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REVIEW

Diagnosis and management of hepatic encephalopathy: The French recommendations

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Abstract

Hepatic encephalopathy (HE) is a frequent and severe complication of liver disease with poor patient outcomes. However, it is a poorly understood complication, with no consensus for diagnosis. Therefore, HE is often underdiagnosed. Differential diagnosis may be cumbersome because of non-specific symptoms, such as confusion, cognitive disorders, the aetiological factors of cirrhosis and comorbidities, which are often observed in cirrhotic patients. Therefore, an overt or covert form of HE should be systematically investigated. Advice is provided to drive patient work-up. Effective treatments are available to prevent or treat HE bouts, but the issue of single or combination therapy has not been resolved. Transjugular intrahepatic portosystemic shunt (TIPS) placement largely improved the prognosis of cirrhotic patients, but HE occurrence of HE is often a fear, even when post-TIPS HE can be avoided by a careful selection of patients and preventive treatment. HE is an indication of liver transplantation. However, its reversibility post-transplantation and the consequences of transplantation in patients with other causes of neurological disorders remain controversial, which supports the performance of an extensive work-up in expert centres for this subset of patients. The present guidelines assist clinicians in the diagnosis of the overt or covert form of HE to implement curative and preventive treatments and clarify which patients require referral to expert centres for consideration for liver transplantation. These guidelines are very clinically oriented and address different frequent clinical issues to help physicians make bedside decisions.

KEYWORDS
ammonia, cirrhosis, hepatic encephalopathy, liver transplantation, TIPS

1 | INTRODUCTION

Hepatic encephalopathy (HE) is a frequent and severe complication of liver disease with poor patient outcomes. HE reduces the patient's and caregiver's quality of life. However, it is a poorly understood complication with no consensus for diagnosis. Therefore, HE is often underdiagnosed. The pathophysiological mechanisms are also poorly understood, and indications for the various treatment options available are not well classified. The present guidelines assist clinicians in the diagnosis of overt and covert forms of HE to implement curative and preventive treatments and lifestyle and therapeutic education measures for patients and clarify which patients require referral to expert centres for consideration for liver transplantation. These guidelines should be envisioned as a complement to international guidelines,[1–3] including the recently published EASL clinical practice guidelines (CPG).[4] The present guidelines adhered to these latest recommendations, especially the semantics. Therefore, we retained the term 'covert' instead of minimal + grade 1 stages, despite ongoing controversies[5] because we did not want to add confusion for readers. Other current controversial

Key points

- Overt and covert presentations of HE should be screened in all patients with cirrhosis regardless of liver function status. Screening of covert HE using an animal naming test is recommended, and a therapeutic test with lactulose of rifaximin may be used to strengthen the diagnosis.
- Overt and covert presentations of HE should be treated. Treatment includes the avoidance of precipitating factors and treatment of HE bout, prophylaxis of recurrence and treatment of minimal HE.
- Hyponatraemia and PPI use are classical precipitating factors of HE. The available treatments primarily include non-absorbable disaccharides and rifaximin.
- A single episode of HE is not a contraindication to TIPS.
- A neurological work-up should be performed before liver transplantation.

points in the field are also identified: the differential diagnosis of HE in patients with non-alcoholic fatty liver disease (NAFLD) is particularly difficult; combination versus single therapy after a first episode of overt HE; pathogenesis and prevention of HE after TIPS placement, if this entity truly exists. We tried to address these controversies in the present guidelines considering the literature and our expert opinion, and all controversial issues are written in italics. The guidelines are clinically oriented and address different frequent clinical issues without significant overlap with the EASL CPG.

2 | METHODS

These guidelines were the work of a panel of experts gathered by the AFEF Management Board and including hepatologists, intensivists, neurologists, biologists, pharmacists and liver surgeons. Briefly, the experts created a list of 16 questions. The questions were formulated using the Patient Intervention Comparison Outcome (PICO) model. The Grade Method (Grade of Recommendation Assessment, Development and Evaluation) was used to compile the guidelines. The quality of evidence and the level of recommendation were rated.

The strength of the recommendations was determined according to key factors and validated by the experts after a vote using the Grade Grid method.[6] The compilation of a guideline required that at least 50% of voting participants had an opinion and that fewer than 20% of participants voted for the opposite proposal. The compilation of a strong agreement required the approval of at least 70% of the voting participants.

The methodology is detailed in the Appendix S1.

3 | RESULTS

Recommendations were made for adults in the three areas: diagnostic management of HE, therapeutic management of HE, and management of HE in two specific contexts, TIPS and liver transplantation.

The summarising work of the experts and the application of the GRADE methodology resulted in a total of 23 recommendations. Among the 23 formal recommendations, three recommendations had a high level of evidence (GRADE 1+/−), and 10 recommendations had a low level of evidence (GRADE 2+/−). The GRADE methodology could not be applied for nine recommendations, which resulted in 10 expert opinions. After two rounds of scoring, strong agreement was reached for all recommendations and protocols.

