PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL

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Recommendations and Rationales

This guideline includes 33 specific recommendations. Please click on a recommendation to review the related rationale and supporting evidence. See Table 1 for an explanation of the grading system for recommendations.

1. Hepatic encephalopathy (HE) should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

2. A diagnostic workup is required, considering other disorders that can alter brain function and mimic HE (GRADE II-2, A, 1).

3. Hepatic encephalopathy should be treated as a continuum ranging from unimpaired cognitive function with intact consciousness through coma (GRADE III, A, 1).

4. The diagnosis of HE is through exclusion of other causes of brain dysfunction (GRADE II-2, A, 1).

5. Hepatic encephalopathy should be divided into various stages of severity, reflecting the degree of self-sufficiency and the need for care (GRADE III, B, 1).

6. Overt hepatic encephalopathy is diagnosed by clinical criteria and can be graded according the West Haven Criteria and the Glasgow Coma Scale (GRADE II-2, B, 1).

7. The diagnosis and grading of minimal HE and covert HE can be made using several neurophysiological and psychometric tests that should be performed by experienced examiners (GRADE II-2, B, 1).

8. Testing for minimal HE and covert HE could be used in patients who would most benefit from testing, such as those with impaired quality of life or implication on employment or public safety (GRADE III, B, 2).

9. Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1).

General recommendations for treatment of episodic overt HE type C include the following (#10 to #13):

10. An episode of overt HE (whether spontaneous or precipitated) should be actively treated (GRADE II-2, A, 1).

11. Secondary prophylaxis after an episode for overt HE is recommended (GRADE I, A, 1).

12. Primary prophylaxis for prevention of episodes of overt HE is not required, except in patients with cirrhosis with a known high risk to develop HE (GRADE II-3, C, 2).

13. Recurrent intractable overt HE, together with liver failure, is an indication for liver transplantation (GRADE I).

Specific approach to overt HE treatment: A four-pronged approach to management of HE is recommended (GRADE II-2, A, 1) (#14 to #17):

14. Initiation of care for patients with altered consciousness

15. Alternative causes of altered mental status should be sought and treated.

16. Identification of precipitating factors and their correction

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17. Commencement of empirical HE treatment

18. Identify and treat precipitating factors for HE (GRADE II-2, A, 1).

19. Lactulose is the first choice for treatment of episodic overt HE (GRADE II-1, B, 1).

20. Rifaximin is an effective add-on therapy to lactulose for prevention of overt HE recurrence (GRADE I, A, 1).

21. Oral branched-chain amino acids can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).

22. Intravenous L-ornithine L-aspartate can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).

23. Neomycin is an alternative choice for treatment of overt HE (GRADE II-1, B, 2).

24. Metronidazole is an alternative choice for treatment of overt HE (GRADE II-3, B, 2).

25. Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1).

26. Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1).

27. Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-transjugular intrahepatic portosystemic shunt (TIPS) HE (GRADE III, B, 1).

28. Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2).

29. Treatment of minimal HE and covert HE is not routinely recommended apart from a case-by-case basis (GRADE II-2, B, 1).

30. Daily energy intakes should be 35-40 kcal/kg ideal body weight (GRADE I, A, 1).

31. Daily protein intake should be 1.2-1.5 g/kg/day (GRADE I, A, 1).

32. Small meals or liquid nutritional supplements evenly distributed throughout the day and a latenight snack should be offered (GRADE I, A, 1).

33. Oral branched-chain amino acid supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein (GRADE II-2, B, 2).

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RECOMMENDATION 1

Hepatic encephalopathy (HE) should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

RATIONALE 1

Definition of HE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

Classification

Hepatic encephalopathy should be classified according to all of the following four factors.[10]

1. **According to the underlying disease,** HE is subdivided into
   - Type A resulting from ALF
   - Type B resulting predominantly from portosystemic bypass or shunting
   - Type C resulting from cirrhosis

The clinical manifestations of types B and C are similar, whereas type A has distinct features and, notably, may be associated with increased intracranial pressure and a risk of cerebral herniation. The management of HE type A is described in recent guidelines on ALF[62,63] and is not included in this document.

2. **According to the severity of manifestations.** The continuum that is HE has been arbitrarily subdivided. For clinical and research purposes, a scheme of such grading is provided (Table 2). Operative classifications that refer to defined functional impairments aim at increasing intra- and inter-rater reliability and should be used whenever possible.
3. **According to its time course,** HE is subdivided into
   - Episodic HE
   - Recurrent HE denotes bouts of HE that occur with a time interval of 6 months or less.
   - Persistent HE denotes a pattern of behavioral alterations that are always present and interspersed with relapses of overt HE.
4. **According to the existence of precipitating factors**, HE is subdivided into
   - Nonprecipitated or
   - Precipitated, and the precipitating factors should be specified. Precipitating factors can be identified in nearly all bouts of episodic HE type C and should be actively sought and treated when found (Table 3).

Every case and bout of HE should be described and classified according to all four factors, and this should be repeated at relevant intervals according to the clinical situation. The recommendations are summarized in Table 5.

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RECOMMENDATION 2

A diagnostic workup is required, considering other disorders that can alter brain function and mimic HE (GRADE II-2, A, 1).

RATIONALE 2

The diagnosis requires the detection of signs suggestive of HE in a patient with severe liver insufficiency and/or PSS who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors (Table 3) for HE (e.g., infection, bleeding, and constipation) supports the diagnosis of HE. The differential diagnosis should consider common disorders altering the level of consciousness (Table 4).

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RECOMMENDATION 3

Hepatic encephalopathy should be treated as a continuum ranging from unimpaired cognitive function with intact consciousness through coma (GRADE III, A, 1).

RATIONALE 3

Hepatic encephalopathy produces a wide spectrum of nonspecific neurological and psychiatric manifestations.[10] In its lowest expression,[43, 44] HE alters only psychometric tests oriented toward attention, working memory (WM), psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures.[45, 46]

As HE progresses, personality changes, such as apathy, irritability, and disinhibition, may be reported by the patient's relatives,[47] and obvious alterations in consciousness and motor function occur. Disturbances of the sleep-wake cycle with excessive daytime sleepiness are frequent,[48] whereas complete reversal of the sleep-wake cycle is less consistently observed.[49, 50] Patients may develop progressive disorientation to time and space, inappropriate behavior, and acute confusional state with agitation or somnolence, stupor, and, finally, coma.[51] The recent ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses the onset of disorientation or asterixis as the onset of OHE.[65]

In noncomatose patients with HE, motor system abnormalities, such as hypertonia, hyper-reflexia, and a positive Babinski sign, can be observed. In contrast, deep tendon reflexes may diminish and even disappear in coma,[52] although pyramidal signs can still be observed. Rarely, transient focal neurological deficits can occur.[53] Seizures are very rarely reported in HE.[54-56]

Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, parkinsonian-like tremor, and dyskinesia with diminished voluntary movements, are common findings; in contrast, the presence of involuntary movements similar to tics or chorea occur rarely.[52, 57]

Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma and is, in actuality, not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers or the rhythmic squeezing of the examiner's fingers. However, asterixis can be observed in other areas, such as the feet, legs, arms, tongue, and eyelids. Asterixis is not pathognomonic of HE because it can be observed in other diseases[57] (e.g., uremia).

Notably, the mental (either cognitive or behavioral) and motor signs of HE may not be expressed, or do not progress in parallel, in each individual, therefore producing difficulties in staging the severity of HE.

Hepatic myelopathy (HM)[58] is a particular pattern of HE possibly related to marked, long-standing portocaval shunting, characterized by severe motor abnormalities exceeding the mental dysfunction. Cases of paraplegia with progressive spasticity and weakness of lower limbs with hyper-reflexia and relatively mild persistent or recurrent mental alterations have been reported and do not respond to standard therapy, including ammonia lowering, but may reverse with liver transplantation (LT).[59]

Persistent HE may present with prominent extrapyramidal and/or pyramidal signs, partially overlapping with HM, in which postmortem brain examination reveals brain atrophy.[60] This condition was previously called

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RATIONALE 3 (cont.)

acquired hepatolenticular degeneration, a term currently considered obsolete. However, this cirrhosis-associated parkinsonism is unresponsive to ammonia-lowering therapy and may be more common than originally thought in patients with advanced liver disease, presenting in approximately 4% of cases.[61]

Apart from these less-usual manifestations of HE, it is widely accepted in clinical practice that all forms of HE and their manifestations are completely reversible, and this assumption still is a well-founded operational basis for treatment strategies. However, research on liver-transplanted HE patients and on patients after resolution of repeated bouts of OHE casts doubt on the full reversibility. Some mental deficits, apart from those ascribable to other transplantation-related causes, may persist and are mentioned later under transplantation.[135] Likewise, episodes of OHE may be associated with persistent cumulative deficits in WM and learning.[14]

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RECOMMENDATION 4

The diagnosis of HE is through exclusion of other causes of brain dysfunction (GRADE II-2, A, 1).

RATIONALE 4

The diagnosis requires the detection of signs suggestive of HE in a patient with severe liver insufficiency and/or PSS who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors for HE (e.g., infection, bleeding, and constipation, Table 3) supports the diagnosis of HE. The differential diagnosis should consider common disorders altering the level of consciousness (Table 4).

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RECOMMENDATION 5

Hepatic encephalopathy (HE) should be divided into various stages of severity, reflecting the degree of self-sufficiency and the need for care (GRADE III, B, 1).

RATIONALE 5

Judging and measuring the severity of HE is approached as a continuum.[65] The testing strategies in place range from simple clinical scales to sophisticated psychometric and neurophysiological tools; however, none of the current tests are valid for the entire spectrum.[11, 66] The appropriate testing and diagnostic options differ according to the acuity of the presentation and the degree of impairment.[67]

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RECOMMENDATION 6

Overt hepatic encephalopathy (OHE) is diagnosed by clinical criteria and can be graded according the West Haven Criteria and the Glasgow Coma Scale (GRADE II-2, B, 1).

RATIONALE 6

The diagnosis of OHE is based on a clinical examination and a clinical decision. Clinical scales are used to analyze its severity. Specific quantitative tests are only needed in study settings. The gold standard is the West Haven criteria (WHC; Table 2, including clinical description). However, they are subjective tools with limited interobserver reliability, especially for grade I HE, because slight hypokinesia, psychomotor slowing, and a lack of attention can easily be overlooked in clinical examination. In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of OHE.[67] Orientation or mixed scales have been used to distinguish the severity of HE.[68, 69] In patients with significantly altered consciousness, the Glasgow Coma Scale (GCS; Table 6) is widely employed and supplies an operative, robust description.

Diagnosing cognitive dysfunction is not difficult. It can be established from clinical observation as well as neuropsychological or neurophysiological tests. The difficulty is to assign them to HE. For this reason, OHE still remains a diagnosis of exclusion in this patient population that is often susceptible to mental status abnormalities resulting from medications, alcohol abuse, drug use, effects of hyponatremia, and psychiatric disease (Table 4). Therefore, as clinically indicated, exclusion of other etiologies by laboratory and radiological assessment for a patient with altered mental status in HE is warranted.

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RECOMMENDATION 7

The diagnosis and grading of minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy (CHE) can be made using several neurophysiological and psychometric tests that should be performed by experienced examiners (GRADE II-2, B, 1).

RATIONALE 7

Minimal hepatic encephalopathy and CHE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with CLD who are not disoriented or display asterixis. The term "minimal" conveys that there is no clinical sign, cognitive or other, of HE. The term "covert" includes minimal and grade 1 HE. Testing strategies can be divided into two major types: psychometric and neurophysiological.[70, 71] Because the condition affects several components of cognitive functioning, which may not be impaired to the same degree, the ISHEN suggests the use of at least two tests, depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to serve as a comparator.

