendation).**	100%
In patients with hepatic myelopathy, liver transplantation should be considered as soon as possible since there is no other therapeutic option **(LoE 4, strong recommendation).**	94%
In patients with cirrhosis-related Parkinsonism, dopaminergic treatment should be tested **(LoE 2, strong recommendation).**	95%
In patients with recurrent/persistent HE, faecal transplantation is not routinely recommended as a treatment option but its validation in large randomised placebo-controlled trials powered for clinical outcomes is warranted **(LoE 2, weak recommendation).**	93%
In patients with covert HE, anti-HE treatment should be considered for purposes of differential diagnosis and to prevent overt HE **(LoE 5, strong recommendation).**	89%
Patients who have had an episode of overt HE should be provided with information on the risks associated with driving and on the appropriateness of formal driving assessment with the relevant authorities **(LoE 5, strong recommendation).**	100%
In patients scheduled for non-urgent TIPS, the presence and/or history of overt and covert HE should be thoroughly assessed. One single episode of HE is not an absolute contraindication, especially if precipitated by bleeding **(LoE 5, strong recommendation).**	89%

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.06.001.

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Update

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It has come to our attention that a copy and paste error has been introduced into the published version of these clinical practice guidelines. Thus, there is an error in Table 1 of the published version of these clinical practice guidelines. The Table has been presented as below:

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

However, the Criteria for Level 3 are incorrect. The correct version of the Table is included below:

Level	Criteria	Simple model for high, intermediate and low evidence
1	Systematic reviews (SR) (with homogeneity) of randomised controlled trials (RCT)	Further research is unlikely to change our confidence in the estimate of benefit and risk
2	Randomised controlled trials (RCT) or observational studies with dramatic effects; systematic reviews (SR) of lower quality studies (*i.e.* non-randomised, retrospective)	
3	Non-randomised controlled cohort/follow-up study/control arm of randomised trial (systematic review is generally better than individual study)	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
4	Case-series, case-control, or historically controlled studies (systematic review is generally better than an individual study)	
5	Expert opinion (mechanism-based reasoning)	Any estimate of effect is uncertain

We apologise for any inconvenience caused.

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Clinical Practice Guideline Panel: Chair: Sara Montagnese; EASL Governing Board representative: Pierre-Emmanuelle Rautou; Panel members: Manuel Romero Gómez, Fin Stolze Larsen, Debbie Shawcross, Dominique Thabut, Hendrik V Arenstorff Vilstrup, Karin Weissenborn.
* Corresponding author. Address: European Association for the Study of the Liver (EASL), The EASL Building – Home of Hepatology, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 (0) 22 807 03 60; fax: +41 (0) 22 328 07 24.
E-mail address: easloffice@easloffice.eu.
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