CME

ACG Clinical Guideline: Hepatic Encephalopathy

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Hepatic encephalopathy is a major and burdensome complication of cirrhosis, with significant consequences for patients, families, and healthcare systems. Its progression from covert to overt disease is not fully reflected in current transplant listing criteria, leaving many patients inadequately prioritized for transplantation despite substantial impairment in quality of life. This guideline of the American College of Gastroenterology presents 24 recommendations for the diagnosis, management, and prevention strategies for hepatic encephalopathy. The Grading of Recommendations, Assessment, Development, and Evaluation process was used to assess the quality of evidence for each statement. Key concepts are also provided for statements to which the Grading of Recommendations, Assessment, Development, and Evaluation process has not been applied.

KEYWORDS: cirrhosis; disorder of gut-brain axis; Bristol Stool scale; liver transplant; caregiver burden; readmission; cognitive testing

ABBREVIATIONS: ACLF, acute on chronic liver failure; AI, artificial intelligence; AKI, acute kidney injury; APRI, AST to Platelet Ratio Index; AUDIT-C, Alcohol Use Disorder Identification Test; BCAA, branched chain amino acids; BM, bowel movements; CHE, covert hepatic encephalopathy; CPAP, continuous positive airway pressure; CT, computed tomography; DAST, Drug Abuse Screen Test; DDLT, deceased donor liver transplant; DM, diabetes mellitus; ER, Emergency room; FMT, fecal microbiota transplant; GABA, gamma aminobutyric acid; GCS, Glasgow Coma Scale; HCC, hepatocellular cancer; HE, hepatic encephalopathy; HEGI, Hepatic Encephalopathy Grading Instrument; HEST, Hepatic Encephalopathy Staging Tool; HRQoL, health-related quality of life; ICU, intensive care unit; IR, interventional radiology; ISHEN, international society for hepatic encephalopathy and nitrogen metabolism; LDLT, living donor liver transplant; LES, late-evening snack; LFI, liver frailty index; LOLA, L-ornithine L-aspartate; LT, liver transplant; MAMC, mid arm muscle circumference; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; MMSE, mini mental status exam; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; NGT, nasogastric tube; OHE, overt hepatic encephalopathy; OSA, obstructive sleep apnea; PETH, phosphatidylethanolamine; PHQ, patient health questionnaire; PMI, psoas muscle index; PO, per oral; PROMIS8, Patient-Reported Outcomes Measurement Information System; PT, physical therapy; PTSD, posttraumatic test disorder; QoL, quality of life; RCT, randomized controlled trial; RR, relative risk; RRT, renal replacement therapy; SBO, small bowel obstruction; SDU/MICU, step-down/medical intensive care unit; SPSS, spontaneous porto-systemic shunts; STOP-BANG, (Snore; Tired, Observed apnea; Pressure (high blood pressure), BMI (>35); Age (>50), Neck circumference (>40cm/17in men, >40cm/16in women), and Gender (male)]; TIPS, transjugular intrahepatic portosystemic shunt; TUG, timed up and go; WH, West Haven

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D846

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INTRODUCTION

Under the auspices of the American College of Gastroenterology (ACG) Practice Parameters Committee, a group of experts in hepatic encephalopathy (HE) were identified for the writing group. The proposed writing group was reviewed by the ACG Practice Parameters Committee and the ACG leadership, and the final approved writing group consisted of the current authorship team.

Regular meetings were conducted among this writing group throughout the guideline development process to formulate PICO questions that guided the subsequent literature search, development of recommendation statements and key concepts, Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessments, and the preparation of the full guideline document. The search strategy was developed and executed in PubMed (MEDLINE) and then adapted to the syntax

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Table 1. Grading of Recommendations, Assessment, Development, and Evaluation: strength of recommendations, certainty of evidence, and implications for the patients and clinicians

Strength of recommendation	Criteria
Factors influencing the strength of the recommendation include the certainty of the evidence, clinical and patient-reported outcomes, risk of harm, and costs/healthcare resource utilization	
Strong	Strong recommendations are offered when the desirable effects of an intervention clearly outweigh the undesirable effects Implications from a patient and clinician perspective: Patients: Most individuals in this situation would prefer the recommended course of action and only a small proportion would choose an alternative Clinicians: Most patients should receive the recommended course of action or an alternative with similar strength of recommendation
Conditional	Conditional recommendations are offered when tradeoffs are less certain—either because of low certainty of evidence or because evidence suggests that desirable and undesirable effects are closely balanced Implications from a patient and clinician perspective: Patients: Some individuals would want the suggested course of action whereas others may not. A discussion regarding pros, cons, and available alternatives is appropriate to reach an individualized patient-specific decision Clinicians: A shared decision-making model through a discussion regarding the available evidence and alternative options is appropriate, taking into consideration the values and preferences of the patient
Quality of evidence	**Criteria**
High	We are very confident that the true effect closely aligns with that of the estimate of the effect
Moderate	We have a moderate level of confidence in the estimate of effect. It is likely that the true effect is close to the estimate of the effect
Low	Our confidence in the effect estimate is limited. The true effect could differ from the estimate of effect
Very low	We have very little confidence in the estimate effect. The true effect may be substantially different from the estimate of effect

and controlled vocabulary of Embase and Cochrane Library. The searches were filtered to fully published articles on human populations in the English language, with a focus on the highest levels of evidence. Priority was given to systematic reviews and meta-analyses, followed by randomized controlled trials (RCTs) whenever available. These guidelines are presented in the format of statements that were deemed to be clinically important by the content authors. The GRADE process was used to assess the quality of evidence for each statement (Table 1) (1–4). The certainty of evidence is expressed high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (2). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs considering perceived patient-based and population-based factors (5). Furthermore, a narrative evidence summary for each section provides important definitions and further details for the data supporting the statements.

In addition to guideline recommendations, the authors have highlighted key concept statements that are not included in the GRADE assessment. Key concepts are statements to which the GRADE process has not been applied and can include both expert opinion recommendations and definitions/epidemiological statements. Tables 2 and 3 have the recommendations and key concepts that have also been displayed in their respective sections below.

BACKGROUND

HE is one of the most impactful complications of cirrhosis (6). The negative effects are felt by the patients, their families, and the healthcare systems (7). The progression of HE from the covert to the overt stage is not completely captured by the current transplant listing criteria, and patients with HE often find themselves in the limbo of not being sick enough to be transplanted and not well enough to live life to their fullest (8).

The term "hepatic encephalopathy" is an oversimplification because the pathogenesis involves several organs and varying precipitants (7). HE development, as noted above, has manifold negative impacts on patients, families, and healthcare systems, and as a testament to the complexity of this syndrome, requires a personalized village to manage this (9). The 3 villages of HE are noted in Figure 1 (village 1: multiple pathogenetic factors within the patient; village 2: negative impact on patients, families, and healthcare systems; and village 3: multiple specialties and practices needed to adequately manage HE).

The definition of HE in prior American Association for the Study of Liver Diseases and European Association for the Study of the Liver Guidelines, which has stood the test of time, is "hepatic encephalopathy (HE) is brain dysfunction resulting from liver impairment or portosystemic shunting, presenting as a spectrum of neurological and psychiatric manifestations" (10,11). Implicit in this definition is (i) HE can occur

Table 2. Recommendations

CHE/MHE
1. In patients being evaluated for MHE or CHE, we suggest a single-test strategy over a 2-test combination strategy (conditional recommendation, very low certainty of evidence)
2. In patients being evaluated for MHE or CHE, we suggest against using serum ammonia levels alone to make the diagnosis (conditional recommendation, very low certainty of evidence)
3. In patients with MHE/CHE, we suggest treatment with lactulose vs no treatment (conditional recommendation, low certainty of evidence)
4. There is insufficient evidence to recommend for or against routine treatment of MHE/CHE for prevention of OHE (insufficient evidence, no recommendation)
Inpatient management of HE
5. In patients with HE, we suggest against routine testing of serum ammonia to guide HE treatment decisions (conditional recommendation, very low certainty of evidence)
6. In patients with cirrhosis and confusion without new-onset focal neurologic deficits, we suggest against routine brain imaging (conditional recommendation, very low certainty of evidence)
7. In patients with OHE, we recommend treatment with lactulose to improve patient outcomes and prevent recurrence of OHE episodes (strong recommendation, moderate certainty of evidence)
8. In patients with OHE, we suggest treatment with high-volume (e.g., 4 L) polyethylene glycol preparations as an alternative option to lactulose therapy (conditional recommendation, low certainty of evidence)
9. In patients with acute OHE, we suggest adding rifaximin to lactulose therapy vs lactulose therapy alone (conditional recommendation, low certainty of evidence)
Prevention of HE recurrence
10. After an initial episode of OHE, we recommend lactulose titrated to 2–3 soft bowel movements daily as outpatient first-line therapy for prevention of HE recurrence (strong recommendations, high certainty of evidence)
11. In patients treated with lactulose for HE, we suggest using the Bristol Stool Scale along with bowel movement frequency for the outpatient titration of lactulose to reduce readmissions (conditional recommendation, very low certainty of evidence)
12. In patients with cirrhosis and OHE, we suggest rifaximin therapy in the outpatient setting to prevent HE recurrence (conditional recommendation, low certainty of evidence)
13. In patients with OHE on lactulose maintenance therapy who experience recurrent episodes of HE, we recommend addition of rifaximin treatment (strong recommendation, high certainty of evidence)
14. In patients with OHE and persistent symptoms despite lactulose and rifaximin therapy, we suggest the addition of zinc supplementation in those with low blood zinc levels (conditional recommendation, very low certainty of evidence)
15. We suggest implementing health information technology interventions, such as the Patient Buddy App or electronic clinical reminders, when feasible, to optimize HE management (conditional recommendations, very low certainty of evidence)
16. We suggest shunt embolization in patients with refractory HE on optimized medical therapy who have adequate hepatic function and no contraindications (conditional recommendation, very low certainty of evidence)
Sarcopenia and nutrition
17. We recommend a protein intake target of 1.2–1.5 g/kg/d in outpatients with HE (strong recommendation, moderate certainty of evidence)
18. We recommend BCAA supplementation in individuals with HE if protein needs cannot be met by food alone (strong recommendation, moderate certainty of evidence)
19. We suggest a late-night snack for patients with cirrhosis to reduce frailty and HE (conditional recommendation, very low certainty of evidence)
20. We suggest against protein restriction in patients with HE because it increases muscle breakdown and does not reduce the duration of HE (conditional recommendation, very low certainty of evidence)
21. We suggest exercise interventions in patients with HE to reduce the risk for falls, lower portal pressure, and increase the capacity of skeletal muscle for ammonia metabolism (conditional recommendation, low certainty of evidence)
HE in the context of TIPS
22. We recommend initiating rifaximin therapy 14 d before elective TIPS insertion and continuing for at least 6 mo in patients with decompensated cirrhosis with or without a prior episode of OHE to decrease the risk of recurrent or de novo OHE (strong recommendation, moderate certainty of evidence)
23. We suggest embolizing extrahepatic collaterals at the time of TIPS to reduce post-TIPS HE (conditional recommendation, low certainty of evidence)
Liver transplant and HE
24. For patients with multiple HE episodes and MELD score <15, we suggest evaluating candidacy for living donor liver transplantation (conditional recommendation, low certainty of evidence)