Testing should be done by a trained examiner adhering to scripts that accompany the testing tools. If the test result is normal (i.e., negative for MHE or CHE), repeat testing in 6 months has been recommended.[77] A diagnosis of MHE or CHE does not automatically mean that the affected subject is a dangerous driver.[78] Medical providers are not trained to formally evaluate fitness to drive and are also not legal representatives. Therefore, providers should act in the best interests of both the patient and society while following the applicable local laws.[78] However, doctors cannot evade the responsibility of counseling patients with diagnosed HE on the possible dangerous consequences of their driving, and, often, the safest advice is to stop driving until the responsible driving authorities have formally cleared the patient for safe driving. In difficult cases, the doctor should consult with the authorities that have the expertise to test driving ability and the authority to revoke the license.

A listing of the most established testing strategies is given below. The test recommendation varies depending on the logistics, availability of tests, local norms, and cost.[65, 66, 71]

1. Portosystemic encephalopathy (PSE) syndrome test. This test battery consists of five paper-pencil tests that evaluate cognitive and psychomotor processing speed and visuomotor coordination. The tests are relatively easy to administer and have good external validity.[76] The test is often referred to as the Psychometric Hepatic Encephalopathy Score (PHES), with the latter being the sum score from all subtests of the battery. It can be obtained from Hannover Medical School (Hannover, Germany), which holds the copyright (Weissenborn.karin@mh-hannover.de). The test was developed in Germany and has been translated for use in many other countries. For illiterate patients, the figure connection test has been used as a subtest instead of the number connection test.[79]
2. The Critical Flicker Frequency (CFF) test is a psychophysiological tool defined as the frequency at which a fused light (presented from 60 Hz downward) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. The CFF test requires several trials, intact binocular vision, absence of red-green blindness, and specialized equipment.[80, 81]

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RATIONALE 7 (cont.)

3. The Continuous Reaction Time (CRT) test. The CRT test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. The test result can differentiate between organic and metabolic brain impairment and is not influenced by the patient's age or gender, and there is no learning or tiring effect. Simple software and hardware are required.[82]
4. The Inhibitory Control Test (ICT) is a computerized test of response inhibition and working memory[83] and is freely downloadable at www.hecme.tv. The ICT test has been judged to have good validity, but requires highly functional patients. The norms for the test have to be elaborated beyond the few centers that have used it.
5. The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name. Recently, mobile application software ("apps" for a smartphone or tablet computer) based on the test has been shown to identify cognitive dysfunction in cirrhosis compared to paper-pencil tests.[84] Further studies are under way to evaluate its potential for screening for MHE and CHE.
6. The SCAN Test is a computerized test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. The SCAN Test has been shown to be of prognostic value.[85]
7. Electroencephalography examination can detect changes in cortical cerebral activity across the spectrum of HE without patient cooperation or risk of a learning effect.[70] However, it is nonspecific and may be influenced by accompanying metabolic disturbances, such as hyponatremia as well as drugs. Possibly, the reliability of EEG analysis can increase with quantitative analysis. This specifically should include the background frequency with mean dominant frequency or spectral band analysis.[60] Also, in most situations, EEG requires an institutional setup and neurological expertise in evaluation, and the cost varies among hospitals.

Although the above-described tests have been used to test for MHE and CHE, there is, most often, a poor correlation between them because HE is a multidimensional dysfunction.[86] Learning effect is often observed with psychometric tests and it is unclear whether current HE therapy plays a role in the test performance. Therefore, interpretation of these tests and consideration of the results for further management need an understanding of the patient's history, current therapy, and effect on the patient's daily activities, if signs of HE are found. For multicenter studies, the diagnosis of MHE or CHE by consensus should utilize at least two of the current validated testing strategies: paper-pencil (PHES) and one of the following: computerized (CRT, ICT, SCAN, or Stroop) or neurophysiological (CFF or EEG).[66] In the clinical routine or single-center studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available and the tests have been validated for use in this patient population.[66]

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RECOMMENDATION 8

Testing for minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy (CHE) could be used in patients who would most benefit from testing, such as those with impaired quality of life or implication on employment or public safety (GRADE III, B, 2).

RATIONALE 8

Testing for MHE and CHE is important because it can prognosticate OHE development, indicate poor quality of life and reduced socioeconomic potential, and help counsel patients and caregivers about the disease. The occurrence of MHE and CHE in patients with CLD seems to be as high as 50%,[72] so, ideally, every patient at risk should be tested. However, this strategy may be costly,[73] and the consequences of the screening procedure are not always clear and treatment is not always recommended. An operational approach may be to test patients who have problems with their quality of life or in whom there are complaints from the patients and their relatives.[74] Tests positive for MHE or CHE before stopping HE drug therapy will identify patients at risk for recurrent HE.[33, 75] Furthermore, none of the available tests are specific for the condition,[76] and it is important to test only patients who do not have confounding factors, such as neuropsychiatric disorders, psychoactive medication, or current alcohol use.

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RECOMMENDATION 9

Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with chronic liver disease. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1).

RATIONALE 9

High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients with CLD.[87] However, in case an ammonia level is checked in a patient with OHE and it is normal, the diagnosis of HE is in question. For ammonia-lowering drugs, repeated measurements of ammonia may be helpful to test the efficacy. There may be logistic challenges to accurately measure blood ammonia, which should be taken into consideration. Ammonia is reported either in venous, arterial blood, or plasma ammonia, so the relevant normal should be used. Multiple methods are available, but measurements should only be employed when laboratory standards allow for reliable analyses.

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RECOMMENDATION 10

An episode of overt hepatic encephalopathy (OHE) (whether spontaneous or precipitated) should be actively treated (GRADE II-2, A, 1).

RATIONALE 10

At this time, only OHE is routinely treated.[10] Minimal hepatic encephalopathy and CHE, as its title implies, is not obvious on routine clinical examination and is predominantly diagnosed by techniques outlined in the previous section. Despite its subtle nature, MHE and CHE can have a significant effect on a patient's daily living. Special circumstances can prevail where there may be an indication to treat such a patient (e.g., impairment in driving skills, work performance, quality of life, or cognitive complaints).

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RECOMMENDATION 11

Secondary prophylaxis after an episode for overt hepatic encephalopathy (OHE) is recommended (GRADE I, A, 1).

RATIONALE 11

There are no randomized, placebo-controlled trials of lactulose for maintenance of remission from OHE. However, it is still widely recommended and practiced. A single-center, open-label RCT of lactulose demonstrated less recurrence of HE in patients with cirrhosis.[33] A recent RCT supports lactulose as prevention of HE subsequent to upper gastrointestinal (GI) bleeding.[110]

Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[101]

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RECOMMENDATION 12

Primary prophylaxis for prevention of episodes of overt hepatic encephalopathy (OHE) is not required, except in patients with cirrhosis with a known high risk to develop HE (GRADE II-3, C, 2).

RATIONALE 12

It was shown, in an open-label study,[115] that lactulose can prevent development of the first episode of OHE, but the study needs to be replicated in a larger study in a blinded fashion before firm recommendations can be made.

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RECOMMENDATION 13

Recurrent intractable overt hepatic encephalopathy (OHE), together with liver failure, is an indication for liver transplant (LT) (GRADE I).

RATIONALE 13

Liver transplantation remains the only treatment option for HE that does not improve on any other treatment, but is not without its risks. The management of these potential transplant candidates as practiced in the United States has been published elsewhere,[131, 132] and European guidelines are under way. Hepatic encephalopathy by itself is not considered an indication for LT unless associated with poor liver function. However, cases do occur where HE severely compromises the patient's quality of life and cannot be improved despite maximal medical therapy and who may be LT candidates despite otherwise good liver status. Large PSSs may cause neurological disturbances and persistent HE, even after LT. Therefore, shunts should be identified and embolization considered before or during transplantation.[133] Also, during the transplant workup, severe hyponatremia should be corrected slowly.

Hepatic encephalopathy should improve after transplant, whereas neurodegenerative disorders will worsen. Therefore, it is important to distinguish HE from other causes of mental impairment, such as Alzheimer's disease and small-vessel cerebrovascular disease. Magnetic resonance imaging and spectroscopy of the brain should be conducted, and the patient should be evaluated by an expert in neuropsychology and neuro-degenerative diseases.[134] The patient, caregivers, and health professionals should be aware that transplantation may induce brain function impairment and that not all manifestations of HE are fully reversible by transplantation.[135]

One difficult and not uncommon problem is the development of a confusional syndrome in the postoperative period. The search of the cause is often difficult, and the problem may have multiple origins. Patients with alcoholic liver disease (ALD) and those with recurrent HE before transplantation are at higher risk. Toxic effects of immunosuppressant drugs are a frequent cause, usually associated with tremor and elevated levels in blood. Other adverse cerebral effects of drugs may be difficult to diagnose. Confusion associated with fever requires a diligent, systematic search for bacterial or viral causes (e.g., cytomegalovirus). Multiple causative factors are not unusual, and the patient's problem should be approached from a broad clinical view.[136]

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RECOMMENDATION 14

Initiation of care for patients with altered consciousness.

RATIONALE 14

Patients with higher grades of HE who are at risk or unable to protect their airway need more intensive monitoring and are ideally managed in an intensive care setting. Alternative causes of encephalopathy (Table 4) are not infrequent in patients with advanced cirrhosis. Technically, if other causes of encephalopathy are present, then the episode of encephalopathy may not be termed HE. In the clinical setting, what transpires is treatment of both HE and non-HE.

Controlling precipitating factors (Table 3) in the management of OHE is of paramount importance, because nearly 90% of patients can be treated with just correction of the precipitating factor.[89] Careful attention to this issue is still the cornerstone of HE management.

In addition to the other elements of the four-pronged approach to treatment of HE, specific drug treatment is part of the management. Most drugs have not been tested by rigorous randomized, controlled studies and are utilized based on circumstantial observations. These agents include nonabsorbable disaccharides, such as lactulose, and antibiotics, such as rifaximin. Other therapies, such as oral branched-chain amino acids (BCAAs), intravenous (IV) L-ornithine L-aspartate (LOLA), probiotics, and other antibiotics, have also been used. In the hospital, a nasogastric tube can be used to administer oral therapies in patients who are unable to swallow or have an aspiration risk.

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RECOMMENDATION 15

Alternative causes of altered mental status should be sought and treated.

RATIONALE 15

Alternative causes of encephalopathy (Table 4) are not infrequent in patients with advanced cirrhosis. Technically, if other causes of encephalopathy are present, then the episode of encephalopathy may not be termed HE. In the clinical setting, what transpires is treatment of both HE and non-HE.

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RECOMMENDATION 16

Identification of precipitating factors and their correction

RATIONALE 16

Controlling precipitating factors (Table 3) in the management of OHE is of paramount importance, because nearly 90% of patients can be treated with just correction of the precipitating factor.[89] Careful attention to this issue is still the cornerstone of HE management.

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RECOMMENDATION 17

Commencement of empirical hepatic encephalopathy (HE) treatment

RATIONALE 17

In addition to the other elements of the four-pronged approach to treatment of HE, specific drug treatment is part of the management. Most drugs have not been tested by rigorous randomized, controlled studies and are utilized based on circumstantial observations. These agents include nonabsorbable disaccharides, such as lactulose, and antibiotics, such as rifaximin. Other therapies, such as oral branched-chain amino acids (BCAAs), intravenous (IV) L-ornithine L-aspartate (LOLA), probiotics, and other antibiotics, have also been used. In the hospital, a nasogastric tube can be used to administer oral therapies in patients who are unable to swallow or have an aspiration risk.

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RECOMMENDATION 18

Identify and treat precipitating factors for hepatic encephalopathy (HE) (GRADE II-2, A, 1).

RATIONALE 18

Controlling precipitating factors (Table 3) in the management of OHE is of paramount importance, because nearly 90% of patients can be treated with just correction of the precipitating factor.[89] Careful attention to this issue is still the cornerstone of HE management.

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RECOMMENDATION 19

Lactulose is the first choice for treatment of episodic overt hepatic encephalopathy (OHE) (GRADE II-1, B, 1).