4 | FIRST AREA: DIAGNOSIS OF HE

4.1 | Clinical diagnosis of HE

HE is a group of neurological or neuropsychiatric symptoms caused by liver disease and/or a portosystemic shunt.[1] Although its exact pathophysiology remains controversial, evidence has established a combined role of hyperammonaemia and systemic inflammation.[7,8] Three types of HE have been defined according to pathogenesis: Type A, HE secondary to acute liver failure; Type B, HE secondary to the presence of portosystemic shunts not associated with liver disease and Type C, *HE secondary to cirrhosis* (*focus of the present guidelines*).

The West-Haven classification is the most frequently used clinical classification of HE. It is generally used in a binary fashion: no overt HE (grades 0–1, includes no HE, and covert HE: minimal + grade 1) and overt HE (grades 2–4). Some patients with no overt HE have no HE at all (grade 0), some patients have minimal HE that is only detected by psychometric tests, and some patients have mild signs that are detected via examination, e.g. impaired calculation ability (grade 1). There is significant overlap between minimal HE and grade 1 HE categories due to the lack of a reference method for diagnosis and the fluctuating course of HE. Therefore, these classifications are merged into the category 'covert HE', which is the term adopted by other international guidelines. Notably, this issue is very controversial in the field. Some international experts do not recognise covert HE as a single entity and differentiate minimal and grade 1 HE. HE may also be episodic, recurrent or persistent. Therefore, it is necessary to provide information on the classification of and therapies for HE.

Question 1: in which patients must HE be investigated?

The experts suggest screening for hepatic encephalopathy in all patients with cirrhosis regardless of their liver function status.

Expert Opinion, *Strong Agreement*.

Overt HE is occurs in 30% to 45% of patients with cirrhosis, with an incidence of 20% per year, and it reaches as high as 50% after TIPS.[9] The prevalence of covert HE is more difficult to estimate due to the lack of a reference diagnostic method. However, it likely affects more than two-thirds of patients with cirrhosis, with some studies indicating a prevalence up to 85%.[10,11] The onset of HE is a leading risk factor for poor outcomes. The occurrence of a first episode of overt HE is independently associated with increased mortality, with 1- and 3-year cumulative survival rates of 42% and 23% respectively.[12,13] However, the existence of covert HE is an independent risk factor for the subsequent development of overt HE.[10] In addition to its association with mortality, the existence of overt and covert HE is associated with a negative effect on quality of life and impaired driving.[14,15] Effective therapeutic strategies for HE are available, and it seems reasonable to screen all cirrhotic patients for HE.

Question 2: How do you investigate overt HE?

We recommend systematically investigating signs strongly suggestive of HE: asterixis, psychomotor slowing, sleep–wake inversion, temporospatial disorientation and impaired consciousness.

Grade 1+, *Strong Agreement*.

Question 3: How do you investigate covert HE?

Covert hepatic encephalopathy should be investigated in all patients with cirrhosis.

The experts suggest using the animal naming test among the available assessments.

Expert Opinion, *Strong Agreement*.

Covert HE is typically characterised by normal neurological examination results and the detection of abnormalities only by neuropsychological and neurophysiological testing.[3] However, elements in favour of neuropsychological impairments (e.g. apraxia, dysexecutive syndrome, joviality, disinhibition, apathy and psychomotor retardation) may be investigated via neurological examination. Interviews with the patient and their family/relatives should allow characterisation of any potential complaints, such as psychomotor slowing, sleep disorders, sleep–wake inversion and impaired calculation ability. Particular attention should be given to activities of daily living and a recent inability to perform tasks that were previously routine. Neuropsychological testing is the reference examination for the diagnosis of covert HE because it allows for precise characterisation of the neuropsychological pattern. A dysexecutive syndrome is strongly suggestive of covert HE. A different clinical profile should raise suspicion of a differential diagnosis or associated diagnosis, such as vascular or alcohol-related dementia, particularly in the context of cirrhosis. However, access to neuropsychological testing for cirrhotic patients is challenging in routine clinical setting. Therefore, the choice of neuropsychological or neurophysiological tests in the absence of easy access should be based on local means and expertise.

4.1.1 | Psychometric Hepatic Encephalopathy Score (PHES)

This test was specifically designed to detect neuropsychological disorders in covert HE by assessing psychomotor speed and visuospatial coordination.[16] It includes five widely validated tests: the Number Connection Test (NCT)-A, the NCT-B, the Line Tracing Test, the Digit Symbol Test and the Serial Dotting Test (SDT).[17,18] It was recently validated in French.[19] The main limitation of this test is the 20–30-minute completion time.

4.1.2 | Critical Flicker Frequency (CFF) test

The CFF is a neurophysiological test that assesses the patient's ability to discriminate flickering light using a device in the form of glasses. This test has been widely validated[20,21] and is comparable to the PHES test. Some authors suggest a value below 38 Hz for the detection of covert HE.[22] This test is easy to perform during a consultation or at the patient's bedside, but the device is expensive and poorly available.

4.1.3 | Executive function tests

Various tests assessing executive functions have been postulated. The use of the widely validated Stroop test in the form of a dedicated application (EncephalApp) has been proposed.[23] This test assesses inhibitory control upon the presentation of the names of colours written in different coloured text, which represents an interference effect. It is available from online smartphone downloading platforms and may be offered to patients at home under the monitoring of a caregiver.