CHE, covert hepatic encephalopathy; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; TIPS, transjugular portosystemic shunt.

Table 3. Key concepts

CHE/MHE
1. Given the low reproducibility of clinical diagnosis of CHE (minimal or grade 1 HE), CHE should be defined by excluding OHE (grade 2 or higher) in the appropriate clinical context
2. Isolated asterixis without alterations in behavior or alertness is not enough to diagnose OHE
3. Patients with cirrhosis and 1 or more of the following features could be prioritized for MHE testing: a. Hypoalbuminemia b. Decompensated cirrhosis (e.g., presence of ascites, variceal bleeding, or jaundice) c. Clinically significant portal hypertension or presence of portosystemic shunts d. Cirrhosis with nonspecific cognitive complaints, difficulties with concentration, impaired quality of life, navigation issues/traffic violations, and falls e. Difficulty operating heavy machinery f. Commercial drivers/pilots
4. Since a large proportion of patients with cirrhosis and cognitive complaints could have conditions other than MHE, specific assessments for alternative diagnoses such as sleep apnea, alcohol-related conditions, and mild cognitive impairment should be performed, ideally in a specialized clinic or through referral, especially in those with isolated delayed memory issues or isolated sleep issues
5. Cognitive testing for CHE/MHE and subsequent therapy with lactulose or rifaximin may improve health-related quality of life
6. In patients with cirrhosis being evaluated for MHE or CHE, several testing options are available according to availability of local expertise and norms: psychometric hepatic encephalopathy score, Stroop EncephalApp, QuickStroop, animal naming test, inhibitory control test, continuous reaction time, and critical flicker frequency
7. A second-line agent could be considered for treating MHE/CHE in certain patients with cirrhosis (e.g., BCAA/LOLA if sarcopenia/frailty, zinc if low serum levels, and l-carnitine if concomitant skeletal muscle cramps)
8. Whenever a theragnostic approach with lactulose is attempted, it should be followed by an evaluation of adherence and potential symptom improvement 4–8 wk after prescription, to inform continuation or not
Inpatient management of OHE
9. In patients with cirrhosis and confusion, clinical scores (WH criteria, GCS) identify patients with high-grade HE requiring appropriate triage/transfer to SDU/MICU to prevent complications such as aspiration pneumonia
10. A thorough evaluation for bleeding, infection, sedating medications, and toxic and metabolic abnormalities is necessary to identify and treat possible precipitating or contributing factors to mental status changes in patients with cirrhosis
11. A normal blood ammonia level in patients with altered mental status should prompt consideration of other potential diagnoses in addition to OHE
12. If a patient does not recover their mental status after 48–72 hours of adequate HE therapy and precipitating factor reversal, evaluation for alternative causes of altered mental status, inadequately addressed or unrecognized precipitating factors, or shunts should be considered
Prevention of HE recurrence
13. Engaging in a multidisciplinary medication reconciliation process at hospital discharge is necessary to ensure patients are prescribed appropriate prophylactic therapies against recurrent HE and that potentially harmful medications are dose reduced or stopped
14. Serum ammonia levels should not be used to guide initiation or titration of HE therapies or in the evaluation of HE recurrence in the outpatient setting
15. A thorough review of medication lists in patients with HE should be performed to identify and minimize therapies that may affect mental status assessment or risk of encephalopathy (e.g., opiates, benzodiazepines, antiepileptic pain medications [gabapentin and pregabalin], sleep medications [zolpidem, zaleplon, and eszopiclone], and proton pump inhibitors)
16. HE therapy may be deescalated and potentially discontinued in a stepwise fashion in patients who clinically recompensate
17. Oral and written advice to avoid driving should be given to patients and caregivers based on expert consensus in patients with recent (<3 mo) episodes of OHE.
18. All patients with HE and their caregivers should receive HE-based educational materials (e.g., www.cirrhosiscare.ca)
19. Caregivers should be screened for caregiver burnout and provided necessary support as appropriate
Sarcopenia and nutrition
20. All patients with HE (including those with MHE/CHE) should be evaluated for impaired muscle health/physical fitness using available tools (e.g., sarcopenia/myosteatosis, skeletal muscle strength, physical function, frailty, or cardiorespiratory fitness) because these are all important targets of HE therapy
21. Patients with impaired muscle health/physical fitness in any of its clinical presentations (i.e., sarcopenia, physical frailty, and deconditioning), and patients with myosteatosis (fat infiltration into muscle), have an increased risk for HE
22. Critically ill patients with HE should receive up to 2 g/kg/d protein intake
23. Although sarcopenia is not by itself an indication or a contraindication for TIPS, it could be associated with increased post-TIPS HE and post-TIPS mortality
24. Increases in ammonia levels after anaerobiosis have not been associated with an elevated risk for HE and should not discourage clinicians from prescribing exercise for patients with cirrhosis
25. Patients with any form of HE may experience an increased risk of exercise-induced injury. Supervision by exercise professionals, caregivers, or other surrogates is key to prevent exercise-related adverse events
Liver transplant and HE
26. Adding 4–5 MELD points regardless of the MELD score iteration used more accurately reflects the 90-day mortality of inpatient OHE and outpatient CHE
27. As multiple HE episodes lead to persistent cognitive impairment which may not recover after LT, early LT could have additional benefits to improve brain function
28. Early evaluation for liver transplantation should be considered in patients with high MELD3.0 scores, severe HE (grades III–IV), or frequent HE episodes, to improve long term outcomes
29. Persistent confusion in an inpatient setting is a relative contraindication to transplant

BCAA, branch-chained amino acid; CHE, covert hepatic encephalopathy; GCS, Glasgow Coma Scale; HE, hepatic encephalopathy; LOLA, l-ornithine-l-aspartate; LT, liver transplant; MELD, model for end-stage liver disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; SDU/MICU, step-down/medical intensive care unit; TIPS, transjugular portosystemic shunt; WH, West Haven.

without cirrhosis with simple portosystemic shunting and (ii) neuropsychiatric and subclinical symptoms can occur as part of this syndrome.

Management of HE requires careful documentation of not only the circumstances surrounding the current episode but also previous episodes (11). Prior guidelines focused on 4 axes: (i) type, (ii) grade or severity, (iii) time course, and (iv) precipitated or not. However, given the major impact that social determinants of health have on HE, we have added a fifth axis. A strong social infrastructure is essential to prevent readmissions or recurrences; it consists of social and family support, financial support to ensure medication adherence and assistance if lower earning or driving capability, and institutional support from the hospitals to ensure timely and meaningful follow-up (Figure 2) (12). Using these axes as a checklist, the clinical and psychosocial determinants of HE recurrence and social determinants of health in this context can be identified and potentially addressed.

The guideline here focuses on clinical aspects of HE in patients with cirrhosis only and provides a framework for ensuring optimal management and improving clinical and psychosocial outcomes during the complex patient journey as illustrated in Figure 3. The focus is on (i) burden of HE from multistakeholder perspective and prognostic factors; (ii) growing importance of comorbid conditions; (iii) diagnosis and management of covert HE (CHE)/minimal HE (MHE); (iv) inpatient management including decision to hospitalize, refractory HE assessment, and transplant assessment; (v) prevention of recurrence using medication and nonmedication strategies; (vi) role of nutrition, sarcopenia in HE management; (vii) emerging management strategies; and (viii) special circumstances.