RATIONALE 19

Lactulose is generally used as initial treatment for OHE. A large meta-analysis of trial data did not completely support lactulose as a therapeutic agent for treatment of OHE, but for technical reasons, it did not include the largest trials, and these agents continue to be used widely.[90] Lack of effect of lactulose should prompt a clinical search for unrecognized precipitating factors and competing causes for the brain impairment. Though it is assumed that the prebiotic effects (the drug being a nondigestible substance that promotes the growth of beneficial microorganisms in the intestines) and acidifying nature of lactulose have an additional benefit beyond the laxative effect, culture-independent studies have not borne those out.[75, 91] In addition, most recent trials on lactulose have been open label in nature. Cost considerations alone add to the argument in support of lactulose.[92] In some centers, lactitol is preferred to lactulose, based on small meta-analyses of even smaller trials.[93, 94]

In populations with a high prevalence of lactose intolerance, the use of lactose has been suggested.[95] However, the only trial to show that stool-acidifying enemas (lactose and lactulose) were superior to tap-water enemas was underpowered.[96] The use of polyethylene glycol preparation[97] needs further validation.

The dosing of lactulose should be initiated[98] when the three first elements of the four-pronged approach are completed, with 25 mL of lactulose syrup every 1-2 hours until at least two soft or loose bowel movements per day are produced. Subsequently, the dosing is titrated to maintain two to three bowel movements per day. This dose reduction should be implemented. It is a misconception that lack of effect of smaller amounts of lactulose is remedied by much larger doses. There is a danger for overuse of lactulose leading to complications, such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation, and overuse can even precipitate HE.[99]

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RECOMMENDATION 20

Rifaximin is an effective add-on therapy to lactulose for prevention of overt hepatic encephalopathy (OHE) recurrence (GRADE I, A, 1).

RATIONALE 20

Rifaximin has been used for the therapy of HE in a number of trials[100] comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies. These trials showed effect of rifaximin that was equivalent or superior to the compared agents with good tolerability. Long-term cyclical therapy over 3-6 months with rifaximin for patients with OHE has also been studied in three trials (two compared to nonabsorbable disaccharides and one against neomycin) showing equivalence in cognitive improvement and ammonia lowering. A multinational study[101] with patients having two earlier OHE bouts to maintain remission showed the superiority of rifaximin versus placebo (in the background of 91% lactulose use). No solid data support the use of rifaximin alone.

Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[101]

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RECOMMENDATION 21

Oral branched-chain amino acids (BCAAs) can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).

RATIONALE 21

An updated meta-analysis of eight randomized, controlled trials (RCTs) indicated that oral BCAA-enriched formulations improve the manifestations of episodic HE whether OHE or MHE.[102, 130] There is no effect of IV BCAA on the episodic bout of HE.[127]

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RECOMMENDATION 22

Intravenous (IV) L-ornithine L-aspartate (LOLA) can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).

RATIONALE 22

An RCT on patients with persistent HE demonstrated improvement by IV LOLA in psychometric testing and postprandial venous ammonia levels.[105] Oral supplementation with LOLA is ineffective.

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RECOMMENDATION 23

Neomycin is an alternative choice for treatment of overt hepatic encephalopathy (OHE) (GRADE II-1, B, 2).

RATIONALE 23

This antibiotic still has its advocates and was widely used in the past for HE treatment; it is a known glutaminase inhibitor.[107]

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RECOMMENDATION 24

Metronidazole is an alternative choice for treatment of overt hepatic encephalopathy (OHE) (GRADE II-3, B, 2).

RATIONALE 24

As short-term therapy,[108] metronidazole also has advocates for its use. However, long-term ototoxicity, nephrotoxicity, and neurotoxicity make these agents unattractive for continuous long-term use.

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RECOMMENDATION 25

Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1).

RATIONALE 25

There are no randomized, placebo-controlled trials of lactulose for maintenance of remission from OHE. However, it is still widely recommended and practiced. A single-center, open-label RCT of lactulose demonstrated less recurrence of HE in patients with cirrhosis.[33] A recent RCT supports lactulose as prevention of HE subsequent to upper gastrointestinal (GI) bleeding.[110]

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RECOMMENDATION 26

Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1).

RATIONALE 26

Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[101]

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RECOMMENDATION 27

Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-transjugular intrahepatic portosystemic shunt (TIPS) hepatic encephalopathy (HE) (GRADE III, B, 1).

RATIONALE 27

Once TIPS was popularized to treat complications of PH, its tendency to cause the appearance of HE, or less commonly, intractable persistent HE, was noted. Faced with severe HE as a complication of a TIPS procedure, physicians had a major dilemma. Initially, it was routine to use standard HE treatment to prevent post-TIPS HE. However, one study illustrated that neither rifaximin nor lactulose prevented post-TIPS HE any better than placebo.[111] Careful case selection has reduced the incidence of severe HE post-TIPS. If it occurs, shunt diameter reduction can reverse HE.[112] However, the original cause for placing TIPS may reappear.

Another important issue with TIPS relates to the desired portal pressure (PP) attained after placement of stents. Too low a pressure because of large stent diameter can lead to intractable HE, as noted above. There is a lack of consensus on whether to aim to reduce PP by 50% or below 12 mmHg. The latter is associated with more bouts of encephalopathy.[113] It is widely used to treat post-TIPS recurrent HE as with other cases of recurrent HE, including the cases that cannot be managed by reduction of shunt diameter.

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RECOMMENDATION 28

Under circumstances where the precipitating factors have been well controlled (i.e., infections and variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2).

RATIONALE 28

There is a nearly uniform policy to continue treatment indefinitely after it has successfully reversed a bout of OHE. The concept may be that once the thresholds for OHE is reached, then patients are at high risk for recurrent episodes. This risk appears to worsen as liver function deteriorates. However, what often occurs are recurrent bouts of OHE from a well-known list of precipitating factors. If a recurrent precipitating factor can be controlled, such as recurrent infections or variceal hemorrhages, then HE recurrence may not be a risk and HE therapy can be discontinued. Even more influential on the risk for further bouts of OHE is overall liver function and body habitus. If patients recover a significant amount of liver function and muscle mass from the time they had bouts of OHE, they may well be able to stop standard HE therapy. There are very little data on this issue, but tests positive for MHE or CHE before stopping HE drug therapy will predict patients at risk for recurrent HE.

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RECOMMENDATION 29

Treatment of minimal hepatic encephalopathy (MHE) and covert hepatic encephalopathy (CHE) is not routinely recommended apart from a case-by-case basis (GRADE II-2, B, 1).

RATIONALE 29

Although it is not standard to offer therapy for MHE and CHE, studies have been performed using several modes of therapy. The majority of studies have been for less than 6 months and do not reflect the overall course of the condition. Trials span the gamut from small open-label trials to larger, randomized, controlled studies using treatments varying from probiotics, lactulose, and rifaximin. Most studies have shown an improvement in the underlying cognitive status, but the mode of diagnosis has varied considerably among studies. A minority of studies used clinically relevant endpoints. It was shown, in an open-label study,[115] that lactulose can prevent development of the first episode of OHE, but the study needs to be replicated in a larger study in a blinded fashion before firm recommendations can be made. Studies using lactulose and rifaximin have shown improvement in quality of life[34, 116] and also in driving simulator performance.[117] Probiotics have also been used, but the open-label nature, varying amounts and types of organisms, and different outcomes make them difficult to recommend as therapeutic options at this time.[118-121]

Because of the multiple methods used to define MHE and CHE, varying endpoints, short-term treatment trials, and differing agents used in trials to date, routine treatment for MHE is not recommended at this stage. Exceptions could be made on a case-by-case basis using treatments that are approved for OHE, particularly for patients with CHE and West Haven Grade I HE.

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RECOMMENDATION 30

Daily energy intakes should be 35-40 kcal/kg ideal body weight (GRADE I, A, 1).

RATIONALE 30

All HE patients should undergo an assessment of nutritional status by taking a good dietary history, with anthropometric data and muscle strength measurement as practical, useful measures of nutritional status. In the undressed patient, particular attention is paid to the muscle structures around the shoulders and gluteal muscles. Pitfalls are water retention and obesity. Although body mass index is rarely helpful, the height-creatinine ratio may be useful, as well as the bioimpedance technique. More advanced techniques, such as dual-energy X-ray absorptiometry/CT/MR, are rarely useful for clinical purposes. The patient should undergo a structured dietary assessment, preferably by a dietician, or other specially trained staff. The majority of HE patients will fulfill criteria for nutritional therapy. The therapy is refeeding by moderate hyperalimentation, as indicated below. Small meals evenly distributed throughout the day and a late-night snack[125] should be encouraged, with avoidance of fasting. Glucose may be the most readily available calorie source, but should not be utilized as the only nutrition. Hyperalimentation should be given orally to patients that can cooperate, by gastric tube to patients who cannot take the required amount, and parenterally to other patients. The nutrition therapy should be initiated without delay and monitored during maintenance visits. The use of a multivitamin is generally recommended, although there are no firm data on the benefits of vitamin and mineral supplementation. Specific micronutrient replacement is given if there are confirmed measured losses, and zinc supplementation is considered when treating HE. If Wernicke's is suspected, large doses of thiamine should be given parenterally and before any glucose administration. Administration of large amounts of nonsaline fluids should be adjusted so as to avoid induction of hyponatremia, particularly in patients with advanced cirrhosis. If severe hyponatremia is corrected, this should be done slowly.

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RECOMMENDATION 31

Daily protein intake should be 1.2-1.5 g/kg/day (GRADE I, A, 1).

RATIONALE 31

Modulation of nitrogen metabolism is crucial to the management of all grades of HE, and nutritional options are relevant. Detailed recent guidelines for nutrition of patients with HE are given elsewhere.[122] Malnutrition is often underdiagnosed, and approximately 75% of patients with HE suffer from moderate-to-severe protein-calorie malnutrition with loss of muscle mass and energy depots. Chronic protein restriction is detrimental because patients' protein requirements are relatively greater than that of healthy patients and they are at risk of accelerated fasting metabolism. Malnutrition and loss of muscle bulk is a risk factor for development of HE and other cirrhosis complications. Sarcopenia has been proven to be an important negative prognostic indicator in patients with cirrhosis.[123, 124]

All HE patients should undergo an assessment of nutritional status by taking a good dietary history, with anthropometric data and muscle strength measurement as practical, useful measures of nutritional status. In the undressed patient, particular attention is paid to the muscle structures around the shoulders and gluteal muscles. Pitfalls are water retention and obesity. Although body mass index is rarely helpful, the height-creatinine ratio may be useful, as well as the bioimpedance technique. More advanced techniques, such as dual-energy X-ray absorptiometry/CT/MR, are rarely useful for clinical purposes. The patient should undergo a structured dietary assessment, preferably by a dietician, or other specially trained staff. The majority of HE patients will fulfill criteria for nutritional therapy. The therapy is refeeding by moderate hyperalimentation, as indicated below. Small meals evenly distributed throughout the day and a late-night snack[125] should be encouraged, with avoidance of fasting. Glucose may be the most readily available calorie source, but should not be utilized as the only nutrition. Hyperalimentation should be given orally to patients that can cooperate, by gastric tube to patients who cannot take the required amount, and parenterally to other patients. The nutrition therapy should be initiated without delay and monitored during maintenance visits. The use of a multivitamin is generally recommended, although there are no firm data on the benefits of vitamin and mineral supplementation. Specific micronutrient replacement is given if there are confirmed measured losses, and zinc supplementation is considered when treating HE. If Wernicke's is suspected, large doses of thiamine should be given parenterally and before any glucose administration. Administration of large amounts of nonsaline fluids should be adjusted so as to avoid induction of hyponatremia, particularly in patients with advanced cirrhosis. If severe hyponatremia is corrected, this should be done slowly.