4.1.4 | Animal naming test (ANT) (Table 1)

A simple bedside test was recently proposed and asks the patient to name as many animals as possible in 1 min. According to a fundamental Italian study by Campagna et al.,[24] a result of less than 15 animals per minute distinguished patients with covert HE from patients without covert HE. The ANT was also predictive of the occurrence of overt HE. This promising test has now been validated by another independent team who also evaluated the characteristics of the test by comparing different cut-off values[25] (Table 1). The cut-off value of 20 animal names in 1 min seemed reasonable. This test may be used as a rapid screening test because it may be easily performed during consultation or at the patient's bedside, without extensive equipment, and it does not take much time. The evolution of ANT for a single patient is important to assess the course of covert HE and the efficacy of treatments.

Because all other previously detailed tests are not reasonably performed in a real-life setting, the experts recommend performing the ANT systematically in cirrhotic patients without overt HE to screen for covert HE. The experts also suggest performing a therapeutic test in cases of an abnormal ANT to strengthen the diagnosis of covert HE.

4.2 | Paraclinical diagnosis of HE (biological, electrophysiological or imaging work-up)

Question 4: What is the role of blood ammonia levels in the paraclinical diagnosis of HE?

In cases of diagnostic doubt in the presence of impaired consciousness, we suggest measuring blood ammonia levels because a normal value casts doubt on the diagnosis of HE.

We suggest not measuring blood ammonia levels to confirm the diagnosis of HE because ammonia may be elevated in cirrhotic patients without any encephalopathy.

Grade 2-, *Strong Agreement*.

Several studies assessed the correlation between ammonia levels and the severity of HE. The following main findings were

TABLE 1 Guidelines for animal naming test assessment

How is the animal naming test performed?
TIME REQUIRED: a maximum of 2 min
EQUIPMENT REQUIRED: paper, pen, stopwatch
INSTRUCTIONS: 'You need to list as many animal names as possible in 1 min. You will start when I say Go'.
INTERPRETATION: The experts suggest setting a cut-off of 20 animal names in 1 min. Covert HE is likely to be below this threshold.

reported: (1) ammonia was always elevated in cases of HE; (2) ammonia levels correlated with the severity/grade of HE and the prognosis[26]; (3) ammonia levels may be elevated without any HE symptoms and (4) ammonia levels sometimes remained sometimes stable and elevated during follow-up, even in patients no longer presenting with overt HE.[27] Therefore, the conclusions drawn from these data are that ammonia measurement cannot help in the positive diagnosis of HE but that a normal value casts doubt on the diagnosis of HE. A very recent study outlined that ammonia levels in outpatients were predictive of further decompensation of cirrhosis.[28]

Ammonia measurement is to obtain when the conditions for measurement are respected (Table 2). For cases of severe hyperammonaemia (>100 μmoL/L), a family history of liver disease and/or neurological disorders, a personal history of neurological disorders and/or HE, slightly abnormal liver function tests and severe neurological impairment, inherited metabolic disorders should be suspected and further explored.[29]

Question 5: Is brain imaging essential for the differential diagnosis of HE?

We suggest performing brain imaging only for differential diagnosis in patients with suspected hepatic encephalopathy.

Grade 2+, *Strong Agreement*.

Brain imaging is not specific for the diagnosis of HE, but it is very important for differential diagnosis. Brain imaging is most important during the first episode of HE. It is routinely indicated for the exclusion of an intracranial lesion when this diagnosis is suspected,[1,3] especially in cases of diagnostic doubts, because the population of patients with cirrhosis or heavy drinkers without cirrhosis have a much higher risk of intracerebral haemorrhage than the general population. Contrast-enhanced cross-sectional imaging using a CT scan or MRI is needed. Spectroscopy (MRS) has good diagnostic performance in HE. A recent meta-analysis revealed that MRS changes in glutamine/glutamate, choline and myo-inositol, particularly in the parietal lobe, correlated with the severity of HE.[30]

One of the main difficulties in using brain MRS is its accessibility, which is essentially restricted to academic hospitals, and this exploration cannot be recommended in clinical practice.

TABLE 2 Guidelines for blood ammonia sampling

Blood ammonia level measurement: biochemical criteria and sampling requirements
IT IS RECOMMENDED THAT VENOUS BLOOD SAMPLING BE PERFORMED: • In a fasting patient • Avoid venous stasis (tourniquet, fist clenching), well-cleaned skin • Collect blood in an EDTA-containing tube, fill well, secure the lid, homogenise by inversion and place immediately on ice (or synthetic ice) • Specify the patient's treatment Fastest possible transport to the laboratory at +4°C (maximum 60–90 min)
INTERFERENCE: sample haemolysis, high lipaemia and jaundice, high-protein diet, smoking, exercise, certain drugs
DELAYED MEASUREMENT: centrifuge at +4°C and freeze the supernatant at −70/−80°C

4.3 | Differential diagnosis of HE

Question 6: How is a differential diagnosis of HE excluded in a cirrhotic patient with a neurological disorder?