BURDEN OF HE

Incidence and prevalence of HE

HE is now the first decompensating event among patients with cirrhosis (13). Estimates of the incidence of a first episode of HE, however, are dependent on the population studied and are highly influenced by the case-mix of etiologies and disease severity of the cohort at baseline (14): 1-year incidence of 10% for Child A and 25% for Child B patients with cirrhosis and portal hypertension (15), 5-year incidence of 3.8% (less advanced cirrhosis, less reliable diagnostic coding) (16) to 43.7% in a Veterans Affairs cohort of patients with cirrhosis and portal hypertension and/or an aspartate aminotransferase to Platelet Ratio Index (APRI) >2.0 (17). Owing to the fractured nature of electronic health records, an accurate estimate of the prevalence of HE is challenging. Using the global burden of disease study, it is estimated that the prevalence of decompensated cirrhosis is 113.2/100,000 adults in the United States (18). If there are 260 million US adults and roughly 40% of patients with decompensated cirrhosis will develop HE (16), then prevalence of HE is roughly 118,000 individuals.

Cost of HE

Per person-year cost data regarding combined inpatient and outpatient expenditures for HE are lacking but the inpatient HE hospitalization costs have risen from $38,897 in 2007 to $49,391 in 2017 (19). HE is the most common cause of readmission among patients hospitalized for complications of cirrhosis with 90-day readmission rates of 21%–53% (20,21). With the inclusion of medication and outpatient care expenditures to those of readmissions, healthcare cost after an initial hospitalization for HE is substantial at around $18,457–$20,030 per person per month during a mean follow-up period of 5.7–6.9 months (22). HE is uniquely associated with collateral damage to the wellbeing of caregivers (23) who report a significant burden, particularly regarding the impact on their schedule, personal health, and sense of entrapment (24). Adding to the social challenges faced by patients with HE, caregivers report debt, food insecurity, difficulty paying bills, and evictions while also being unable to attend to their own health needs (24). Their health-related quality-of-life measures are also impaired (25,26) and reveal severe limitations, frustration, sadness, and even resentment (25–27).

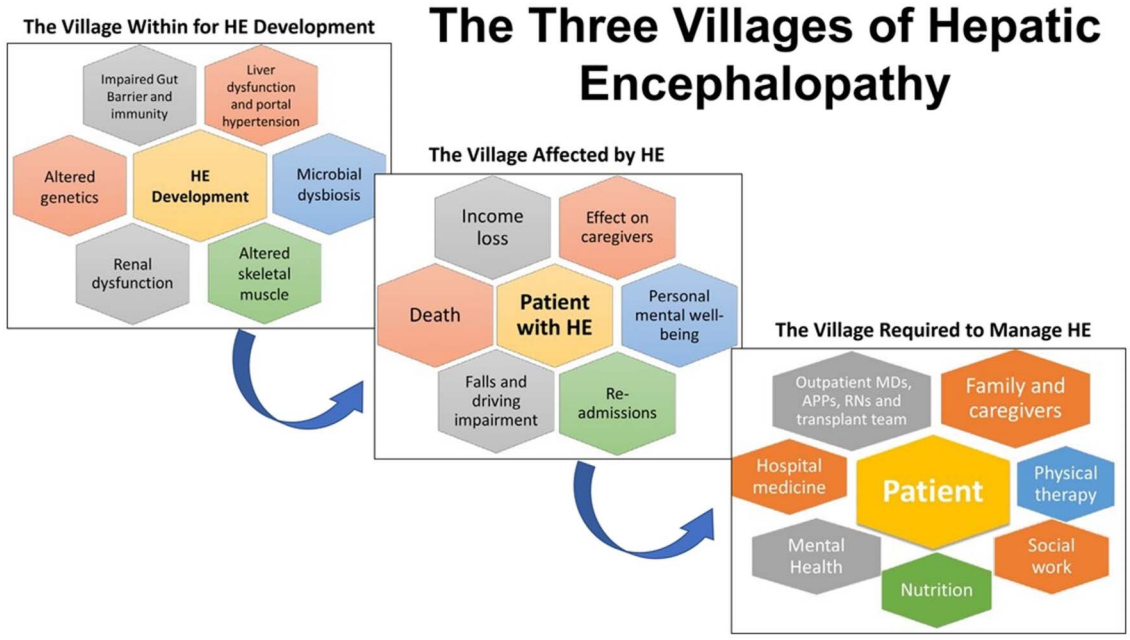

Figure 1. The 3 villages of HE (First published in Am J Gastroenterol. 2021;116(6):1184–1186. doi:10.14309/ajg.0000000000001212). Villages center around pathogenesis (village 1), impact of HE (village 2), and village needed to manage HE (village 3). HE, hepatic encephalopathy.

CHE AND MHE

Recommendations

1. In patients being evaluated for MHE or CHE, we suggest a single-test strategy over a 2-test combination strategy (conditional recommendation, very low certainty of evidence).
2. In patients being evaluated for MHE or CHE, we suggest against using serum ammonia levels alone to make the diagnosis (conditional recommendation, very low certainty of evidence).
3. In patients with MHE/CHE, we suggest treatment with lactulose vs no treatment (conditional recommendation, low certainty of evidence).
4. There is insufficient evidence to recommend for or against routine treatment of MHE/CHE for prevention of overt HE (OHE) (insufficient evidence, no recommendation).

Key concepts

1. Given the low reproducibility of clinical diagnosis of CHE (minimal or grade 1 HE), CHE should be defined by excluding OHE (grade 2 or higher) in the appropriate clinical context.
2. Isolated asterixis without alterations in behavior or alertness is not enough to diagnose OHE.
3. Patients with cirrhosis and 1 or more of the following features could be prioritized for MHE testing:
   a. Hypoalbuminemia
   b. Decompensated cirrhosis (e.g., presence of ascites, variceal bleeding, or jaundice)
   c. Clinically significant portal hypertension or presence of portosystemic shunts
   d. Cirrhosis with nonspecific cognitive complaints, difficulties with concentration, impaired quality of life, navigation issues/traffic violations, and falls
   e. Difficulty operating heavy machinery
   f. Commercial drivers/pilots
4. Cognitive testing for CHE/MHE and subsequent therapy with lactulose or rifaximin may improve health-related quality of life.
5. Since a large proportion of patients with cirrhosis and cognitive complaints could have conditions other than MHE, specific assessments for alternative diagnoses such as sleep apnea, alcohol-related conditions, and mild cognitive impairment should be performed, ideally in a specialized clinic or through referral, especially in those with isolated delayed memory issues or isolated sleep issues.
6. In patients with cirrhosis being evaluated for MHE or CHE, several testing options are available according to availability of local expertise and norms: psychometric HE score, Stroop EncephalApp, QuickStroop, animal naming test, inhibitory control test, continuous reaction time, and critical flicker frequency.
7. A second-line agent could be considered for treating MHE/CHE in certain patients (e.g., branch-chained amino acid [BCAA]/l-ornithine-l-aspartate [LOLA] if sarcopenia/frailty; zinc if low serum levels, and l-carnitine if concomitant skeletal muscle cramps).
8. Whenever a theragnostic approach (positive therapeutic challenge) with lactulose is attempted, it should be followed by an evaluation of adherence and potential symptom improvement 4–8 weeks after prescription, to inform continuation or not.

Clinical and psychosocial relevance of CHE/MHE

MHE is the subclinical form of HE that can only be identified through specialized neuropsychological or neurophysiological testing (28). This is often combined with grade 1 HE by the West Haven criteria, which is also difficult to diagnose in clinical practice (28), under the term of CHE. This is to differentiate it from the clinically obvious overt HE (OHE) forms (i.e., grades 2–4) (29). Since patients with grade 1 HE show abnormal neuropsychological or neurophysiological testing—similar to patients with MHE—and telling these 2 apart is clinically challenging, MHE and CHE are usually used interchangeably.

Subtle cognitive or behavioral changes are reported by patients or their caregivers and/or identified by an experienced clinician. Flapping tremor or asterixis can occur in patients with CHE. Furthermore, bradykinesia, rigidity, and other parkinsonian-like extrapyramidal signs can also be observed in CHE when carefully investigated (30–32). By itself, the presence of motor abnormalities on physical examination without a cognitive or arousal deficit should not automatically classify patients as having OHE. As such, asterixis alone is not enough to diagnose OHE, and rather, its presence should direct physicians to pursue a detailed cognitive history. Recent regulatory updates in HE drug development have determined that asterixis without behavioral abnormalities should not be considered or treated as OHE.

Despite the difficult diagnosis, CHE carries clinical relevance (28). One of the earliest manifestations of CHE is an attention deficit—affecting both attention span and attention shift—which generates dire consequences such as a failing working memory deficit and impaired learning (33,34). These can result in diminished work productivity or financial mishaps. Reduced motor coordination and psychomotor speed, along with fatigue make patients with CHE prone to falls and self-injury (35–37). Furthermore, deficits in visuospatial orientation, response inhibition, and speed of information processing affect their navigation skills, can make them unfit to drive, and result in motor vehicle crashes (38,39). Patients with CHE have a higher risk for incidental OHE and admission to the hospital, and it has been reported that CHE is associated with accelerated cirrhosis progression and death (40–42). Finally, CHE is associated with decreased quality of life, as shown in multiple studies through various patient-reported outcomes tools.