There is consensus that low-protein nutrition should be avoided for patients with HE. Some degree of protein restriction may be inevitable in the first few days of OHE treatment, but should not be prolonged. Substitution of milk-based or vegetable protein or supplementing with BCAAs is preferable to reduction of total protein intake. Oral BCAA-enriched nutritional formulation may be used to treat HE and generally improves the nutritional status of patients with cirrhosis,[126] but IV BCAA for an episode of HE has no effect.[127] The studies on the effect of oral BCAA have been more encouraging[128, 129] and confirmed by a recent meta-analysis of 11 trials.[130] Ultimately, the effects of these amino acids may turn out to have more important effects on promotion of maintenance of lean body mass than a direct effect on HE.

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RECOMMENDATION 32

Small meals or liquid nutritional supplements evenly distributed throughout the day and a late-night snack should be offered (GRADE I, A, 1).

RATIONALE 32

All HE patients should undergo an assessment of nutritional status by taking a good dietary history, with anthropometric data and muscle strength measurement as practical, useful measures of nutritional status. In the undressed patient, particular attention is paid to the muscle structures around the shoulders and gluteal muscles. Pitfalls are water retention and obesity. Although body mass index is rarely helpful, the height-creatinine ratio may be useful, as well as the bioimpedance technique. More advanced techniques, such as dual-energy X-ray absorptiometry/CT/MR, are rarely useful for clinical purposes. The patient should undergo a structured dietary assessment, preferably by a dietician, or other specially trained staff. The majority of HE patients will fulfill criteria for nutritional therapy. The therapy is refeeding by moderate hyperalimentation, as indicated below. Small meals evenly distributed throughout the day and a late-night snack[125] should be encouraged, with avoidance of fasting. Glucose may be the most readily available calorie source, but should not be utilized as the only nutrition. Hyperalimentation should be given orally to patients that can cooperate, by gastric tube to patients who cannot take the required amount, and parenterally to other patients. The nutrition therapy should be initiated without delay and monitored during maintenance visits. The use of a multivitamin is generally recommended, although there are no firm data on the benefits of vitamin and mineral supplementation. Specific micronutrient replacement is given if there are confirmed measured losses, and zinc supplementation is considered when treating HE. If Wernicke's is suspected, large doses of thiamine should be given parenterally and before any glucose administration. Administration of large amounts of nonsaline fluids should be adjusted so as to avoid induction of hyponatremia, particularly in patients with advanced cirrhosis. If severe hyponatremia is corrected, this should be done slowly.

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RECOMMENDATION 33

Oral branched-chain amino acid (BCAA) supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein (GRADE II-2, B, 2).

RATIONALE 33

There is consensus that low-protein nutrition should be avoided for patients with HE. Some degree of protein restriction may be inevitable in the first few days of OHE treatment, but should not be prolonged. Substitution of milk-based or vegetable protein or supplementing with BCAAs is preferable to reduction of total protein intake. Oral BCAA-enriched nutritional formulation may be used to treat HE and generally improves the nutritional status of patients with cirrhosis,[126] but IV BCAA for an episode of HE has no effect.[127] The studies on the effect of oral BCAA have been more encouraging[128, 129] and confirmed by a recent meta-analysis of 11 trials.[130] Ultimately, the effects of these amino acids may turn out to have more important effects on promotion of maintenance of lean body mass than a direct effect on HE.

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Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL

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Abbreviations

AASLD: American Association for the Study of Liver Diseases

ACLF: acute-on-chronic liver failure

ALD: alcoholic liver disease

ALF: acute liver failure

BCAAs: branched-chain amino acids

CFF: Critical Flicker Frequency

CHE: covert HE

CLD: chronic liver disease

CRT: Continuous Reaction Time

CT: computed tomography

DM: diabetes mellitus

EASL: European Association for the Study of the Liver

EEG: electroencephalography

GI: gastrointestinal

GRADE: the Grading of Recommendation Assessment, Development, and Evaluation

GCS: Glasgow Coma Scale

GPB: glyceryl phenylbutyrate

HCV: hepatitis C virus

HE: hepatic encephalopathy

HM: hepatic myelopathy

ICT: Inhibitory Control Test

ISHEN: International Society for Hepatic Encephalopathy and Nitrogen Metabolism

IV: intravenous

LOLA: L-ornithine L-aspartate

LT: Liver transplantation

MHE: minimal HE

MR: magnetic resonance

OHE: overt HE

PH: portal hypertension

PHES: Psychometric Hepatic Encephalopathy Score

PP: portal pressure

PSE: portosystemic encephalopathy

PSS: portosystemic shunting

RCT: randomized, controlled trial

TIPS: transjugular intrahepatic portosystemic shunt

VB: variceal bleeding

WHC: West Haven Criteria

WM: working memory

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The AASLD/EASL Practice Guideline Subcommittee on Hepatic Encephalopathy are: Jayant A. Talwalkar (Chair, AASLD), Hari S. Conjeevaram, Michael Porayko, Raphael B. Merriman, Peter L.M. Jansen, and Fabien Zoulim. This guideline has been approved by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and represents the position of both associations.

PREAMBLE

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) Policy on the Joint Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD/EASL Practice Guidelines Subcommittee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup, with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong (1) or weak (2).

TABLE 1. GRADE SYSTEM FOR EVIDENCE

GRADE	EVIDENCE	
I	Randomized, controlled trials	
II-1	Controlled trials without randomization	
II-2	Cohort or case-control analytic studies	
II-3	Multiple time series, dramatic uncontrolled experiments	
III	Opinions of respected authorities, descriptive epidemiology	
EVIDENCE	**DESCRIPTION**	
High quality	Further research is very unlikely to change our confidence in the estimated effect.	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate effect and may change the estimate.	B
Low quality	Further research is likely to have an important impact on our confidence in the estimate effect and is likely to change the estimate. Any change of estimate is uncertain.	C
RECOMMENDATION		
Strong	Factors influencing the strength of recommendation included the quality of evidence, presumed patient-important outcomes, and costs.	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher costs, or resource consumption.	2

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LITERATURE REVIEW AND ANALYSIS

The literature databases and search strategies are outlined below. The resulting literature database was available to all members of the writing group (i.e., the authors). They selected references within their field of expertise and experience and graded the references according to the GRADE system.[1] The selection of references for the guideline was based on a validation of the appropriateness of the study design for the stated purpose, a relevant number of patients under study, and confidence in the participating centers and authors. References on original data were preferred and those that were found unsatisfactory in any of these respects were excluded from further evaluation. There may be limitations in this approach when recommendations are needed on rare problems or problems on which scant original data are available. In such cases, it may be necessary to rely on less-qualified references with a low grading. As a result of the important changes in the treatment of complications of cirrhosis (renal failure, infections, and variceal bleeding [VB]), studies performed more than 30 years ago have generally not been considered for these guidelines.

INTRODUCTION

Hepatic encephalopathy (HE) is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers. Furthermore, cognitive impairment associated with cirrhosis results in utilization of more health care resources in adults than other manifestations of liver disease.[2] Progress in the area has been hindered by the complex pathogenesis that is not yet fully elucidated. Apart from such biological factors, there remains the larger obstacle that there are no universally accepted standards for the definition, diagnosis, classification, or treatment of HE, mostly as a result of insufficient clinical studies and standardized definitions. Clinical management tends to be dependent on local standards and personal views. This is an unfavorable situation for patients and contrasts with the severity of the condition and the high level of standardization in other complications of cirrhosis. The lack of consistency in the nomenclature and general standards renders comparisons among studies and patient populations difficult, introduces bias, and hinders progress in clinical research for HE. The latest attempts to standardize the nomenclature were published in 2002 and suggestions for the design of HE trials in 2011. Because there is an unmet need for recommendations on the clinical management of HE, the EASL and the AASLD jointly agreed to create these practice guidelines. It is beyond the scope of these guidelines to elaborate on the theories of pathogenesis of HE, as well as the management of encephalopathy resulting from acute liver failure (ALF), which has been published as guidelines recently. Rather, its aim is to present standardized terminology and recommendations to all health care workers who have patients with HE, regardless of their medical discipline, and focus on adult patients with chronic liver disease (CLD), which is, by far, the most frequent scenario.

As these guidelines on HE were created, the authors found a limited amount of high-quality evidence to extract from the existing literature. There are many reasons for this; the elusive character of HE is among them, as well as the lack of generally accepted and utilized terms for description and categorization of HE. This makes a practice guideline all the more necessary for future improvement of clinical studies and, subsequently, the quality of management of patients with HE. With the existing body of evidence, these guidelines encompass the authors' best, carefully considered opinions. Although not all readers may necessarily agree with all aspects of the guidelines, their creation and adherence to them is the best way forward, with future adjustments when there is emergence of new evidence.

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DEFINITION OF THE DISEASE/CONDITION

OVERVIEW

Advanced liver disease and portosystemic shunting (PSS), far from being an isolated disorder of the liver, have well-known consequences on the body and, notably, on brain functioning. The alterations of brain functioning, which can produce behavioral, cognitive, and motor effects, were termed portosystemic encephalopathy (PSE)[3] and later included in the term HE.[4]

Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence.[5, 6] Even in its mildest form, HE reduces health-related quality of life and is a risk factor for bouts of severe HE.[7-9]

DEFINITION OF HE

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.

This definition, in line with previous versions,[10, 11] is based on the concept that encephalopathies are "diffuse disturbances of brain function"[5] and that the adjective "hepatic" implies a causal connection to liver insufficiency and/or perihepatic vascular shunting.[6]

EPIDEMIOLOGY

The incidence and prevalence of HE are related to the severity of the underlying liver insufficiency and PSS.[12-15] In patients with cirrhosis, fully symptomatic overt HE (OHE) is an event that defines the decompensated phase of the disease, such as VB or ascites.[7] Overt hepatic encephalopathy is also reported in subjects without cirrhosis with extensive PSS.[8, 9]

The manifestation of HE may not be an obvious clinical finding and there are multiple tools used for its detection, which influences the variation in the reported incidence and prevalence rates.

The prevalence of OHE at the time of diagnosis of cirrhosis is 10%-14% in general,[16-18] 16%-21% in those with decompensated cirrhosis,[7, 19] and 10%-50% in patients with transjugular intrahepatic portosystemic shunt (TIPS).[20, 21] The cumulated numbers indicate that OHE will occur in 30%-40% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly.[22] Minimal HE (MHE) or covert HE (CHE) occurs in 20%-80% of patients with cirrhosis.[23-27, 81] The prevalence of HE in prehepatic noncirrhotic portal hypertension (PH) is not well defined.

The risk for the first bout of OHE is 5%-25% within 5 years after cirrhosis diagnosis, depending on the presence of risk factors, such as other complications to cirrhosis (MHE or CHE, infections, VB, or ascites) and probably diabetes and hepatitis C.[28-32] Subjects with a previous bout of OHE were found to have a 40% cumulative risk of recurring OHE at 1 year,[33] and subjects with recurrent OHE have a 40% cumulative risk of another recurrence within 6 months, despite lactulose treatment. Even individuals with cirrhosis and only mild cognitive dysfunction or mild electroencephalography (EEG) slowing develop approximately one bout of OHE per 3 years of survival.[34, 35]

After TIPS, the median cumulative 1-year incidence of OHE is 10%-50%[36, 37] and is greatly influenced by the patient selection criteria adopted.[38] Comparable data were obtained by PSS surgery.[39]

It gives an idea of the frequent confrontation of the health care system by patients with HE that they accounted for approximately 110,000 hospitalizations yearly (2005-2009)[40] in the United States. Though numbers in the European

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Union (EU) are not readily available, these predictions are expected to be similar. Furthermore, the burden of CLD and cirrhosis is rapidly increasing,[41, 42] and more cases will likely be encountered to further define the epidemiology of HE.