The experts suggest that any initial evaluation of a neurological disorder in a cirrhotic patient should include a clinical and paraclinical work-up to exclude a differential or associated diagnosis. Blood tests and brain imaging, preferably MRI, are essential. For cases of overt HE recurrence, only blood tests are systematically recommended for differential diagnosis.

Expert Opinion, *Strong Agreement*.

The experts suggest the establishment of internal standard operating procedures that allow for neurological expertise to be provided within a suitable time delay.

Expert Opinion, *Strong Agreement*.

Within the clinical spectrum of HE, covert and overt HE should lead to several differential diagnoses.

A clinical and paraclinical diagnostic work-up for investigations of a differential or associated diagnosis with HE is essential in any initial evaluation of neurological symptoms in cirrhotic patients. The following main elements should be systematically specified:

1. Recent medical history (infections, trauma, withdrawal and psychotropic drugs);
2. Complete medical history (diabetes, neurovascular diseases, epilepsy, known complications of cirrhosis and liver failure);
3. Neurological examination including cognitive, motor, sensory, neurovisual and cranial nerve testing; and asterixis, which is included in the grade 2 West-Haven score, that is, overt HE,[31] is strongly suggestive of metabolic encephalopathy (see differential diagnosis of asterixis Table 3); and
4. Common blood tests (blood electrolytes, blood glucose, blood calcium, cell blood count haemostasis, inflammatory proteins, blood urea and creatinine), brain imaging (preferably MRI) and sometimes EEG.

4.3.1 | Differential diagnosis of covert HE

Evoking a differential (or associated) diagnosis must be systematic in the presence of any clinical or paraclinical features that may be attributed to a different or associated disease (Table 4). *Cognitive impairment is isolated in covert HE and is primarily comprised of slower thinking, impaired attention and frontal-subcortical syndrome (memory retrieval impairments without storage impairment). This general semiology of*

TABLE 3 Differential diagnosis of asterixis

Differential diagnosis of asterixis
METABOLIC ENCEPHALOPATHY: uraemia, hypercapnia, hypoglycaemia, urea cycle defects
HYDROELECTROLYTIC DISORDERS: hypokalaemia, hypomagnesaemia
DRUGS: Antiepileptic drugs, Levodopa, opiates, anticholinergics, benzodiazepines, lithium, Clozapine
FOCAL BRAIN LESION(S)

TABLE 4 Differential diagnosis of covert HE

Differential diagnoses of covert HE
ASSOCIATED WITH CHRONIC ALCOHOL MISUSE: • Vitamin deficiencies: Wernicke–Korsakoff syndrome, vitamin B12/folate deficiency • Post-traumatic dementia • Alcohol-related dementia
CEREBRAL MICROANGIOPATHY (VASCULAR LEUKOENCEPHALOPATHY)
NEURODEGENERATIVE DISEASES
TOXIC CAUSES, DRUGS AND WITHDRAWAL
PSYCHIATRIC DISORDERS: Anxiety disorders, major depressive disorder, psychotic disorders
METABOLIC/ENDOCRINE DISORDERS: Uraemic encephalopathy, recurrent hypoglycaemia, hypo/hyperthyroidism, inherited metabolic disorders (especially urea cycle defects)
CHRONIC INFECTIOUS AND AUTOIMMUNE MENINGOENCEPHALITIS
SLEEP APNOEA SYNDROME AND SLEEP DISORDERS

cognitive impairment in cirrhotic patients with covert HE is non-specific. Other cognitive impairments, including significant temporospatial disorientation, anterograde episodic memory impairment, visuoconstructive impairments (e.g. *problems getting dressed and difficulties in reproducing a drawing) and abnormalities in speech production* (e.g. *word-finding problems), must evoke alternative diagnoses, particularly when they are accompanied by a progressive evolution or the absence of fluctuations* (e.g. *neurodegenerative diseases and Gayet–Wernicke–Korsakoff syndrome). This issue is particularly tricky in patients with NAFLD, which is an increasing cause of chronic liver disease, because patients with metabolic syndrome often exhibit associated vascular disorders and may exhibit vascular dementia. Ammonia measurement may be helpful in these cases, but hyperammonaemia may also be observed in the absence of encephalopathy. Neurological expertise may be needed; when doubt persists, a good clinical response to the specific treatment of HE* (e.g. *lactulose and rifaximin) may also favour the diagnosis of HE. Overall, the characterisation of cognitive disorders in patients with NAFLD must be refined in future studies.*

4.3.2 | Differential diagnosis of overt HE

Overt HE is characterised by the general non-specific signs of confusion with impaired vigilance and attention and temporospatial disorientation. Examinations should investigate symptoms and signs of an alternative or associated cause (Table 5). The observation of focal signs requires investigation, especially brain imaging.