Overall strategy to triage CHE testing

When tested, CHE is found in 20%–80% of patients with cirrhosis and no prior history of OHE, its prevalence depending on the degree of hepatic impairment (i.e., highest frequency in Child-Turcotte-Pugh C) (43–45). Despite its high prevalence and providers' recognition of its importance, less than 15% of centers routinely test for CHE and at least one-third of practices never test for CHE (46,47). The low enthusiasm for testing for CHE likely relates to (i) the lack of a target population gaining a clear benefit from standardized screening; (ii) the lack of a clear screening pathway using sufficiently accurate and user-friendly tests that is easy to implement; and (iii) the lack of consistent proof of improved outcomes after treatment and resolution of CHE, although there is improvement in quality of life.

Studies have shown that patients with hypoalbuminemia or hyperammonemia are more likely to test positive for CHE (42,48). Moreover, those with decompensated liver disease (i.e., ascites variceal bleeding, or jaundice) are at risk of further decompensation in the form of OHE and would benefit from

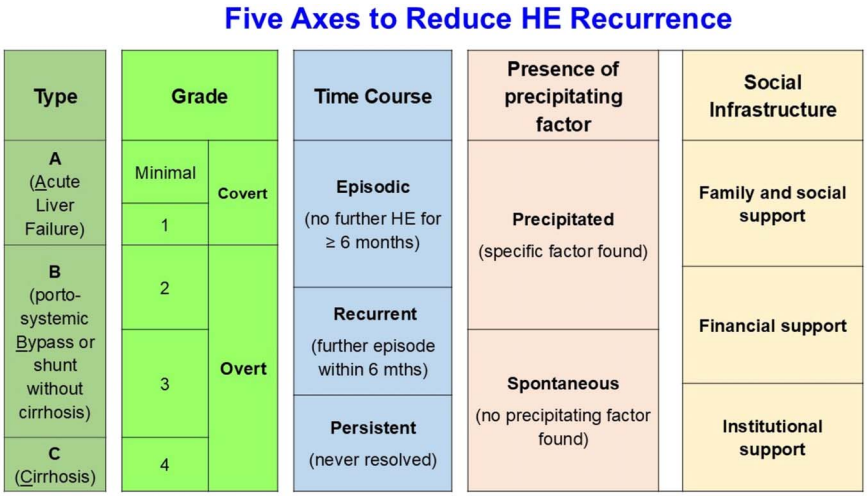

Figure 2. Five axes to assess and reduce HE recurrence (modified from AASLD/EASL HE Guidelines 2014 Hepatology). Type, grade, time course, precipitating factor, and social infrastructure are all important in appropriate clinical management and prevention of recurrence of HE. AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; HE, hepatic encephalopathy.

refined risk estimation (49), similar to patients showing portosystemic shunts (particularly if large, ≥8 mm) on imaging (50). As such, it is reasonable to test for patients with the aforementioned conditions, as well as those complaining of mild and unspecific cognitive deficits not compatible with OHE—by patient or caregiver—or experiencing work difficulties, traffic violations, motor vehicle accidents, or unprovoked falls (28). Clinical investigations for unexplained fatigue or deteriorating quality of life should also include testing for CHE (51). Finally, although patients with CHE are more prone to exhibit poor sleep quality, the changes are subtle (52,53) and a standard differential diagnosis for sleep disorders should be followed. This includes ruling out obstructive sleep apnea, which is more frequent in patients with ascites (54,55).

Individual tests for CHE/MHE

Although many tests have been developed to investigate CHE, not all of them count with both cross-sectional validation, where the populations of interest are contrasted to existing norms, and longitudinal validation, where the patients with and without CHE are followed up over time to determine the associated risk(s) for incidental clinical outcomes (56). A pertinent note on cross-sectional validation is that it bases the diagnosis of CHE on patients showing a test result—or battery of tests—that is more extreme (i.e., worse) than a control population adjusted by age, sex, level of education, and/or other features known to affect cognition. Since cognitive skills are also highly dependent on upbringing and cultural environment, it is recommended to use nationally and culturally validated tests (57–61). In this regard, complex batteries testing alphabetical or mathematical skills can show wider variability across countries and cultural identities. Neurophysiological tests potentially offer more intercultural stability by testing neurocognitive pathways linked to CHE pathophysiology. Although few laboratory tests have been investigated for the detection of CHE—including blood ammonia levels—none has been sufficiently validated or accurate enough to reach the clinical arena (62–69), and at the present time, there is no laboratory test sufficient to diagnose or rule out this condition.

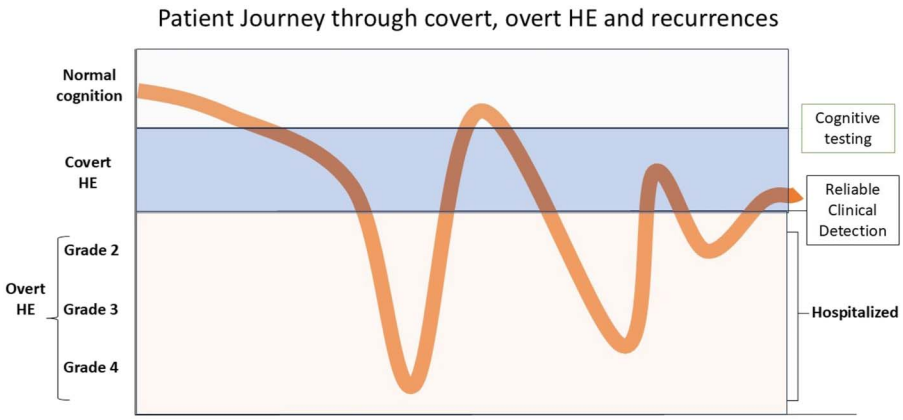

Figure 3. A typical patient journey through HE depicted by the orange line. Covert HE can be diagnosed definitively using cognitive testing, while overt HE (starting from grade 2 or higher West-Haven criteria) often requires hospitalization. A typical patient course includes multiple HE recurrences. HE, hepatic encephalopathy.

Table 4 summarizes some tests that could be performed in clinics, while Supplementary Table S1 (Supplementary Digital Content 1, http://links.lww.com/AJG/D846) shows all tests that have a published record. Tests should be performed in a quiet, well-lit room with no distractions or interruptions. Importantly, agreement between CHE diagnostic tests is poor given that they all assess different aspects of cognitive functioning, with little to no overlap. Thus, to strengthen CHE diagnosis, professional societies have recommended using a 2-test strategy with expected agreement between the 2 tests to call CHE out (11). Although attractive, when tested in the real-world, the 2-test strategy resulted in no improved accuracy for incidental OHE prediction, when compared with single testing. Furthermore, the former resulted in a lower sensitivity making it less appealing—and practical—for screening (85). Given the intricacies of CHE testing, including the need for a dedicated history and physical to explore cognitive and sleep disorders alike, a dedicated clinic with a streamlined workflow would constitute an ideal setup for patients in need of multidisciplinary expertise (86,87).

The Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA) test has been used particularly in the research setting to screen for dementia, where patients with a positive result are referred for in-depth neuropsychological evaluation. However, MMSE and MoCA can be abnormal in CHE (61,88,89), and no specific threshold can help differentiate the CHE spectrum from other forms of cognitive deterioration (i.e., delirium or dementia). Usually, although some MMSE or MoCA patterns could sway the diagnosis toward dementia, these escape standard hepatology practice and would require specialized interpretation, without offering complementary screening information to CHE-dedicated testing in clinical practice. Whenever mild cognitive deterioration, dementia, or delirium are being suspected, a referral to specialists in the field should be sought. Usually, patients with isolated delayed memory issues or isolated sleep issues have overlapping or other explanations for these issues other than HE (86,87,90).

Treatment for CHE/MHE

Lactulose has been studied to treat CHE in multiple RCTs. Almost universally, improvement in neuropsychological tests has been reported (91), including a higher MHE reversal rate, when compared with control group/placebo (92). Quality of life also improves after treatment (93), and participants under the active arm experienced a decreased rate of incidental OHE (94,95), although evidence on improved mortality is lacking. Comparisons of rifaximin to placebo have yielded similar results to those of lactulose, and rifaximin remained within the noninferiority margin in an RCT against lactulose (96–98). Rifaximin has also been reported to help with driving simulation performance (99). Despite its potential benefit, the cost of rifaximin and difficulties with third-payer approval may make it difficult to justify its use for CHE treatment.

A theragnostic approach has resurfaced as part of a novel emphasis on symptom-based management, where a positive therapeutic challenge can be taken as proof for concept for underlying CHE. As an example, a patient with difficulties with concentration or navigating skill experiencing symptomatic improvement after a short trial of lactulose would provide both diagnostic and therapeutic justification for continued treatment. Importantly, whenever a clinician decides to follow the theragnostic route, it should contemplate a limited trial duration (e.g., 4–8 weeks) and a clear symptom-based response, a priori. It would be unjustified to keep patients exposed to the adverse effects of a medication for a long period or for unclear clinical reasons.