CLINICAL PRESENTATION

Hepatic encephalopathy produces a wide spectrum of nonspecific neurological and psychiatric manifestations.[10] In its lowest expression,[43, 44] HE alters only psychometric tests oriented toward attention, working memory (WM), psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures.[45, 46]

As HE progresses, personality changes, such as apathy, irritability, and disinhibition, may be reported by the patient's relatives,[47] and obvious alterations in consciousness and motor function occur. Disturbances of the sleep-wake cycle with excessive daytime sleepiness are frequent,[48] whereas complete reversal of the sleep-wake cycle is less consistently observed.[49, 50] Patients may develop progressive disorientation to time and space, inappropriate behavior, and acute confusional state with agitation or somnolence, stupor, and, finally, coma.[51] The recent ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses the onset of disorientation or asterixis as the onset of OHE.[65]

In noncomatose patients with HE, motor system abnormalities, such as hypertonia, hyper-reflexia, and a positive Babinski sign, can be observed. In contrast, deep tendon reflexes may diminish and even disappear in coma,[52] although pyramidal signs can still be observed. Rarely, transient focal neurological deficits can occur.[53] Seizures are very rarely reported in HE.[54-56]

Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, parkinsonian-like tremor, and dyskinesia with diminished voluntary movements, are common findings; in contrast, the presence of involuntary movements similar to tics or chorea occur rarely.[52, 57]

Asterixis or "flapping tremor" is often present in the early to middle stages of HE that precede stupor or coma and is, in actuality, not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers or the rhythmic squeezing of the examiner's fingers. However, asterixis can be observed in other areas, such as the feet, legs, arms, tongue, and eyelids. Asterixis is not pathognomonic of HE because it can be observed in other diseases[57] (e.g., uremia).

Notably, the mental (either cognitive or behavioral) and motor signs of HE may not be expressed, or do not progress in parallel, in each individual, therefore producing difficulties in staging the severity of HE.

Hepatic myelopathy (HM)[58] is a particular pattern of HE possibly related to marked, long-standing portocaval shunting, characterized by severe motor abnormalities exceeding the mental dysfunction. Cases of paraplegia with progressive spasticity and weakness of lower limbs with hyper-reflexia and relatively mild persistent or recurrent mental alterations have been reported and do not respond to standard therapy, including ammonia lowering, but may reverse with liver transplantation (LT).[59]

Persistent HE may present with prominent extrapyramidal and/or pyramidal signs, partially overlapping with HM, in which postmortem brain examination reveals brain atrophy.[60] This condition was previously called acquired hepatolenticular degeneration, a term currently considered obsolete. However, this cirrhosis-associated parkinsonism is unresponsive to ammonia-lowering therapy and may be more common than originally thought in patients with advanced liver disease, presenting in approximately 4% of cases.[61]

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Apart from these less-usual manifestations of HE, it is widely accepted in clinical practice that all forms of HE and their manifestations are completely reversible, and this assumption still is a well-founded operational basis for treatment strategies. However, research on liver-transplanted HE patients and on patients after resolution of repeated bouts of OHE casts doubt on the full reversibility. Some mental deficits, apart from those ascribable to other transplantation-related causes, may persist and are mentioned later under transplantation.[135] Likewise, episodes of OHE may be associated with persistent cumulative deficits in WM and learning.[14]

CLASSIFICATION

Hepatic encephalopathy should be classified according to all of the following four factors.[10]

1. According to the underlying disease, HE is subdivided into
   - Type A resulting from ALF
   - Type B resulting predominantly from portosystemic bypass or shunting
   - Type C resulting from cirrhosis

The clinical manifestations of types B and C are similar, whereas type A has distinct features and, notably, may be associated with increased intracranial pressure and a risk of cerebral herniation. The management of HE type A is described in recent guidelines on ALF[62, 63] and is not included in this document.

2. According to the severity of manifestations. The continuum that is HE has been arbitrarily subdivided. For clinical and research purposes, a scheme of such grading is provided (Table 2). Operative classifications that refer to defined functional impairments aim at increasing intra- and inter-rater reliability and should be used whenever possible.

3. According to its time course, HE is subdivided into
   - Episodic HE
   - Recurrent HE denotes bouts of HE that occur with a time interval of 6 months or less.
   - Persistent HE denotes a pattern of behavioral alterations that are always present and interspersed with relapses of overt HE.

4. According to the existence of precipitating factors, HE is subdivided into
   - Nonprecipitated or
   - Precipitated, and the precipitating factors should be specified. Precipitating factors can be identified in nearly all bouts of episodic HE type C and should be actively sought and treated when found (Table 3).

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TABLE 2. WHC AND CLINICAL DESCRIPTION

WHC INCLUDING MHE	ISHEN	DESCRIPTION	SUGGESTED OPERATIVE CRITERIA	COMMENT
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS.

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TABLE 3. PRECIPITATING FACTORS FOR OHE BY DECREASING FREQUENCY

EPISODIC	RECURRENT
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Modified from Strauss E, da Costa MF. The importance of bacterial infections as precipitating factors of chronic hepatic encephalopathy in cirrhosis. Hepatogastroenterology 1998;45:900-904.
**More recent unpublished case series confirm the dominant role of infections.*

A fifth classification, according to whether or not the patient has acute-on-chronic liver failure (ACLF), has recently been suggested.[64] Although the management, mechanism, and prognostic impact differ, this classification is still a research area.

DIFFERENTIAL DIAGNOSES

The diagnosis requires the detection of signs suggestive of HE in a patient with severe liver insufficiency and/or PSS who does not have obvious alternative causes of brain dysfunction. The recognition of precipitating factors for HE (e.g., infection, bleeding, and constipation) supports the diagnosis of HE. The differential diagnosis should consider common disorders altering the level of consciousness (Table 4).

TABLE 4. DIFFERENTIAL DIAGNOSIS OF HE

Overt HE or acute confusional state
Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea
Hyponatremia and sepsis can both produce encephalopathy per se and precipitate HE by interactions with the pathophysiological mechanisms. In end-stage liver disease, uremic encephalopathy and HE may overlap.

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RECOMMENDATIONS:

1. **Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).**
2. **A diagnostic workup is required, considering other disorders that can alter brain function and mimic HE (GRADE II-2, A, 1).**

Every case and bout of HE should be described and classified according to all four factors, and this should be repeated at relevant intervals according to the clinical situation. The recommendations are summarized in Table 5.

TABLE 5. HE DESCRIPTION AND CLINICAL EXAMPLE

Type	Grade		Time Course	Spontaneous or Precipitated
A	MHE	Covert	Episodic	Spontaneous
	1			
B	2	Overt	Recurrent	Precipitated (specify)
	3			
C			Persistent	
	4			

The HE patient should be characterized by one component from each of the four columns. Example of a recommended description of a patient with HE: "The patient has HE, Type C, Grade 3, Recurrent, Precipitated (by urinary tract infection)." The description may be supplemented with operative classifications (e.g., the Glasgow Coma Score or psychometric performance).

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DIAGNOSIS AND TESTING

CLINICAL EVALUATION

Judging and measuring the severity of HE is approached as a continuum.[65] The testing strategies in place range from simple clinical scales to sophisticated psychometric and neurophysiological tools; however, none of the current tests are valid for the entire spectrum.[11, 66] The appropriate testing and diagnostic options differ according to the acuity of the presentation and the degree of impairment.[67]

DIAGNOSIS AND TESTING FOR OHE

The diagnosis of OHE is based on a clinical examination and a clinical decision. Clinical scales are used to analyze its severity. Specific quantitative tests are only needed in study settings. The gold standard is the West Haven criteria (WHC; Table 2, including clinical description). However, they are subjective tools with limited interobserver reliability, especially for grade I HE, because slight hypokinesia, psychomotor slowing, and a lack of attention can easily be overlooked in clinical examination. In contrast, the detection of disorientation and asterixis has good inter-rater reliability and thus are chosen as marker symptoms of OHE.[67] Orientation or mixed scales have been used to distinguish the severity of HE.[68, 69] In patients with significantly altered consciousness, the Glasgow Coma Scale (GCS; Table 6) is widely employed and supplies an operative, robust description.

TABLE 6. GCS[169]

GCS						
	1	2	3	4	5	6
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	N/A	N/A
Verbal	Makes no sounds	Incomprehensible sounds	Utters inappropriate words	Confused, disoriented	Oriented, converses normally	N/A
Motor	Makes no movements	Extension to painful stimuli (decerebrate response)	Abnormal flexion to painful stimuli (decorticate response)	Flexion/ withdrawal to painful stimuli	Localizes painful stimuli	Obeys commands

The scale comprises three tests: eyes, verbal, and motor responses. The three values separately as well as their sum are considered. The lowest possible GCS (the sum) is 3 (deep coma or death), whereas the highest is 15 (fully awake person). Abbreviation: N/A, not applicable.

Diagnosing cognitive dysfunction is not difficult. It can be established from clinical observation as well as neuropsychological or neurophysiological tests. The difficulty is to assign them to HE. For this reason, OHE still remains a diagnosis of exclusion in this patient population that is often susceptible to mental status abnormalities resulting from medications, alcohol abuse, drug use, effects of hyponatremia, and psychiatric disease (Table 4). Therefore, as clinically indicated, exclusion of other etiologies by laboratory and radiological assessment for a patient with altered mental status in HE is warranted.

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TESTING FOR MHE AND CHE

Minimal hepatic encephalopathy and CHE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with CLD who are not disoriented or display asterixis. The term "minimal" conveys that there is no clinical sign, cognitive or other, of HE. The term "covert" includes minimal and grade 1 HE. Testing strategies can be divided into two major types: psychometric and neurophysiological.[70, 71] Because the condition affects several components of cognitive functioning, which may not be impaired to the same degree, the ISHEN suggests the use of at least two tests, depending on the local population norms and availability, and preferably with one of the tests being more widely accepted so as to serve as a comparator.

Testing for MHE and CHE is important because it can prognosticate OHE development, indicate poor quality of life and reduced socioeconomic potential, and help counsel patients and caregivers about the disease. The occurrence of MHE and CHE in patients with CLD seems to be as high as 50%,[72] so, ideally, every patient at risk should be tested. However, this strategy may be costly,[73] and the consequences of the screening procedure are not always clear and treatment is not always recommended. An operational approach may be to test patients who have problems with their quality of life or in whom there are complaints from the patients and their relatives.[74] Tests positive for MHE or CHE before stopping HE drug therapy will identify patients at risk for recurrent HE.[33, 75] Furthermore, none of the available tests are specific for the condition,[76] and it is important to test only patients who do not have confounding factors, such as neuropsychiatric disorders, psychoactive medication, or current alcohol use.

Testing should be done by a trained examiner adhering to scripts that accompany the testing tools. If the test result is normal (i.e., negative for MHE or CHE), repeat testing in 6 months has been recommended.[77] A diagnosis of MHE or CHE does not automatically mean that the affected subject is a dangerous driver.[78] Medical providers are not trained to formally evaluate fitness to drive and are also not legal representatives. Therefore, providers should act in the best interests of both the patient and society while following the applicable local laws.[78] However, doctors cannot evade the responsibility of counseling patients with diagnosed HE on the possible dangerous consequences of their driving, and, often, the safest advice is to stop driving until the responsible driving authorities have formally cleared the patient for safe driving. In difficult cases, the doctor should consult with the authorities that have the expertise to test driving ability and the authority to revoke the license.