TABLE 5 Differential diagnosis of overt HE

Differential diagnosis of overt HE
TOXIC AND DRUG-INDUCED ENCEPHALOPATHY
SEPTIC ENCEPHALOPATHY
OTHER METABOLIC ENCEPHALOPATHIES: uraemia, hypercapnia, inherited metabolic disorders (especially urea cycle defects)
NEUROLOGICAL COMPLICATIONS RELATED TO ALCOHOLISM: • Acute alcohol intoxication • Withdrawal/delirium tremens • Vitamin deficiencies: Gayet-Wernicke's encephalopathy (vitamin B1), pellagrous encephalopathy (vitamin B3), Marchiafava–Bignami disease • Metabolic disorders (hyponatraemia, hypoglycaemia) • Pancreatic encephalopathy • Subdural haematoma, haemorrhagic contusion
NON-CONVULSIVE STATUS EPILEPTICUS
FOCAL BRAIN LESION (S): vascular, infectious, tumour, etc.
AUTOIMMUNE MENINGITIS/MENINGOENCEPHALITIS

5 | SECOND AREA: THERAPEUTIC MANAGEMENT OF HE

5.1 | Preventive treatment of overt HE and prevention and treatment of covert HE

Because covert HE is a risk factor for overt HE, the treatment of covert HE is considered a preventive treatment of overt HE in this section.

Question 7: What measures can be suggested during the course of cirrhosis to reduce or eliminate the main predisposing factors of covert HE?

We suggest monitoring blood sodium levels in decompensated cirrhosis because severe hyponatraemia is a predisposing factor for hepatic encephalopathy.

Grade 2+, Strong Agreement.

We suggest limiting the prescription of proton pump inhibitors to their strict validated indications (doses and durations).

Grade 2+, Strong Agreement.

We suggest a contraindication for the prescription of benzodiazepines in patients with decompensated cirrhosis.

Grade 2+, Strong Agreement.

The concept of precipitating factors for the development of HE in cirrhotic patients was established nearly 50 years ago. These factors are essentially non-specific factors related to other complications of cirrhosis (e.g. gastrointestinal bleeding, infection, dehydration-diuretics, digestive losses, metabolic disorders-hyponatraemia, dyskalaemia, acute kidney injury and constipation). Control of one or more of these predisposing factors, which are present in approximately 50% of cases, leads to an improvement of symptoms in

approximately 90% of cases.[32] Some of these factors deserve special focus because they can be prevented or corrected. Notably, all of these factors may induce encephalopathy outside the setting of HE (with hyperammonaemia) and should be prevented in all cirrhotic patients.

5.1.1 | Hyponatraemia

It is difficult to know whether metabolic disturbances themselves cause the onset of HE or whether they are an indication of cirrhosis severity.[33] The most frequently related disturbance is hyponatraemia.[34] Hyponatraemia causes cerebral oedema with extracellular hypo-osmolality, which is compensated by an intracellular decrease in organic osmolytes, such as myo-inositol, in astrocytes. The effect of these intracerebral cellular disturbances is likely synergistic with the effects of hyperammonaemia.[35] Several studies stressed that hyponatraemia was an independent risk factor for HE[36–38] and identified a cut-off of 130 mmoL/L. Notably, hyponatraemia is associated with non-response to pharmacological treatment with lactulose in patients with overt HE.[39] These results suggest a direct link between hyponatraemia and HE. This hypothesis is supported by the improvement in cognitive impairments in patients treated with aquaretics that correct hyponatraemia with cerebral oedema.[40,41] Therefore, prevention of hyponatraemia appears essential in patients with cirrhosis, based on strict monitoring of blood electrolytes and early adjustment of diuretic dose to maintain blood sodium levels >135 mmol/L if possible and always >130 mmol/L.

5.1.2 | Drugs

Proton pump inhibitors

Proton pump inhibitors (PPIs) increase the incidence of HE by increasing gastric pH, which promotes microbial proliferation/dysbiosis in the small intestine to cause the formation of products, such as ammonia and bacterial endotoxins. Increased intestinal membrane permeability and bacterial translocation likely underlie systemic inflammation, which is the putative backbone of HE pathophysiology. Other mechanisms of action of PPIs include impaired absorption of micronutrients and increased hyponatraemia, which is a direct side effect of PPIs.

Three retrospective studies were published.[42–44] PPI exposure was more frequently observed in patients with HE, with a significant association between the PPI dose and the risk for HE. A recent cohort study found an increased risk for covert HE and development of overt HE in cirrhotic patients with long-term use of PPIs.[45] Therefore, it is mandatory to systematically re-evaluate the benefit–risk balance and appropriateness of PPI prescriptions in patients with cirrhosis and cease the use of PPIs in the absence of formal indication.

Sedatives and psychotropic drugs

Most benzodiazepines (BZDs) are used as anxiolytics for sedation. BZD receptor agonist hypersensitivity during the course of cirrhosis with potential promotion of HE has been reported.[46] The use of BZDs and opioid analgesics was independently associated with an increased risk for HE. However, this association was not found for antipsychotics.

Question 8: What treatments can be offered to prevent or treat covert HE?

The experts suggest primary prophylaxis with lactulose for HE in patients with upper gastrointestinal bleeding.

Expert Opinion, *Strong Agreement*.

We suggest treating all covert HE patients with lactulose or rifaximin to improve quality of life and reduce the risk of overt HE.

Grade 2+, *Strong Agreement*.