Apart from first-line OHE medications, other agents have been tested as treatment for CHE either with less consistent positive results or in trials which designs were affected by confounding. These include LOLA, BCAAs, prebiotics/probiotics, l-carnitine, zinc, and others (100–110). Although blood ammonia level, inflammatory parameters, and magnetic resonance spectroscopy improve after treatment of CHE, results are less consistent (98,109,111–114). Remarkably, there is no firm evidence

Table 4. Cognitive tests for practical use in clinic

	Test description	Resources and time complete	Tested domains	Reported MHE or CHE prevalence	Clinical utility	Pros and cons
Stroop EncephalApp (Full) (61,70–72)	App-based version of Stroop test	Smartphone or tablet 5–15 min	Psychomotor speed, cognitive flexibility	45%–55%	Predicts OHE	Easy to apply, although full version can be long for some patients
Quickstroop (73,74)	Shorter version of EncephalApp	Smartphone or tablet 1–2 min	Psychomotor speed	45%–55%	Predicts HE	Not for color blind subjects
Animal Naming Test (75–78)	Recall of animal names	Non 1 min	Memory, verbal retrieval, recall self-monitoring	30%–40%	Predicts OHE and death	Practical and easy to apply, appropriate for transcultural testing; however, it is not specific for MHE/CHE
Critical flicker frequency (79–84)	Response to a fused/single light becoming a flickering light	Computer and specialized viewing chamber vs smartphone and light source	Integrity of visual tract and reaction time	40%–55%	Predicts OHE and death	Appropriate for transcultural testing, but needs specialized equipment; affected if visual acuity is impaired

CHE, covert hepatic encephalopathy; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy.

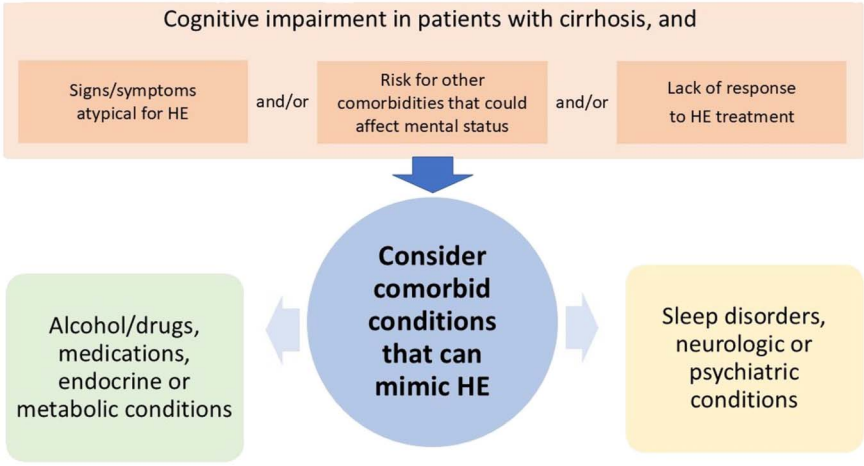

Figure 4. Potential causes of cognitive impairment in patients with cirrhosis that can mimic or worse HE symptoms. HE, hepatic encephalopathy.

to substantiate that treating CHE with a second-line agent decreases the rate of incidental OHE (115), and no effect on mortality has been found. Finally, treating CHE with either a first-line or second-line agent can result in nonserious adverse effects and financial stress that need to be weighed in when contemplating treatment (116). The main beneficial outcome of CHE therapy is improvement in daily function and quality of life (95,99,117). The decision to treat and choice of medication should be discussed with patient/caregiver through a shared-decision-making process, considering the impact of their symptoms and potential challenges related to treatment.

COMORBID CONDITIONS AND CHE/MHE

In the outpatient setting, symptoms such as sleep-wake alterations, changes in behavior or mood, forgetfulness, slow mentation, and speech are very common in patients with cirrhosis (118). The assumption that these patients have HE ignores other potential contributors to cognitive impairment such as dementia (87); sleep apnea (54); psychiatric and substance use disorders (119); and endocrine, metabolic, or medication-related conditions (Figure 4) (118). Older patients with cirrhosis may have several comorbidities that could mimic HE symptoms (120–122). An accurate diagnosis of cognitive impairment to differentiate HE from other conditions entails a detailed neuropsychological assessment, which is time-consuming, requires expertise and specific equipment. Nevertheless, lack of consideration of other causes of cognitive problems and the tendency to treat these symptoms with HE therapies results in patients' exposure to unwarranted medications (lactulose, rifaximin) with significant side effects and cost, as well as delays in the diagnosis and treatment of the actual problems. An analysis of 286 patients with cirrhosis and cognitive complaints referred through a dedicated consult pathway using detailed history, medication review, standardized tests (MMSE, Psychometric HE Score, and others), and obstructive sleep apnea screening found that more than 50% of patients did not have MHE (86). The differential diagnosis for non-HE cognitive symptoms included mild cognitive impairment and dementia, mood disorders, posttraumatic stress disorder, and obstructive sleep apnea. Table 5 includes testing modalities to help diagnose some of these conditions. An overall flowchart is in Figure 5.

The management of comorbidities in the holistic approach to HE can be crystalized as a 3-pronged approach: addressing factors that worsen liver function, supporting bodily functions that aid in ammonia clearance, and improving conditions that could worsen HE. First, patients with alcohol use disorder should be referred for therapy and intervention, and sobriety can halt the progression if not reverse the course of cirrhosis. A similar effect is true for eradication of hepatitis C and likely so for hepatitis B (131). Second, as reviewed elsewhere, ameliorating malnutrition including micronutrients such as zinc and macronutrients such as protein and calories is critical for the support of extrahepatic metabolism of ammonia. Third, it is possible, although robust studies are needed, that improvements in glycemic control could improve response to HE therapies (132).

OHE MANAGEMENT

Decision for outpatient vs inpatient management

Deciding if a patient requires outpatient vs inpatient evaluation is based on several factors and must be individualized. Some factors that need to be considered include HE severity (grade), certainty of HE diagnosis, need for further evaluation/treatment of possible precipitants, and ability of family and patient to manage in an outpatient setting (Figure 6). The guiding principles are as follows:

1. The severity of mental status changes dictates the need for emergency room evaluation and hospitalization; CHE and selected patients with grade 2 HE could be managed as outpatient.
2. For patients presenting with their first episode of mental status changes, evaluation in the emergency department may be necessary to exclude other etiology rather than assuming HE. A typical presentation consistent with prior HE episodes could be managed as outpatient if HE grade 2 or less.
3. If there is suspicion of infection, bleeding, dehydration, or other precipitant requiring further evaluation and treatment, patients may need emergency room evaluation and possible hospitalization.
4. If the patient is agitated or unlikely to comply or there is no reliable support/supervision, outpatient management is not an option.

Table 5. Comorbid conditions that may cause or exacerbate cognitive impairment in patients with cirrhosis in outpatient and inpatient settings

Outpatients and cognitive impairment	
Comorbid condition(s)	**Diagnostic approach**
Mild cognitive impairment, dementia	MMSE or Montreal cognitive assessment (88,89,123)
Endocrine or electrolyte disorders (DM, hypothyroidism, hyponatremia/hypernatremia, hypocalcemia/hypercalcemia)	Hemoglobin A1c Thyroid panel Chemistry panel
Sleep disorders	STOP-BANG questionnaires for Obstructive Sleep Apnea (124); assess adherence if already on CPAP; PROMIS8 sleep (125)
Mood disorders	PHQ-9 for depression (126), Beck Anxiety Inventory (127)
Posttraumatic test disorder	PCL-5: PTSD Checklist for DSM-5 (128)
Substance abuse	Toxicology screen, DAST (129), AUDIT-C (130)
Medication effect	Medication review, especially for pain (opioids, gabapentin), anxiety (benzodiazepines), and insomnia
Neurologic conditions (stroke, brain lesions or bleeding, neurological infections, epilepsy)	Brain CT or MRI Electroencephalogram Lumbar puncture
Inpatient diagnosis and alternatives	
Exclude other causes of acute mental status	
Sepsis Diabetes complications causing encephalopathy (hypoglycemic, hyperosmolar, and ketoacidosis) Uremic encephalopathy Severe electrolyte disorders (hyponatremia/hypernatremia, hypocalcemia/hypercalcemia) Other hyperosmolar conditions: diabetes insipidus, and intoxication (ethylene glycol, methanol) Intoxication or withdrawal (alcohol, benzodiazepines, opiates, and other drugs) Wernicke's encephalopathy Hypoxic or hypercapnic encephalopathy Neurological conditions (intracranial bleed, stroke, trauma, malignancy, and neuroinfection) Epilepsy (nonconvulsive epilepsy, postictal state) Endocrine (hypothyroidism/hyperthyroidism, adrenal insufficiency, and panhypopituitarism) Exposures (carbon monoxide, heavy metals) Acute psychosis Dementia	
Identify and treat precipitating factors for hepatic encephalopathy	
Infection Gastrointestinal bleeding Electrolyte disorder Acute kidney injury Constipation Dehydration	

AUDIT-C, Alcohol Use Disorder Identification Test; CPAP, continuous positive airway pressure; CT, computed tomography; DAST, Drug Abuse Screen Test; DM, diabetes mellitus; MMSE, Mini-Mental Status Examination; PHQ, patient health questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; PTSD, posttraumatic test disorder.

If there are no precipitating factors other than the need to adjust lactulose regimen, many patients with CHE or selected grade 2 HE could be managed with careful medication review and close outpatient follow-up. Adjusting HE treatment early prevents progression and avoids complications such as aspiration pneumonia which could significantly alter the patients' outcome.