A listing of the most established testing strategies is given below. The test recommendation varies depending on the logistics, availability of tests, local norms, and cost.[65, 66, 71]

1. Portosystemic encephalopathy (PSE) syndrome test. This test battery consists of five paper-pencil tests that evaluate cognitive and psychomotor processing speed and visuomotor coordination. The tests are relatively easy to administer and have good external validity.[76] The test is often referred to as the Psychometric Hepatic Encephalopathy Score (PHES), with the latter being the sum score from all subtests of the battery. It can be obtained from Hannover Medical School (Hannover, Germany), which holds the copyright (Weissenborn.karin@mh-hannover.de). The test was developed in Germany and has been translated for use in many other countries. For illiterate patients, the figure connection test has been used as a subtest instead of the number connection test.[79]
2. The Critical Flicker Frequency (CFF) test is a psychophysiological tool defined as the frequency at which a fused light (presented from 60 Hz downward) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. The CFF test requires several trials, intact binocular vision, absence of red-green blindness, and specialized equipment.[80, 81]
3. The Continuous Reaction Time (CRT) test. The CRT test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. The test result can differentiate between organic and metabolic brain impairment and is not influenced by the patient's age or gender, and there is no learning or tiring effect. Simple software and hardware are required.[82]

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4. The Inhibitory Control Test (ICT) is a computerized test of response inhibition and working memory[83] and is freely downloadable at www.hecme.tv. The ICT test has been judged to have good validity, but requires highly functional patients. The norms for the test have to be elaborated beyond the few centers that have used it.
5. The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name. Recently, mobile application software ("apps" for a smartphone or tablet computer) based on the test has been shown to identify cognitive dysfunction in cirrhosis compared to paper-pencil tests.[84] Further studies are under way to evaluate its potential for screening for MHE and CHE.
6. The SCAN Test is a computerized test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. The SCAN Test has been shown to be of prognostic value.[85]
7. Electroencephalography examination can detect changes in cortical cerebral activity across the spectrum of HE without patient cooperation or risk of a learning effect.[70] However, it is nonspecific and may be influenced by accompanying metabolic disturbances, such as hyponatremia as well as drugs. Possibly, the reliability of EEG analysis can increase with quantitative analysis. This specifically should include the background frequency with mean dominant frequency or spectral band analysis.[60] Also, in most situations, EEG requires an institutional setup and neurological expertise in evaluation, and the cost varies among hospitals.

Although the above-described tests have been used to test for MHE and CHE, there is, most often, a poor correlation between them because HE is a multidimensional dysfunction.[86] Learning effect is often observed with psychometric tests and it is unclear whether current HE therapy plays a role in the test performance. Therefore, interpretation of these tests and consideration of the results for further management need an understanding of the patient's history, current therapy, and effect on the patient's daily activities, if signs of HE are found. For multicenter studies, the diagnosis of MHE or CHE by consensus should utilize at least two of the current validated testing strategies: paper-pencil (PHES) and one of the following: computerized (CRT, ICT, SCAN, or Stroop) or neurophysiological (CFF or EEG).[66] In the clinical routine or single-center studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available and the tests have been validated for use in this patient population.[66]

LABORATORY TESTING

High blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients with CLD.[87] However, in case an ammonia level is checked in a patient with OHE and it is normal, the diagnosis of HE is in question. For ammonia-lowering drugs, repeated measurements of ammonia may be helpful to test the efficacy. There may be logistic challenges to accurately measure blood ammonia, which should be taken into consideration. Ammonia is reported either in venous, arterial blood, or plasma ammonia, so the relevant normal should be used. Multiple methods are available, but measurements should only be employed when laboratory standards allow for reliable analyses.

BRAIN SCANS

Computed tomography (CT) or magnetic resonance (MR) or other image modality scans do not contribute diagnostic or grading information. However, the risk of intracerebral hemorrhage is at least 5-fold increased in this patient group,[88] and the symptoms may be indistinguishable, so a brain scan is usually part of the diagnostic workup of first-time HE and on clinical suspicion of other pathology.

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RECOMMENDATIONS:

3. **Hepatic encephalopathy should be treated as a continuum ranging from unimpaired cognitive function with intact consciousness through coma (GRADE III, A, 1).**
4. **The diagnosis of HE is through exclusion of other causes of brain dysfunction (GRADE II-2, A, 1).**
5. **Hepatic encephalopathy should be divided into various stages of severity, reflecting the degree of self-sufficiency and the need for care (GRADE III, B, 1).**
6. **Overt hepatic encephalopathy is diagnosed by clinical criteria and can be graded according the WHC and the GCS (GRADE II-2, B, 1).**
7. **The diagnosis and grading of MHE and CHE can be made using several neurophysiological and psychometric tests that should be performed by experienced examiners (GRADE II-2, B, 1).**
8. **Testing for MHE and CHE could be used in patients who would most benefit from testing, such as those with impaired quality of life or implication on employment or public safety (GRADE III, B, 2).**
9. **Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1).**

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TREATMENT

GENERAL PRINCIPLES

At this time, only OHE is routinely treated.[10] Minimal hepatic encephalopathy and CHE, as its title implies, is not obvious on routine clinical examination and is predominantly diagnosed by techniques outlined in the previous section. Despite its subtle nature, MHE and CHE can have a significant effect on a patient's daily living. Special circumstances can prevail where there may be an indication to treat such a patient (e.g., impairment in driving skills, work performance, quality of life, or cognitive complaints). Liver transplantation is mentioned under the treatment recommendations.

RECOMMENDATIONS:

General recommendations for treatment of episodic OHE type C include the following:

10. **An episode of OHE (whether spontaneous or precipitated) should be actively treated (GRADE II-2, A, 1).**
11. **Secondary prophylaxis after an episode for overt HE is recommended (GRADE I, A, 1).**
12. **Primary prophylaxis for prevention of episodes of OHE is not required, except in patients with cirrhosis with a known high risk to develop HE (GRADE II-3, C, 2).**
13. **Recurrent intractable OHE, together with liver failure, is an indication for LT (GRADE I).**

SPECIFIC APPROACH TO OHE TREATMENT

A four-pronged approach to management of HE is recommended (GRADE II-2, A, 1):

14. **Initiation of care for patients with altered consciousness**
15. **Alternative causes of altered mental status should be sought and treated.**
16. **Identification of precipitating factors and their correction**
17. **Commencement of empirical HE treatment**

COMMENTS ON MANAGEMENT STRATEGY

Patients with higher grades of HE who are at risk or unable to protect their airway need more intensive monitoring and are ideally managed in an intensive care setting. Alternative causes of encephalopathy are not infrequent in patients with advanced cirrhosis. Technically, if other causes of encephalopathy are present, then the episode of encephalopathy may not be termed HE. In the clinical setting, what transpires is treatment of both HE and non-HE.

Controlling precipitating factors in the management of OHE is of paramount importance, because nearly 90% of patients can be treated with just correction of the precipitating factor.[89] Careful attention to this issue is still the cornerstone of HE management.

THERAPY FOR EPISODES OF OHE

In addition to the other elements of the four-pronged approach to treatment of HE, specific drug treatment is part of the management. Most drugs have not been tested by rigorous randomized, controlled studies and are utilized based on circumstantial observations. These agents include nonabsorbable disaccharides, such as lactulose, and

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antibiotics, such as rifaximin. Other therapies, such as oral branched-chain amino acids (BCAAs), intravenous (IV) L-ornithine L-aspartate (LOLA), probiotics, and other antibiotics, have also been used. In the hospital, a nasogastric tube can be used to administer oral therapies in patients who are unable to swallow or have an aspiration risk.

Nonabsorbable Disaccharides

Lactulose is generally used as initial treatment for OHE. A large meta-analysis of trial data did not completely support lactulose as a therapeutic agent for treatment of OHE, but for technical reasons, it did not include the largest trials, and these agents continue to be used widely.[90] Lack of effect of lactulose should prompt a clinical search for unrecognized precipitating factors and competing causes for the brain impairment. Though it is assumed that the prebiotic effects (the drug being a nondigestible substance that promotes the growth of beneficial microorganisms in the intestines) and acidifying nature of lactulose have an additional benefit beyond the laxative effect, culture-independent studies have not borne those out.[75, 91] In addition, most recent trials on lactulose have been open label in nature. Cost considerations alone add to the argument in support of lactulose.[92] In some centers, lactitol is preferred to lactulose, based on small meta-analyses of even smaller trials.[93, 94]

In populations with a high prevalence of lactose intolerance, the use of lactose has been suggested.[95] However, the only trial to show that stool-acidifying enemas (lactose and lactulose) were superior to tap-water enemas was underpowered.[96] The use of polyethylene glycol preparation[97] needs further validation.

The dosing of lactulose should be initiated[98] when the three first elements of the four-pronged approach are completed, with 25 mL of lactulose syrup every 1-2 hours until at least two soft or loose bowel movements per day are produced. Subsequently, the dosing is titrated to maintain two to three bowel movements per day. This dose reduction should be implemented. It is a misconception that lack of effect of smaller amounts of lactulose is remedied by much larger doses. There is a danger for overuse of lactulose leading to complications, such as aspiration, dehydration, hypernatremia, and severe perianal skin irritation, and overuse can even precipitate HE.[99]

Rifaximin

Rifaximin has been used for the therapy of HE in a number of trials[100] comparing it with placebo, other antibiotics, nonabsorbable disaccharides, and in dose-ranging studies. These trials showed effect of rifaximin that was equivalent or superior to the compared agents with good tolerability. Long-term cyclical therapy over 3-6 months with rifaximin for patients with OHE has also been studied in three trials (two compared to nonabsorbable disaccharides and one against neomycin) showing equivalence in cognitive improvement and ammonia lowering. A multinational study[101] with patients having two earlier OHE bouts to maintain remission showed the superiority of rifaximin versus placebo (in the background of 91% lactulose use). No solid data support the use of rifaximin alone.

Other Therapies

Many drugs have been used for treatment of HE, but data to support their use are limited, preliminary, or lacking. However, most of these drugs can safely be used despite their limited proven efficacy.

BCAAs

An updated meta-analysis of eight randomized, controlled trials (RCTs) indicated that oral BCAA-enriched formulations improve the manifestations of episodic HE whether OHE or MHE.[102, 130] There is no effect of IV BCAA on the episodic bout of HE.[127]

Metabolic Ammonia Scavengers

These agents, through their metabolism, act as urea surrogates excreted in urine. Such drugs have been used for treatment of inborn errors of the urea cycle for many years. Different forms are available and currently present as promising investigational agents. Ornithine phenylacetate has been studied for HE, but further clinical reports are awaited.[103] Glyceryl phenylbutyrate (GPB) was tested in a recent RCT[104] on patients who had experienced two or

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more episodes of HE in the last 6 months and who were maintained on standard therapy (lactulose ± rifaximin). The GPB arm experienced fewer episodes of HE and hospitalizations as well as longer time to first event. More clinical studies on the same principle are under way and, if confirmed, may lead to clinical recommendations.

L-ornithine L-aspartate (LOLA)
An RCT on patients with persistent HE demonstrated improvement by IV LOLA in psychometric testing and postprandial venous ammonia levels.[105] Oral supplementation with LOLA is ineffective.

Probiotics
A recent, open-label study of either lactulose, probiotics, or no therapy in patients with cirrhosis who recovered from HE found fewer episodes of HE in the lactulose or probiotic arms, compared to placebo, but were not different between either interventions. There was no difference in rates of readmission in any of the arms of the study.[106]

Glutaminase Inhibitors
Portosystemic shunting up-regulates the intestinal glutaminase gene so that intestinal glutaminase inhibitors may be useful by reducing the amounts of ammonia produced by the gut.

Neomycin
This antibiotic still has its advocates and was widely used in the past for HE treatment; it is a known glutaminase inhibitor.[107]

Metronidazole
As short-term therapy,[108] metronidazole also has advocates for its use. However, long-term ototoxicity, nephrotoxicity, and neurotoxicity make these agents unattractive for continuous long-term use.

Flumazenil
This drug is not frequently used. It transiently improves mental status in OHE without improvement on recovery or survival. The effect may be of importance in marginal situations to avoid assisted ventilation. Likewise, the effect may be helpful in difficult differential diagnostic situations by confirming reversibility (e.g., when standard therapy unexpectedly fails or when benzodiazepine toxicity is suspected).

Laxatives
Simple laxatives alone do not have the prebiotic properties of disaccharides, and no publications have been forthcoming on this issue.

Albumin
A recent RCT on OHE patients on rifaximin given daily IV albumin or saline showed no effect on resolution of HE, but was related to better postdischarge survival.[109]

RECOMMENDATIONS:

18. **Identify and treat precipitating factors for HE (GRADE II-2, A, 1).**
19. **Lactulose is the first choice for treatment of episodic OHE (GRADE II-1, B, 1).**
20. **Rifaximin is an effective add-on therapy to lactulose for prevention of OHE recurrence (GRADE I, A, 1).**
21. **Oral BCAAs can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).**
22. **IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy (GRADE I, B, 2).**

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23. Neomycin is an alternative choice for treatment of OHE (GRADE II-1, B, 2).