Few therapeutic studies specifically addressed patients with covert HE. Most data are from studies with the primary aim of evaluating the efficacy of curative or preventive treatment of overt HE. These studies included a variable proportion of patients with covert HE. Therefore, it is difficult to make reliable and robust recommendations.[47] There are several arguments in favour of preventing overt HE, which supports the treatment of covert HE.[48]

5.1.3 | Non-absorbable disaccharides (lactulose, lactitol)

Numerous studies over the last 20 years evaluated the efficacy of non-absorbable disaccharides (considered prebiotics) in the management of HE. Most of these studies showed a significant improvement in psychometric performance and quality of life of patients with covert HE after treatment.[49] The occurrence of overt HE in patients with covert HE treated with lactulose appears to be reduced, but no significant improvement in survival has been shown.[50] A meta-analysis of five small and predominantly open-label studies including a total of 197 patients suggested an efficacy of lactulose over placebo in the improvement of cognitive functions in covert HE.[51] There was an increase in the incidence of side effects, including an increase in gastrointestinal motility disorders, in treated patients. More recent studies[39,52] and a recent meta-analysis of 15 randomised controlled trials (RCTs) confirmed these results.

Two recent open-label studies showed that treatment with lactulose during gastrointestinal bleeding significantly reduced the incidence of HE but did not affect survival.[53,54] The meta-analysis of these two studies confirmed the efficacy of lactulose on the incidence of HE versus placebo (7% vs. 28%, $p < 0.01$) with no effect on mortality.[55] Lactulose was administered orally in all studies.

5.1.4 | Rifaximin

Rifaximin is an antibiotic with low gastrointestinal absorption. This treatment modulates the intestinal microbiota and improved neuropsychiatric performance and cognitive functions in patients with

covert HE.[56] A 2014 meta-analysis of 19 RCTs on the prevention of HE reported the results from two specific studies on the prevention of covert HE using rifaximin, and the results showed that rifaximin significantly improved cognitive performance.[57] Despite the heterogeneity of the available studies, it appears reasonable to recommend the use of lactulose or rifaximin for the treatment of covert HE. This recommendation is due to the safety of these treatments and the burden of HE on quality of life, hospital readmissions and the onset of overt HE.

5.2 | Curative treatment of overt HE

Question 9: Which treatment should be used for the resolution of overt HE?

We recommend prioritising the treatment of precipitating factor(s) of hepatic encephalopathy and initiating treatment with a non-absorbable disaccharide (lactulose or lactitol) in cirrhotic patients with overt hepatic encephalopathy.

Grade 1+, Strong Agreement.

A discussion of the precipitating factors is reported in the previous chapter.

5.2.1 | Lactulose

A recent meta-analysis (reported in two different reviews[32,58]) of 16 RCTs evaluated the effect of non-absorbable disaccharides in patients with overt HE (acute or chronic) compared to placebo or no therapeutic intervention. Non-absorbable disaccharides were associated with significantly more frequent resolution of acute or chronic overt HE and a reduction in mortality in patients with overt HE. Treatment with non-absorbable disaccharides was also associated with a reduced risk of severe adverse effects, including gastrointestinal bleeding, bacterial infections and hepatorenal syndrome. Treatment with non-absorbable disaccharides was associated with a non-significant increase in non-severe side effects, such as diarrhoea, bloating and nausea. We recommend the treatment of precipitating factor(s) of HE as a priority and the initiation of treatment using a non-absorbable disaccharide (lactulose or lactitol) without delay.

5.2.2 | Rifaximin

A recent meta-analysis comparing rifaximin with placebo (or non-absorbable disaccharides/other antibiotics)[57] found that rifaximin showed a beneficial effect on the complete resolution of HE and on mortality. Notably, there was no difference in these two outcomes (complete resolution of HE and mortality) according to the type of control used (placebo/non-absorbable disaccharides/other antibiotics). None of the 13 RCTs demonstrated an increased risk of bacterial resistance or Clostridium difficile-associated colitis. Analysis of the potential biases of the RCTs included in this meta-analysis suggested that we cannot recommend rifaximin alone as a treatment for overt HE.

Overall, the treatment of overt HE is based on the recognition and treatment of the precipitating factor(s) and treatment with lactulose or lactitol.

Question 10: Which treatments should be used to avoid recurrence of HE?

We recommend the use of a non-absorbable disaccharide (lactulose or lactitol) to prevent the recurrence of hepatic encephalopathy in patients with cirrhosis.

Grade 1+, Strong Agreement.

We suggest the addition of rifaximin to prevent the recurrence of hepatic encephalopathy in cases of failed prevention with a non-absorbable disaccharide (lactulose or lactitol) in patients with cirrhosis.

Grade 2+, Strong Agreement.

The experts suggest using rifaximin alone to prevent recurrence of hepatic encephalopathy when lactulose is poorly tolerated in patients with cirrhosis.

Expert Opinion, Strong Agreement.

To improve quality of life and limit hospitalisations, the experts suggest that a therapeutic education program should be offered to the patient and caregiver.

Expert Opinion, Strong Agreement.

5.2.3 | Non-absorbable disaccharides

Two RCTs including 298 patients investigated the secondary prevention of overt HE and showed that non-absorbable disaccharides significantly reduced the risk of recurrent HE (RR = 0.44, 95% CI: 0.31–0.64).[59,60] We recommend first-line treatment with lactulose (or lactitol) to prevent recurrence of overt HE.