Inpatient management of HE

Recommendations

5. In patients with HE, we suggest against routine testing of serum ammonia to guide HE treatment decisions (conditional recommendation, very low certainty of evidence).
6. In patients with cirrhosis and confusion without new-onset focal neurologic deficits, we suggest against routine brain imaging (conditional recommendation, very low certainty of evidence).
7. In patients with OHE, we recommend treatment with lactulose to improve patient outcomes and prevent recurrence of OHE episodes (strong recommendation, moderate certainty of evidence).
8. In patients with OHE, we suggest treatment with high-volume (e.g., 4 L) polyethylene glycol preparations as an alternative option to lactulose therapy (conditional recommendation, low certainty of evidence).
9. In patients with acute OHE, we suggest adding rifaximin to lactulose therapy vs lactulose therapy alone (conditional recommendation, low certainty of evidence).

Key concepts

10. In patients with cirrhosis and confusion, clinical scores (West Haven criteria, Glasgow Coma Scale) identify patients with high-grade HE requiring appropriate triage/transfer to step-down/medical intensive care unit to prevent complications such as aspiration pneumonia.
11. A thorough evaluation for bleeding, infection, sedating medications, and toxic and metabolic abnormalities is necessary to identify and treat possible precipitating or contributing factors to mental status changes in patients with cirrhosis.
12. A normal blood ammonia level in patients with altered mental status should prompt consideration of other potential diagnoses in addition to OHE.
13. If a patient does not recover their mental status after 48–72 hours of adequate HE therapy and precipitating factor reversal, evaluation for alternative causes of altered mental status, inadequately addressed or unrecognized precipitating factors, or shunts should be considered.
14. Engaging in a multidisciplinary medication reconciliation process at hospital discharge is necessary to ensure that patients are prescribed appropriate prophylactic therapies against recurrent HE and that potentially harmful medications are dose reduced or stopped.

HE should be suspected in any patient with cirrhosis and altered mental status (Figures 7 and 8). The initial evaluation should focus on:

1. grading the severity of mental status changes, to appropriately triage the level of care (outpatient vs regular floor vs step-down/intensive care) and interventions;
2. determining if HE is indeed the cause of mental status changes (with or without other conditions that can cause cognitive changes);
3. identification of precipitating or contributing factors which will require treatment in addition to the specific therapy for HE; common precipitating factors are constipation, gastrointestinal (GI) bleeding, infections, hyponatremia, and dehydration/diuretic overdose.

HE diagnosis is based on clinical symptoms and examination findings. There is no test to specifically confirm HE, and HE is ultimately a diagnosis of exclusion. HE is assumed to be the most likely explanation of mental status changes when careful evaluation for other conditions is negative. HE is suspected in patients with cirrhosis who present with deficits in attention and concentration, from shortened attention span to disorientation, confusion, and somnolence, and it can further progress to lethargy and coma. Patients can also have sleep disturbances, personality changes, bizarre behavior, and sometimes psychiatric and neurological symptoms (133).

A thorough clinical examination, including a full neurological assessment, will help determine the following:

1. The severity of cognitive deficits will appropriately triage the initial interventions (such as intubation to secure airways) and disposition (need for step-down or intensive care unit). West Haven criteria (134) (Figures 7 and 8) should be used to determine the grade of HE on initial presentation and throughout hospital course. The Glasgow Coma Scale (135) (Figures 7 and 8) should be used to assess and monitor patients with significant impairment of their level of consciousness. Other scales are used for inpatient trials to standardize OHE severity. The Hepatic Encephalopathy Scoring Algorithm is a tool validated across all grades of HE and uses the clinical and paper-pencil test to incorporate attention, memory, and psychomotor function (Figure 7) (136). It uses a point based system for both clinical and neuropsychological assessment to determine the grade of HE; however, it takes about 20 minutes to administer, and it is used in the research setting rather than in clinical practice. Other scales such as Hepatic Encephalopathy Grading Instrument and Hepatic Encephalopathy Staging Tool have also been studied in trials to increase the specificity of the semiquantitative West-Haven criteria (137,138).
2. Asterixis (flapping tremor of the hand when wrists are hyperextended) can be elicited in patients with lower grade HE, but it can be observed in metabolic encephalopathy of other etiology (uremia).
3. Presence of new focal neurological findings would make HE less likely or will point to a neurological condition that requires further evaluation with brain imaging and neurology consult.
4. Presence of precipitating/contributing factors, such as infection (including skin or oral cavity) or bleeding, will require further evaluation and treatment.

Laboratory evaluation will help determine precipitating/contributing factors, such as bleeding, infection, and toxic and electrolyte/metabolic abnormalities (Table 5). Infections are the most common cause of hospital admission in cirrhosis and a common precipitating factor for HE; therefore, culture of blood, ascites, and urine should be performed in all patients, as well as stool and sputum if clinical suspicion (139). Venous ammonia should not be routinely measured because it is not a diagnostic test for HE (140). It can be used to rule out HE because diagnosis is questionable if a patient is stuporous or comatose and ammonia level is normal. HE therapy should not be adjusted based on the ammonia level (141), but rather on clinical improvement. Despite its central role in the pathophysiology of HE, ammonia testing in clinical laboratories is unreliable and should not inform diagnosis or treatment decisions in the inpatient or outpatient management of HE (142). For example, in a study of 551 patients diagnosed

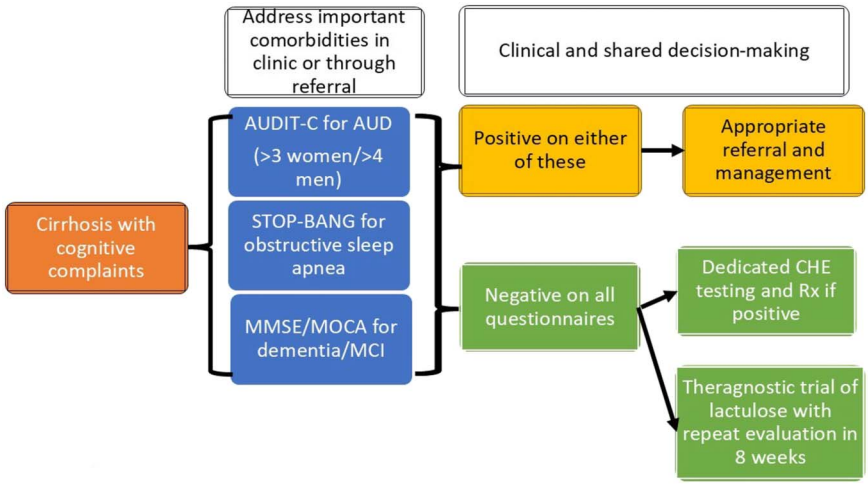

Figure 5. Proposed flow chart to evaluate patients with cirrhosis and cognitive complaints. This specifically addresses the 3 most common comorbid conditions (alcohol use disorder, obstructive sleep apnea, and dementia/mild cognitive impairment). AUDIT-C, Alcohol Use Disorders Identification Test-Concise; CHE, covert hepatic encephalopathy; MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment.

with HE, 40% had normal serum ammonia levels, and lactulose therapy did not differ between those with normal and elevated ammonia (143). Sample handing and processing as well as protein intake all interfere with or affect blood ammonia values (144). Furthermore, venous ammonia levels do not correlate with severity of HE (142), and prognosis of patients with cirrhosis admitted with confusion was similar regardless of ammonia level increase (145). Clinical assessment should therefore be relied on for the diagnosis of HE, grading of severity, and response to treatment including remission and recurrence.

For patients with cirrhosis and acute mental status changes requiring hospitalization, especially with seizures and new focal deficits, the differential diagnosis should include neurological conditions (intracranial bleed, stroke, brain lesion, nonconvulsive epilepsy, neurological infections, and dementia) or other metabolic encephalopathy (sepsis, uremia, and hypoxia), especially if clinical findings suggestive of these etiologies, or lack of response to primary HE treatment.

Brain imaging performed clinically (routine computed tomography scan or MRI) does not diagnose HE, and it has limited value in patients without focal neurological deficits, seizures, or those with multiple prior episodes (146–148). It is useful to investigate other conditions such as acute and chronic subdural hematoma, subarachnoid bleeding, stroke, or brain lesion in patients with situations mentioned earlier (149). This is separate from research-related brain multimodal imaging, which has a role in determining the pathophysiology of HE.