24. Metronidazole is an alternative choice for treatment of OHE (GRADE II-3, B, 2).

PREVENTION OF OVERT HEPATIC ENCEPHALOPATHY

After an Episode of OHE

There are no randomized, placebo-controlled trials of lactulose for maintenance of remission from OHE. However, it is still widely recommended and practiced. A single-center, open-label RCT of lactulose demonstrated less recurrence of HE in patients with cirrhosis.[33] A recent RCT supports lactulose as prevention of HE subsequent to upper gastrointestinal (GI) bleeding.[110]

Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[101]

Hepatic Encephalopathy After TIPS

Once TIPS was popularized to treat complications of PH, its tendency to cause the appearance of HE, or less commonly, intractable persistent HE, was noted. Faced with severe HE as a complication of a TIPS procedure, physicians had a major dilemma. Initially, it was routine to use standard HE treatment to prevent post-TIPS HE. However, one study illustrated that neither rifaximin nor lactulose prevented post-TIPS HE any better than placebo.[111] Careful case selection has reduced the incidence of severe HE post-TIPS. If it occurs, shunt diameter reduction can reverse HE.[112] However, the original cause for placing TIPS may reappear.

Another important issue with TIPS relates to the desired portal pressure (PP) attained after placement of stents. Too low a pressure because of large stent diameter can lead to intractable HE, as noted above. There is a lack of consensus on whether to aim to reduce PP by 50% or below 12 mmHg. The latter is associated with more bouts of encephalopathy.[113] It is widely used to treat post-TIPS recurrent HE as with other cases of recurrent HE, including the cases that cannot be managed by reduction of shunt diameter.

Hepatic Encephalopathy Secondary to Portosystemic Shunts (PSSs)

Recurrent bouts of overt HE in patients with preserved liver function consideration should lead to a search for large spontaneous PSSs. Certain types of shunts, such as splenorenal shunts, can be successfully embolized with rapid clearance of overt HE in a fraction of patients in a good liver function status, despite the risk for subsequent VB.[114]

RECOMMENDATIONS:

25. Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1).

26. Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1).

27. Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1).

Discontinuation of Prophylactic Therapy

There is a nearly uniform policy to continue treatment indefinitely after it has successfully reversed a bout of OHE. The concept may be that once the thresholds for OHE is reached, then patients are at high risk for recurrent

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episodes. This risk appears to worsen as liver function deteriorates. However, what often occurs are recurrent bouts of OHE from a well-known list of precipitating factors. If a recurrent precipitating factor can be controlled, such as recurrent infections or variceal hemorrhages, then HE recurrence may not be a risk and HE therapy can be discontinued. Even more influential on the risk for further bouts of OHE is overall liver function and body habitus. If patients recover a significant amount of liver function and muscle mass from the time they had bouts of OHE, they may well be able to stop standard HE therapy. There are very little data on this issue, but tests positive for MHE or CHE before stopping HE drug therapy will predict patients at risk for recurrent HE.

RECOMMENDATION:

28. Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2).

TREATMENT OF MINIMAL HE AND COVERT HE

Although it is not standard to offer therapy for MHE and CHE, studies have been performed using several modes of therapy. The majority of studies have been for less than 6 months and do not reflect the overall course of the condition. Trials span the gamut from small open-label trials to larger, randomized, controlled studies using treatments varying from probiotics, lactulose, and rifaximin. Most studies have shown an improvement in the underlying cognitive status, but the mode of diagnosis has varied considerably among studies. A minority of studies used clinically relevant endpoints. It was shown, in an open-label study,[115] that lactulose can prevent development of the first episode of OHE, but the study needs to be replicated in a larger study in a blinded fashion before firm recommendations can be made. Studies using lactulose and rifaximin have shown improvement in quality of life[34, 116] and also in driving simulator performance.[117] Probiotics have also been used, but the open-label nature, varying amounts and types of organisms, and different outcomes make them difficult to recommend as therapeutic options at this time.[118-121]

Because of the multiple methods used to define MHE and CHE, varying endpoints, short-term treatment trials, and differing agents used in trials to date, routine treatment for MHE is not recommended at this stage. Exceptions could be made on a case-by-case basis using treatments that are approved for OHE, particularly for patients with CHE and West Haven Grade I HE.

RECOMMENDATION:

29. Treatment of MHE and CHE is not routinely recommended apart from a case-by-case basis (GRADE II-2, B, 1).

NUTRITION

Modulation of nitrogen metabolism is crucial to the management of all grades of HE, and nutritional options are relevant. Detailed recent guidelines for nutrition of patients with HE are given elsewhere.[122] Malnutrition is often underdiagnosed, and approximately 75% of patients with HE suffer from moderate-to-severe protein-calorie malnutrition with loss of muscle mass and energy depots. Chronic protein restriction is detrimental because patients' protein requirements are relatively greater than that of healthy patients and they are at risk of accelerated fasting metabolism. Malnutrition and loss of muscle bulk is a risk factor for development of HE and other cirrhosis complications. Sarcopenia has been proven to be an important negative prognostic indicator in patients with cirrhosis.[123, 124] All HE patients should undergo an assessment of nutritional status by taking a good dietary history,

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with anthropometric data and muscle strength measurement as practical, useful measures of nutritional status. In the undressed patient, particular attention is paid to the muscle structures around the shoulders and gluteal muscles. Pitfalls are water retention and obesity. Although body mass index is rarely helpful, the height-creatinine ratio may be useful, as well as the bioimpedance technique. More advanced techniques, such as dual-energy X-ray absorptiometry/CT/MR, are rarely useful for clinical purposes. The patient should undergo a structured dietary assessment, preferably by a dietician, or other specially trained staff. The majority of HE patients will fulfill criteria for nutritional therapy. The therapy is refeeding by moderate hyperalimentation, as indicated below. Small meals evenly distributed throughout the day and a late-night snack[125] should be encouraged, with avoidance of fasting. Glucose may be the most readily available calorie source, but should not be utilized as the only nutrition. Hyperalimentation should be given orally to patients that can cooperate, by gastric tube to patients who cannot take the required amount, and parenterally to other patients. The nutrition therapy should be initiated without delay and monitored during maintenance visits. The use of a multivitamin is generally recommended, although there are no firm data on the benefits of vitamin and mineral supplementation. Specific micronutrient replacement is given if there are confirmed measured losses, and zinc supplementation is considered when treating HE. If Wernicke's is suspected, large doses of thiamine should be given parenterally and before any glucose administration. Administration of large amounts of nonsaline fluids should be adjusted so as to avoid induction of hyponatremia, particularly in patients with advanced cirrhosis. If severe hyponatremia is corrected, this should be done slowly.

There is consensus that low-protein nutrition should be avoided for patients with HE. Some degree of protein restriction may be inevitable in the first few days of OHE treatment, but should not be prolonged. Substitution of milk-based or vegetable protein or supplementing with BCAAs is preferable to reduction of total protein intake. Oral BCAA-enriched nutritional formulation may be used to treat HE and generally improves the nutritional status of patients with cirrhosis,[126] but IV BCAA for an episode of HE has no effect.[127] The studies on the effect of oral BCAA have been more encouraging[128, 129] and confirmed by a recent meta-analysis of 11 trials.[130] Ultimately, the effects of these amino acids may turn out to have more important effects on promotion of maintenance of lean body mass than a direct effect on HE.

RECOMMENDATIONS:

30. **Daily energy intakes should be 35-40 kcal/kg ideal body weight (GRADE I, A, 1).**
31. **Daily protein intake should be 1.2-1.5 g/kg/day (GRADE I, A, 1).**
32. **Small meals or liquid nutritional supplements evenly distributed throughout the day and a late-night snack should be offered (GRADE I, A, 1).**
33. **Oral BCAA supplementation may allow recommended nitrogen intake to be achieved and maintained in patients intolerant of dietary protein (GRADE II-2, B, 2).**

LIVER TRANSPLANTATION (LT)

Liver transplantation remains the only treatment option for HE that does not improve on any other treatment, but is not without its risks. The management of these potential transplant candidates as practiced in the United States has been published elsewhere,[131, 132] and European guidelines are under way. Hepatic encephalopathy by itself is not considered an indication for LT unless associated with poor liver function. However, cases do occur where HE severely compromises the patient's quality of life and cannot be improved despite maximal medical therapy and who may be LT candidates despite otherwise good liver status. Large PSSs may cause neurological disturbances and persistent HE, even after LT. Therefore, shunts should be identified and embolization considered before or during transplantation.[133] Also, during the transplant workup, severe hyponatremia should be corrected slowly.

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Hepatic encephalopathy should improve after transplant, whereas neurodegenerative disorders will worsen. Therefore, it is important to distinguish HE from other causes of mental impairment, such as Alzheimer's disease and small-vessel cerebrovascular disease. Magnetic resonance imaging and spectroscopy of the brain should be conducted, and the patient should be evaluated by an expert in neuropsychology and neuro-degenerative diseases.[134] The patient, caregivers, and health professionals should be aware that transplantation may induce brain function impairment and that not all manifestations of HE are fully reversible by transplantation.[135]

One difficult and not uncommon problem is the development of a confusional syndrome in the postoperative period. The search of the cause is often difficult, and the problem may have multiple origins. Patients with alcoholic liver disease (ALD) and those with recurrent HE before transplantation are at higher risk. Toxic effects of immunosuppressant drugs are a frequent cause, usually associated with tremor and elevated levels in blood. Other adverse cerebral effects of drugs may be difficult to diagnose. Confusion associated with fever requires a diligent, systematic search for bacterial or viral causes (e.g., cytomegalovirus). Multiple causative factors are not unusual, and the patient's problem should be approached from a broad clinical view.[136]

ECONOMIC/COST IMPLICATIONS

As outlined under epidemiology, the burden of HE is rapidly increasing and more cases of HE will be encountered, with substantial direct costs being attributed to hospitalizations for HE and to indirect costs. The patients with HE hospitalized in the United States in 2003 generated charges of approximately US$ 1 billion.[40, 137] Resource utilization for this group of patients is also increasing as a result of longer lengths of stay and more complex and expensive hospital efforts, as well as a reported in-patient mortality of 15%. There are no directly comparable EU cost data, but by inference from epidemiological data, the event rate should be approximately the same and the costs comparable, differences between U.S. and EU hospital financing notwithstanding. These costs are an underestimate, because out-patient care, disability and lost productivity, and the negative effect on the patient's family or support network were not quantified.[138]

The cost of medications is very variable to include in analyses because it varies widely from country to country and are usually determined by what the pharmaceutical companies believe the market can sustain. Regarding the beneficial effects of rifaximin, cost-effective analyses based on current drug prices favor treatments that are lactulose based,[92, 139] as do analyses of accidents, deaths/morbidity, and time off from work[73] in patients with MHE or CHE. Therefore, until the costs of other medications fall, lactulose continues to be the least expensive, most cost-effective treatment.

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ALTERNATIVE CAUSES OF ALTERED MENTAL STATUS

DISORDERS TO BE CONSIDERED

The neurological manifestations of HE are nonspecific. Therefore, concomitant disorders have to be considered as an additional source of central nervous system dysfunction in any patient with CLD. Most important are renal dysfunction, hyponatremia, diabetes mellitus (DM), sepsis, and thiamine deficiency (Wernicke's encephalopathy); noteworthy also is intracranial bleeding (chronic subdural hematoma and parenchymal bleeding).

INTERACTION BETWEEN CONCOMITANT DISORDERS AND LIVER DISEASE WITH REGARD TO BRAIN FUNCTION

Hyponatremia is an independent risk factor for development of HE in patients with cirrhosis.[140, 141] The incidence of HE increases[142] and the response rate to lactulose therapy decreases[143] with decreasing serum sodium concentrations.