5.2.4 | Rifaximin

An international, double-blind, placebo-controlled RCT including 299 cirrhotic patients with at least two resolved episodes of overt HE within the previous 6 months showed that the twice daily administration of 550 mg rifaximin (approximately 90% of patients were also taking lactulose) reduced the risk of recurrent HE by 58% compared to placebo. Treatment with rifaximin versus placebo also reduced the risk of readmissions and improved quality of life.[61] Continuation of open-label treatment with rifaximin for more than 24 months prevented recurrence of HE with a good rifaximin safety profile.[62] Post hoc analysis[63] assessed the repeatability of these results by switching their treatment to rifaximin for 6 months, and rifaximin effectively reduced the number of HE recurrences.[63] We recommend a rifaximin add-on when lactulose alone fails in the prevention of recurrent overt HE. It is difficult to recommend the use of rifaximin alone in the prevention

of recurrent HE because no RCTs adequately evaluated rifaximin over placebo. The experts suggest the use of rifaximin alone to prevent recurrence of HE when lactulose is poorly tolerated. *The issue of single versus combined therapy in the prevention of HE recurrence remains controversial and requires further study. Another issue that lacks data is the use of combined therapy as first-line treatment to prevent HE recurrence. Further studies, including real-life studies that address treatment adherence and quality of life, are certainly warranted.*

5.2.5 | Therapeutic education

More than one in three cirrhotic patients are readmitted within 30 days after hospitalisation for complications, and readmissions are associated with a 50% 1-year mortality and significant additional cost.[64,65] Multiple prescriptions also promote patient drug misuse, which increases the risk of HE and drug interactions. Volk et al.[65] showed that 22% of readmissions could have been avoided by the patient or caregiver with the introduction of appropriate lactulose titration, diuresis or weight control or with better knowledge of the warning signs. However, these readmissions could also have been due to a failure of the healthcare system due to multiple prescriptions, errors in scheduling examinations or a poorly coordinated discharge procedure for the patient's caregivers (e.g. community, hospital and home-based health professionals).[66]

6 | THIRD AREA: MANAGEMENT OF HE IN SPECIFIC CONTEXTS

6.1 | TIPS

Question 11: What are the contraindications to TIPS due to the associated increased risk of HE?

The experts suggest that a single episode of overt HE is not a formal contraindication to elective TIPS creation, and this indication should be discussed on a case-by-case basis.

Expert Opinion, Strong Agreement.

The creation of a shunt, which is sometimes associated with a deterioration in liver function, results in an accumulation of neurotoxic substances that promote the onset of HE. TIPS-related HE occurs in approximately 35% of cases. Most of the literature is observational and does not allow for recommendations based on a high level of evidence. Notably, most randomised controlled trials compared TIPS to other standard treatments (e.g. variceal ligations and ß-blockers or large volume paracenteses), and not all of these studies showed that TIPS increased the risk of developing HE compared to standard treatment. This controversy is particularly true in the most recent studies that included more selected patients and/or covered stents, and HE occurrence was often significantly decreased in the TIPS groups. Therefore, the entity of post-TIPS HE itself remains controversial.

For cases of refractory gastrointestinal bleeding, there is no contraindication to TIPS because there is no therapeutic alternative. Various studies on the subject do not always describe the existence of HE before or after TIPS and did not investigate the risk factors for HE after TIPS in this context. The available studies on pre-emptive TIPS (e.g. RCTs, meta-analyses and case–control studies) have not shown an increased incidence of HE after TIPS.[67–70] Overt HE was not a criterion for exclusion in the randomised controlled trials, and it is not a contraindication to pre-emptive TIPS.

All studies of scheduled TIPS for refractory ascites or secondary prophylaxis of gastrointestinal bleeding excluded patients with overt HE at the time of inclusion. Therefore, this therapy cannot be offered in cases of overt HE. The analysis of risk factors for HE after TIPS is based on observational cohorts, randomised trials or meta-analyses and history of overt HE, higher age, MELD and Child-Pugh scores are associated with post-TIPS HE.

Although the risk factors have been well analysed, there is no method to identify patients who will develop HE after TIPS. On a case-by-case basis, TIPS or an alternative treatment (transplant) may be more suitable if available. Therefore, liver transplantation feasibility should be considered for all patients for whom TIPS is indicated.[71]

Question 12: Should prophylaxis be used to prevent the occurrence of HE after TIPS?

We suggest prophylaxis with rifaximin to prevent the occurrence of HE after non-urgent TIPS.

Grade 2+, Strong Agreement.

Two small randomised trials did not show the efficacy of prophylactic treatment (lactulose, rifaximin and LOLA) initiated prior to TIPS.[72,73] Recent results of a French RCT comparing rifaximin to placebo in the primary prevention of post-TIPS HE showed a significantly lower occurrence of post-TIPS HE in patients treated with rifaximin from 2 weeks before non-urgent TIPS and for the next 6 months.[74] This criterion was the primary outcome, which justifies our statement. Therefore, rifaximin is now recommended in this setting in France. However, the French RCT is the only available RCT that covered TIPS and had a reasonable size. Therefore, the recent EASL and Baveno guidelines recommended rifaximin prophylaxis only in patients with previous HE episodes.