Medications for inpatient HE

First-line treatment includes nonabsorbable disaccharides (lactulose), treatment of precipitating/contributing factors, and

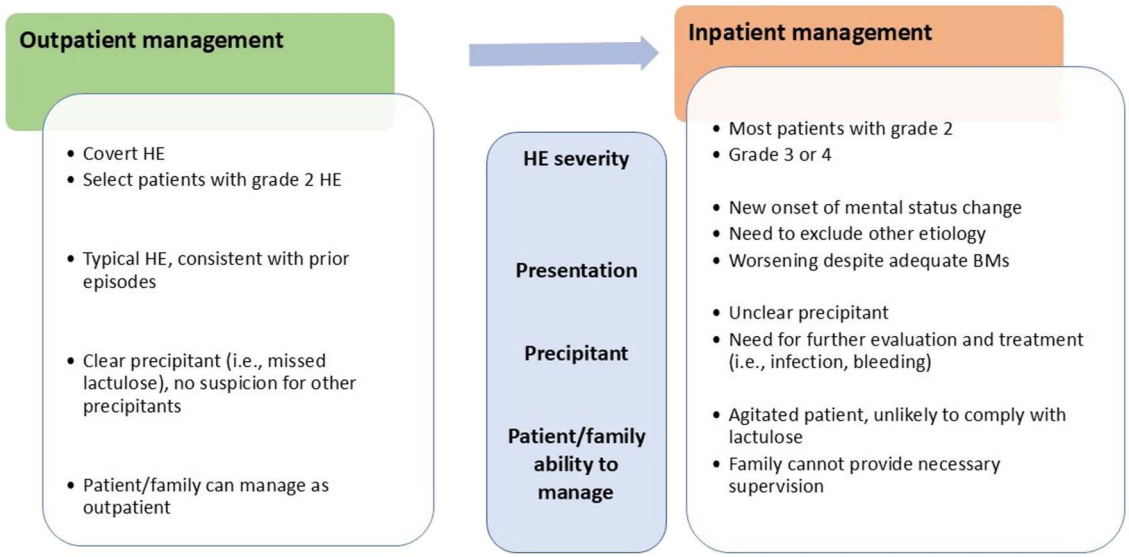

Figure 6. Decision-making aid in whether to hospitalize a patient with suspected HE that focuses on severity, presentation, precipitants, and social infrastructure. HE, hepatic encephalopathy.

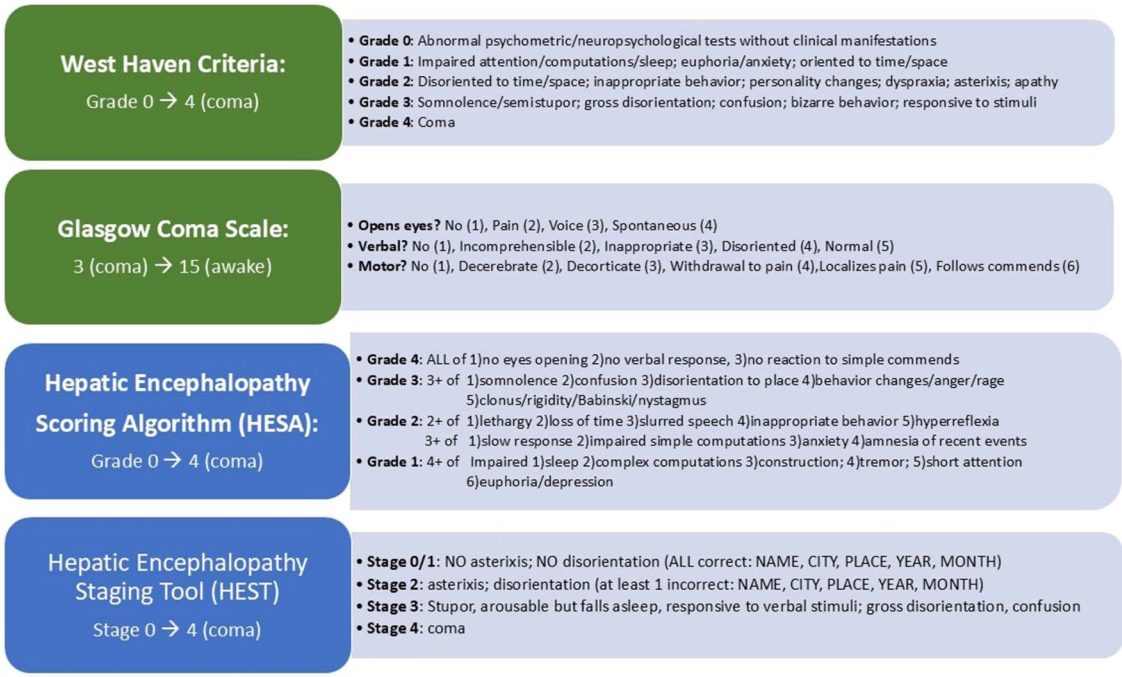

Figure 7. Outline of the major scales that have been used to grade inpatients with HE. HE, hepatic encephalopathy.

optimization of nutritional status (Figure 8). Nonabsorbable disaccharides such as lactulose have been used for the management of HE for decades (150). The mechanism of action of lactulose is controversial and is based on its ability to acidify the gut lumen (preventing the absorption of ammonia by trapping it as ammonium ions in the gut, and increasing its elimination with the stool through its laxative effect), presumed prebiotic effect (inhibiting ammoniagenic bacteria and promoting acidophilic bacteria lacking urease such as lactobacilli, which produce less ammonia), and inhibition of intestinal glutamine uptake and subsequent decreased ammoniagenesis (151). Lactulose for the treatment of acute HE can be administered orally for patients with grade 2 HE (152,153), using a dose of 10–20 g (15–30 mL) every 2 hours until the patient has 2 soft bowel movements, with subsequent dose reduction to 2–4 times per day, to maintain 2–3 bowel movements daily (154). Patients with grade 3–4 HE who

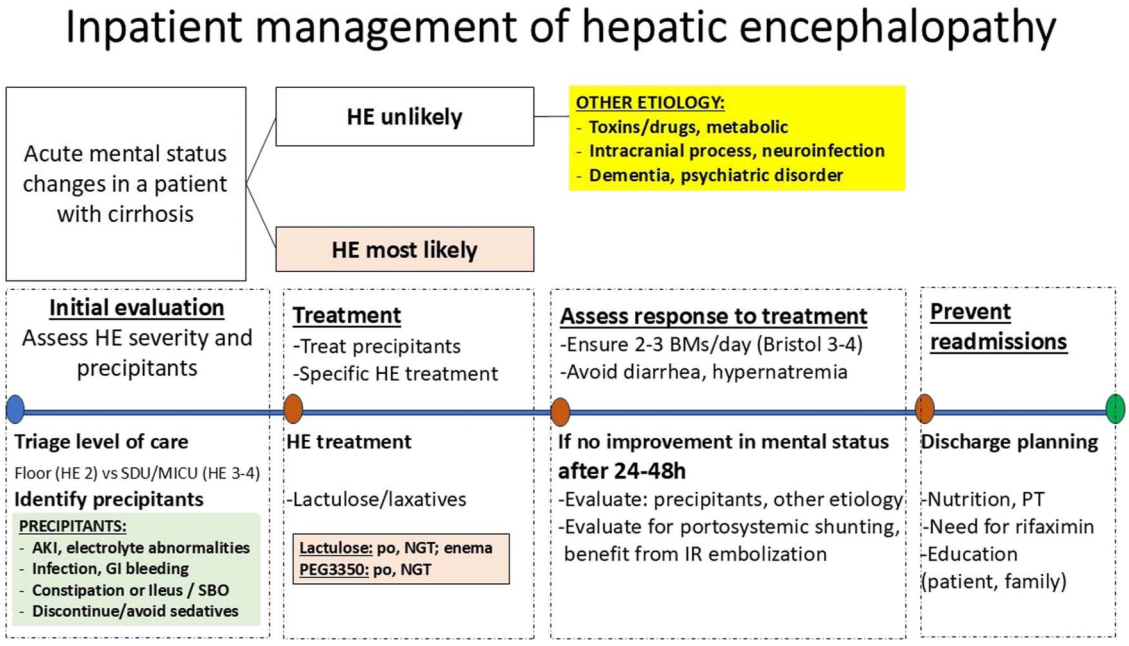

Figure 8. Flowchart for inpatient management and discharge transitions for patients with HE. AKI, acute kidney injury; BM, bowel movements; HE, hepatic encephalopathy; IR, interventional radiology; NGT, nasogastric tube; PO, per oral; PT, physical therapy; SBO, small bowel obstruction; SDU/MICU, step-down/medical intensive care unit.

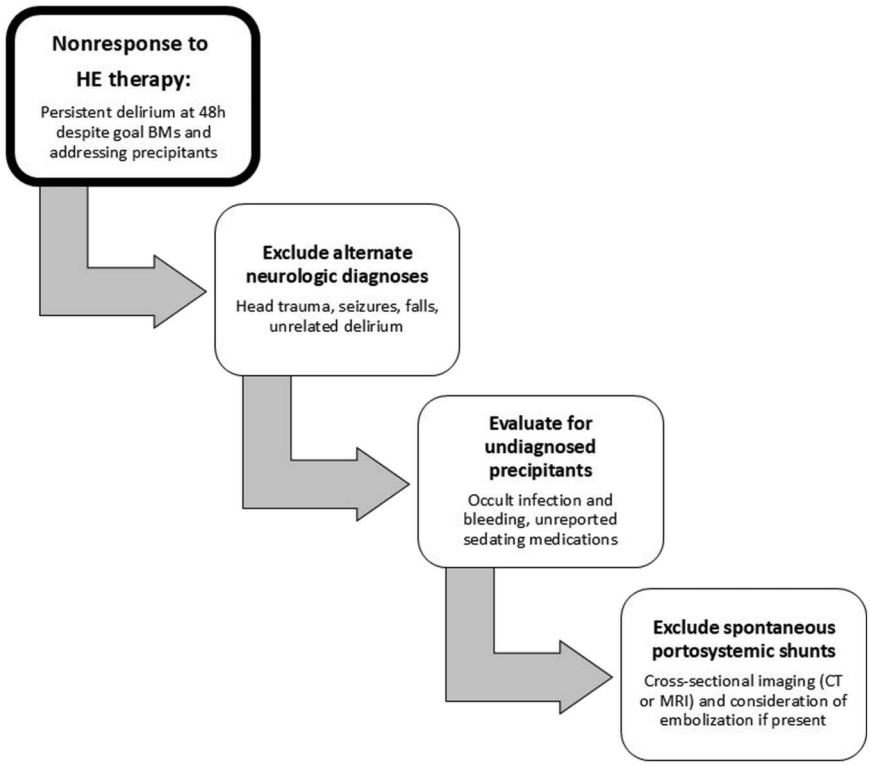

Figure 9. Proposed flowchart for patients with HE who do not respond to initial therapy. HE, hepatic encephalopathy.

are unable to swallow or patients who are at risk of aspiration will require placement of nasogastric tube, using similar dosing to oral administration, or lactulose enema in patients with preserved anal sphincter tone (200 g lactulose or 300 mL of lactulose solution with 700 mL of water or normal saline, retain for 30–60 minutes, repeat every 4–6 hours until improvement in mental status) (155). Careful titration of lactulose is critical because overuse can lead to complications such as perianal skin irritation/infection, ileus, aspiration, dehydration, hypernatremia, and hypokalemia, which can become potential precipitants of HE recurrence (156).