Diabetes mellitus (DM) has been suggested as a risk factor for development of HE, especially in patients with hepatitis C virus (HCV) cirrhosis,[144] but the relationship may also be observed in other cirrhosis etiologies.[145]

An increased risk to develop HE has also been shown in patients with cirrhosis with renal dysfunction,[146] independent of the severity of cirrhosis.

Neurological symptoms are observed in 21%-33% of patients with cirrhosis with sepsis and in 60%-68% of those with septic shock.[147] Patients with cirrhosis do not differ from patients without cirrhosis regarding their risk to develop brain dysfunction with sepsis,[148] although it is assumed that systemic inflammation and hyperammonemia act synergistically with regard to the development of HE.

Thiamine deficiency predominantly occurs in patients with ALD, but may also occur as a consequence of malnutrition in end-stage cirrhosis of any cause. The cerebral symptoms disorientation, alteration of consciousness, ataxia, and dysarthria cannot be differentiated as being the result of thiamine deficiency or hyperammonemia by clinical examination.[149] In any case of doubt, thiamine should be given IV before glucose-containing solutions.

EFFECT OF THE ETIOLOGY OF THE LIVER DISEASE UPON BRAIN FUNCTION

Data upon the effect of the underlying liver disease on brain function are sparse, except for alcoholism and hepatitis C. Rare, but difficult, cases may be the result of Wilson's disease.

Even patients with alcohol disorder and no clinical disease have been shown to exhibit deficits in episodic memory,[150] working memory and executive functions,[151] visuoconstruction abilities,[152] and upper- and lower-limb motor skills.[153] The cognitive dysfunction is more pronounced in those patients with alcohol disorder who are at risk of Wernicke's encephalopathy as a result of malnutrition or already show signs of the problem.[154] Thus, it remains unclear whether the disturbance of brain function in patients with ALD is the result of HE, alcohol toxicity, or thiamine deficiency.

There is mounting evidence that HCV is present and replicates within the brain.[155-158] Approximately half of HCV patients suffer chronic fatigue irrespective of the grade of their liver disease,[159, 160] and even patients with only mild liver disease display cognitive dysfunction,[161, 162] involving verbal learning, attention, executive function, and memory. Likewise, patients with primary biliary cirrhosis and primary sclerosing cholangitis may have severe fatigue and impairment of attention, concentration, and psychomotor function irrespective of the grade of liver disease.[163-168]

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DIAGNOSTIC MEASURES TO DIFFERENTIATE BETWEEN HE AND CEREBRAL DYSFUNCTION RESULTING FROM OTHER CAUSES

Because HE shares symptoms with all concomitant disorders and underlying diseases, it is difficult in the individual case to differentiate between the effects of HE and those resulting from other causes. In some cases, the time course and response to therapy may be the best support of HE. As mentioned, a normal blood ammonia level in a patient suspected of HE calls for consideration. None of the diagnostic measures used at present has been evaluated for their ability to differentiate between HE and other causes of brain dysfunction. The EEG would not be altered by DM or alcohol disorders, but may show changes similar to those with HE in cases of renal dysfunction, hyponatremia, or septic encephalopathy. Psychometric tests are able to detect functional deficits, but are unable to differentiate between different causes for these deficits. Brain imaging methods have been evaluated for their use in diagnosing HE, but the results are disappointing. Nevertheless, brain imaging should be done in every patient with CLD and unexplained alteration of brain function to exclude structural lesions. In rare cases, reversibility by flumazenil may be useful.

FOLLOW-UP

After a hospital admission for HE, the following issues should be addressed.

DISCHARGE FROM HOSPITAL

1. The medical team should confirm the neurological status before discharge and judge to what extent the patient's neurological deficits could be attributable to HE, or to other neurological comorbidities, for appropriate discharge planning. They should inform caregivers that the neurological status may change once the acute illness has settled and that requirement for medication could change.
2. Precipitating and risk factors for development of HE should be recognized. Future clinical management should be planned according to (1) potential for improvement of liver function (e.g., acute alcoholic hepatitis, autoimmune hepatitis, and hepatitis B), (2) presence of large portosystemic shunts (which may be suitable for occlusion), and (3) characteristics of precipitating factors (e.g., prevention of infection, avoidance of recurrent GI bleeding, diuretics, or constipation).
3. Out-patient postdischarge consultations should be planned to adjust treatment and prevent the reappearance of precipitating factors. Close liaison should be made with the patient's family, the general practitioner, and other caregivers in the primary health service, so that all parties involved understand how to manage HE in the specific patient and prevent repeated hospitalizations.

PREVENTIVE CARE AFTER DISCHARGE

1. Education of patients and relatives should include (1) effects of medication (lactulose, rifaximin, and so on) and the potential side effects (e.g., diarrhea), (2) importance of adherence, (3) early signs of recurring HE, and (4) actions to be taken if recurrence (e.g., anticonstipation measures for mild recurrence and referral to general practitioner or hospital if HE with fever).
2. Prevention of recurrence: the underlying liver pathology may improve with time, nutrition, or specific measures, but usually patients who have developed OHE have advanced liver failure without much hope for functional improvements and are often potential LT candidates. Managing the complications of cirrhosis (e.g., spontaneous bacterial peritonitis and GI bleeding) should be instituted according to available guidelines. Pharmacological secondary prevention is mentioned above.

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3. Monitoring neurological manifestations is necessary in patients with persisting HE to adjust treatment and in patients with previous HE to investigate the presence and degree of MHE or CHE or signs of recurring HE. The cognitive assessment depends on the available normative data and local resources. The motor assessment should include evaluation of gait and walking and consider the risk of falls.
4. The socioeconomic implications of persisting HE or MHE or CHE may be very profound. They include a decline in work performance, impairment in quality of life, and increase in the risk of accidents. These patients often require economic support and extensive care from the public social support system and may include their relatives. All these issues should be incorporated into the follow-up plan.
5. Treatment endpoints depend on the monitoring used and the specialist clinic, but at least they have to cover two aspects: (1) cognitive performance (improvement in one accepted test as a minimum) and (2) daily life autonomy (basic and operational abilities).
6. Nutritional aspects: weight loss with sarcopenia may worsen HE, and, accordingly, the nutritional priority is to provide enough protein and energy to favor a positive nitrogen balance and increase in muscle mass, as recommended above.
7. Portosystemic shunt: occlusion of a dominant shunt may improve HE in patients with recurring HE and good liver function.[114] Because the current experience is limited, the risks and benefits must be weighed before employing this strategy.

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SUGGESTIONS FOR FUTURE RESEARCH

This section deals with research into the management of HE. However, such research should always be based on research into the pathophysiology of HE. It is necessary to gain more insight into which liver functions are responsible for maintenance of cerebral functions, which alterations in intestinal function and microbiota make failure of these liver functions critical, which brain functions are particularly vulnerable to the combined effects of the aforementioned events, and, finally, which factors outside this axis that result in the emergence of HE (e.g., inflammation, endocrine settings, or malnutrition). Therefore, the research fields into pathophysiology and clinical management should remain in close contact. Such collaboration should result in new causal and symptomatic treatment modalities that need and motivate clinical trials.

There is a severe and unmet need for controlled clinical trials on treatment effects on all the different forms of HE. Decisive clinical studies are few, although the number of patients and their resource utilization is high. There are no data on which factors and patients represent the higher costs, and research is needed to examine the effect of specific cirrhosis-related complications. At present, there is an insufficient basis for allocating resources and establishing priority policies regarding management of HE. Many drugs that were assessed for HE several decades ago were studied following a standard of care that, at present, is obsolete. Any study of treatment for HE should be reassessed or repeated using the current standard of care. It is critical to develop protocols to identify precipitating factors and ACLF. The benefit of recently assessed drugs is concentrated in the prevention of recurrence, and there is a large need for trials on episodic HE.

There is also an unmet need for research into diagnostic methods that is necessary to form a basis for clinical trials. The diagnosis of MHE and CHE has received enormous interest, but it is still not possible to compare results among studies and the precision should be improved. It may be useful to develop, validate, and implement HE scales that combine the degree of functional liver failure and PSS with more than one psychometric method.

One important area of uncertainty is whether the term CHE, which was introduced to expand MHE toward grade I of oriented patients, is informative and clinically valuable. This needs to be evaluated by a data-driven approach. Likewise, the distinction between isolated liver failure and ACLF-associated HE should be evaluated by independent data.

A closer scientific collaboration between clinical hepatologists and dedicated brain researchers, including functional brain imaging experts, is needed. Likewise, neuropsychologists and psychiatrists are needed to clarify the broad spectrum of neuropsychiatric symptoms that can be observed in patients with liver disease. Syndrome diagnoses should be more precisely classified and transformed into classifiable entities based on pathophysiology and responding to the requirements of clinical hepatology practice and research.

Future studies should fill our gaps in knowledge. They should be focused on assessing the effects of HE on individuals and society, how to use diagnostic tools appropriately, and define the therapeutic goals in each clinical scenario (Table 7).

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TABLE 7. SUGGESTED AREAS OF FUTURE RESEARCH IN HE

Aspect	Need	Suggestions
Effect on individuals and society	Demonstrate the effects of HE on patients and society in order to encourage diagnosis and therapy	1. Studies on economic and social burden among different societies 2. Studies on cultural aspects on therapy and compliance with treatment 3. Long-term natural history studies
Diagnostic improvement	Enhance the diagnostic accuracy	1. Studies on clinically applicable high-sensitivity screening tests that can guide which patients may benefit from dedicated testing 2. Development of algorithms to decide when and how to apply the diagnostic process 3. Studies on competing factors (i.e., HCV, delirium, depression, and narcotic use on diagnosis) 4. Studies on biomarkers for presence and progression of neurological dysfunction
Treatment goals	Improve the appropriate use of therapeutic tools in different clinical scenarios	1. Studies on selecting who will benefit from preventing the first OHE episode 2. Studies for >6 months to evaluate compliance and continued effects on cognitive improvement 3. Develop protocols focused on how to diagnose and treat precipitating factors 4. Determine what should be the standard protocol to investigate new therapies 5. Decide which therapies have been adequately studied and are not a priority for additional studies

RECOMMENDATIONS ON FUTURE RESEARCH IN HE

The existing literature suffers from a lack of standardization, and this heterogeneity makes pooling of data difficult or meaningless. Recommendations to promote consistency across the field have been published by ISHEN.[66] Following is a synopsis of the recommendations.

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TRIALS IN PATIENTS WITH EPISODIC OHE

1. Patients who are not expected to survive the hospitalization, who are terminally ill or have ACLF should be excluded.
2. A detailed standard-of-care algorithm must be agreed upon *a priori* and must be instituted and monitored diligently throughout the trial.
3. Patients should not be entered into trials until after the institution of optimal standard-of-care therapy and only if their mental state abnormalities persist.
4. Provided the optimal standard of care is instituted and maintained, the treatment trial can be initiated earlier if they include a placebo comparator; this would allow an evaluation of the trial treatment as an adjuvant to standard therapy.
5. Large-scale, multicenter treatment trials should be evaluated using robust clinical outcomes, such as in-hospital and remote survival, liver-related and total deaths, completeness and speed of recovery from HE, number of days in intensive care, total length of hospital stay, quality-of-life measures, and associated costs. Markers for HE, such as psychometric testing, can be employed if standardized and validated tools are available in all centers. Individual centers can utilize additional, accessible, validated markers if they choose.
6. Proof-of-concept trials will additionally be monitored using tools that best relate to the endpoints anticipated or expected; this may involve use of neural imaging or measurement of specific biomarkers.

TRIALS IN PATIENTS WITH MHE OR CHE

Trials in this population should be randomized and placebo controlled.

1. Patients receiving treatment for OHE or those with previous episodes of OHE should be excluded.
2. In single-center or proof-of-concept studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available and the tests have been validated for use in this patient population.
3. Further information is needed on the interchangeability and standardization of tests to assess the severity of HE for use in multicenter trials. As an interim, two or more of the current validated tests should be used and applied uniformly across centers.

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