Question 13: What specific management of portosystemic shunts can be offered?

We do not suggest systematically performing portosystemic shunt ligation/embolisation to treat hepatic encephalopathy. The management of portosystemic shunts should be considered on a case-by-case basis.

Grade 2-, Strong Agreement.

The presence of HE episodes correlates with the presence/size of portosystemic shunts.[75] The radiological embolisation of large portosystemic shunts or the splenic vein,[76] or their surgical ligation via covertly invasive intervention,[77] appears feasible in cirrhotic patients with HE under satisfactory safety conditions,[78] and results in HE recovery in 46%[79] to 100%[80] of cases. The MELD score is the

strongest positive predictive factor of HE recurrence, and a cut-off of 11 is used for patient selection. The main complications are local complications (haematoma), aggravation of ascites or oesophageal varices. The small number of studies performed does not allow us to recommend systematic embolisation or ligation of portosystemic shunts. The management of portosystemic shunts in HE should be performed on a case-by-case basis in selected patients with low MELD scores and after a multidisciplinary decision, with preference given to minimally invasive approaches.

6.2 | Liver transplantation

Question 14: Does liver transplantation result in neurological improvement in patients with HE?

We suggest offering liver transplantation to patients with disabling symptoms of hepatic encephalopathy that are refractory to drug and non-drug treatments.

Grade 2+, Strong Agreement.

The diagnosis of cognitive disorders after LT is challenging. Patients may develop cognitive symptoms even in the absence of these symptoms before LT and generally have many risk factors for cognitive impairment, including comorbidities and aetiology of liver disease (e.g. alcohol with cerebral atrophy and metabolic syndrome with vascular lesions). We do not know whether HE is reversible post-LT. We also do not know whether pre-LT HE favours decompensation of other brain disorders related to comorbidities. Pre-transplant HE appears to be a risk factor for immediate post-transplant neurological complications (e.g. HE, seizures, drug toxicity[81] and delayed recovery of consciousness[82]). Liver transplantation (LT) leads to significant improvement in most cognitive functions in patients with HE. Cognitive performance improves beginning 6 months after LT,[83] although it may remain slightly lower than in patients without pre-transplant HE.[84–86] EEG normalisation has also been demonstrated.[84] Some cognitive functions are improved, including learning ability[87] at 6–18 months,[88] and visuospatial ability, verbal fluency, psychomotor speed and spatial orientation.[88,89] Some functions or radiological signs do not improve as well post-transplant, and there is persistence of visuomotor deficits[90] and changes in white matter of the temporal lobe on MRI.[91] Cognitive sequelae of HE may persist in less than 5% of patients, predominantly patients with grade 3–4 HE before LT.[92] LT results in improved QoL for patients with HE,[83,93,94] and the presence of pre-transplant HE did not affect the return to work after transplantation.[95]

Question 15: What neurological work-up should be performed prior to liver transplantation?

The experts suggest that MRI, EEG and blood ammonia level measurements should be systematically performed to exclude other causes of neurological or neuropsychological impairments that may persist after liver transplantation.

Expert Opinion, Strong Agreement.

Questioning the diagnosis of HE in the LT field arises from the pre-transplant assessment. It is important not to miss a differential diagnosis of neuropsychological symptoms that could persist after the transplant and to identify subclinical forms of HE that could affect outcomes if the waiting time is long.[96] A neurological work-up should be part of the evaluation of any liver transplant candidate to exclude a differential diagnosis of HE. This work-up should preferably be performed in expert centres.

Question 16: Should the presence of HE be considered for access to LT in patients with decompensated cirrhosis or hepatocellular carcinoma?

The experts suggest that overt HE should be considered in the rules for graft allocation and that a standardised and reproducible assessment of HE should be performed in all transplant candidates. The experts suggest redefining the rules for graft allocation in patients with HE regardless of the stage or MELD score.

Expert Opinion, Strong Agreement.

Over the last decade, several studies showed that the occurrence of HE in patients with equivalent MELD scores significantly increased short- and medium-term risk of death[12] with a 2–4 times increased relative risk of death compared to patients without HE. The prognostic effect of HE in all patients with cirrhosis is greater when HE occurs in the context of 'acute-on-chronic liver failure (ACLF)'. Therefore whether access to LT should be facilitated for patients with decompensated cirrhosis and HE on the transplant waiting list to limit the risk of death while waiting is an important issue. Several studies showed that the addition of an encephalopathy score to the MELD score significantly improved the short- and medium-term predictive value of mortality.[13,97–99]

7 | CONCLUSION

These recommendations should help physicians seek, prevent and treat HE and are clinically oriented. They should be seen as a guide for physicians for the management of cirrhotic patients regarding HE. The goal is to prevent and treat these patients each time it is needed to decrease the burden of HE and improve outcomes and patient quality of life.

CONFLICT OF INTEREST

Dominique Thabut and Christophe Bureau received speaker fees from Gore and are board members of Alfasigma/Norgine.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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