Other laxative agents such as magnesium salts were used before the introduction of lactulose, suggesting that catharsis alone may be effective for treatment of HE. In a RCT, polyethylene glycol 3350-electrolyte solution (PEG3350) led to more rapid HE resolution than standard lactulose therapy (157). PEG3350, oral or through nasogastric tube, should be considered in patients who have abdominal discomfort or gas distension or ileus from lactulose (158).

Tap water enema has the benefit of rapid access and wide availability, but acidifying agents such as lactose and lactitol were found to be superior to tap water enemas for acute management of HE (159,160).

Rifaximin (a nonabsorbable antibiotic that affects ammonia production by modulating intestinal bacterial composition) is an established treatment for HE recurrence (161,162), but the impact of rifaximin use for acute treatment of HE is less defined (163). There are data suggesting that rifaximin in combination with lactulose might be more effective than lactulose alone for the inpatient treatment of HE (164). A RCT showed that the combination of rifaximin and lactulose resulted in a higher rate of complete reversal of HE, a reduction in hospital stay and mortality (165).

Albumin was investigated as an adjunct to lactulose for treatment of HE, with limited data showing an increased rate of complete HE reversal and reduction in mortality (166,167), but its role remains unclear.

Treatment of precipitating factors is important not only because it addresses the underlying cause for admission (infection, bleeding, and dehydration), but it may also reverse HE. Concomitant disorders with a significant effect on mental status in patients with cirrhosis include hyponatremia, hyperglycemia, and thiamine deficiency. Of note, hyponatremia, hyperglycemia, and sepsis can independently cause metabolic encephalopathy or precipitate HE through their impact on HE pathophysiological mechanisms (168,169). Timely diagnosis of potential precipitants requires a high index of suspicion especially if patients' mental status interferes with a complete history. As such, a thorough investigation for infection including diagnostic paracentesis is of utmost importance for early diagnosis and treatment (139,140). Empirical broad-spectrum antibiotics should not be used in the absence of symptoms or laboratory findings suggestive of active infection and if started should be tailored quickly based on culture results or discontinued if no signs of infection are found.

Treatment of HE for patients in intensive care unit (ICU). Various liver or nonliver injuries (viral hepatitis, drug-induced liver injury, alcohol-associated hepatitis, pneumonia, or other infections) in patients with chronic liver disease might result in hepatic and extrahepatic organ failures (termed acute on chronic liver failure or ACLF) (170). Management of HE for these patients is addressed in the recent 2022 ACG guidelines (171), including considerations on evaluation, concomitant medications use for pain, agitation, and/or sedation, as well as goals of care. For patients who require ICU management in the absence of ACLF, all those principles apply, but there are a few additional aspects to consider.

1. Use of lactulose will require adjustment primarily based on bowel movements because mental status assessment will not be possible in a patient intubated and sedated. In patients with fecal incontinence requiring use of a fecal management system (rectal tube), lactulose and other laxatives should be held if >300 mL stool per day. Monitoring for hypernatremia that suggests dehydration and efforts to prevent aspiration are critical.
2. Use of rifaximin in ICU is of limited value especially in patients who are already on broad-spectrum antibiotics. A recent double-blind trial of patients with OHE admitted to the ICU showed that reversal of OHE was similar in the group on antibiotics alone when compared with antibiotics plus rifaximin (172).
3. Use of nontraditional therapies for HE. Ammonia is a small molecule, water soluble, and not significantly protein-bound; therefore, it is highly dialyzable. Early start of renal replacement therapy for hyperammonemia (level >100 μmol/L) may have a beneficial role in patients with acute liver failure (8) or for patients with urea cycle disorders (173), but there are insufficient data to support its use for patients with cirrhosis, solely for the purpose of decreasing serum ammonia. High-volume plasma exchange may improve HE and have survival benefit in patients with acute liver failure (174), but this is not demonstrated in patients with cirrhosis. Albumin dialysis (molecular adsorbent recirculating system) has been shown to reduce the grade of HE in cirrhosis and potentially bridge to transplant (175), but further studies are necessary to define its impact and role in HE management.

NONRESPONSE TO HE THERAPY

Improvement in mental status with first-line treatment is expected within 24–48 hours. If there is nonresponse with persistence of delirium after 48 hours despite optimal bowel movements and treatment of precipitating factors, the patients should be re-evaluated for other causes of altered mentation (Figure 9):

1. Explore an alternate diagnosis: In clinical practice, ammonia levels are checked haphazardly by varying healthcare providers, and if the levels are normal, alternative causes of altered mentation should be investigated. Low or normal ammonia levels in patients with cirrhosis have a negative predictive value for HE being the cause of altered mentation. Recent head trauma, falls, seizures, and/or surgeries should all be considered in the differential diagnosis after all of the potential precipitants have been investigated.
2. Determine undiagnosed precipitants: Healthcare providers should monitor blood work for electrolyte disorders and renal failure, take a thorough history regarding central acting medications or recreational drugs (while verifying with urine drug screen and phosphatidylethanolamine testing), clinically be aware of any overt GI bleeding that can be therapeutically addressed; however, it is important to always search for an infectious etiology (pan culture, perform paracentesis, and chest x-ray) if there is nonresponse within 48 hours of lactulose ± rifaximin treatment for HE, because in this specific setting, OHE will not improve unless directed treatment toward specific infections are targeted. Furthermore, cross-sectional imaging can help aid in the diagnosis of prior transjugular portosystemic shunt (TIPS) placement vs having spontaneous portosystemic shunts (SPSSs) that could be investigated in the appropriate clinical setting (see point 3 below) in nonresponse to standard treatments.
3. Identify impact of other factors such as portosystemic shunts (TIPS or spontaneous) which may require closure. Persistent encephalopathy despite appropriate medical treatment should always be investigated using cross-sectional imaging such as computed tomography or MRI (also mentioned in preventing recurrence). The incidence of SPSSs ranges from 46% to 71% in cases of HE refractory to medical therapy compared with 14% without SPSS (176). Further details are in the section below focused on SPSS.

PREVENTION OF HE RECURRENCE

Recommendations

10. After an initial episode of OHE, we recommend lactulose titrated to 2–3 soft bowel movements daily as outpatient first-line therapy for prevention of HE recurrence (strong recommendations, high certainty of evidence).
11. In patients treated with lactulose for HE, we suggest using the Bristol Stool Scale with bowel movement frequency for the outpatient titration of lactulose to reduce readmissions (conditional recommendation, very low certainty of evidence).
12. In patients with cirrhosis and OHE, we suggest rifaximin therapy in the outpatient setting to prevent HE recurrence (conditional recommendation, low certainty of evidence).
13. In patients with OHE on lactulose maintenance therapy who experience recurrent episodes of HE, we recommend addition of rifaximin treatment (strong recommendation, high certainty of evidence).
14. In patients with OHE and persistent symptoms despite lactulose and rifaximin therapy, we suggest the addition of zinc supplementation in those with low blood zinc levels (conditional recommendation, very low certainty of evidence).
15. We suggest implementing health information technology interventions, when feasible, to optimize HE management (conditional recommendations, very low certainty of evidence).
16. We suggest shunt embolization in patients with refractory HE on optimized medical therapy who have adequate hepatic function and no contraindications (conditional recommendation, very low certainty of evidence).

Key concepts

14. Serum ammonia levels should not be used to guide initiation or titration of HE therapies or in the evaluation of HE recurrence in the outpatient setting.
15. A thorough review of medication lists in patients with HE should be performed to identify and minimize therapies that may affect mental status assessment or risk of encephalopathy (e.g., opiates, benzodiazepines, antiepileptic pain medications [gabapentin and pregabalin], sleep medications [zolpidem, zaleplon, and eszopiclone], and proton pump inhibitors).
16. HE therapy may be deescalated and potentially discontinued in a stepwise fashion in patients who clinically recompensate.
17. Oral and written advice to avoid driving should be given to patients and caregivers based on expert consensus in patients with recent (<3 months) episodes of OHE.
18. All patients with HE and their caregivers should receive HE-based educational materials (e.g., www.cirrhosiscare.ca).
19. Caregivers should be screened for caregiver burnout and provided necessary support as appropriate.

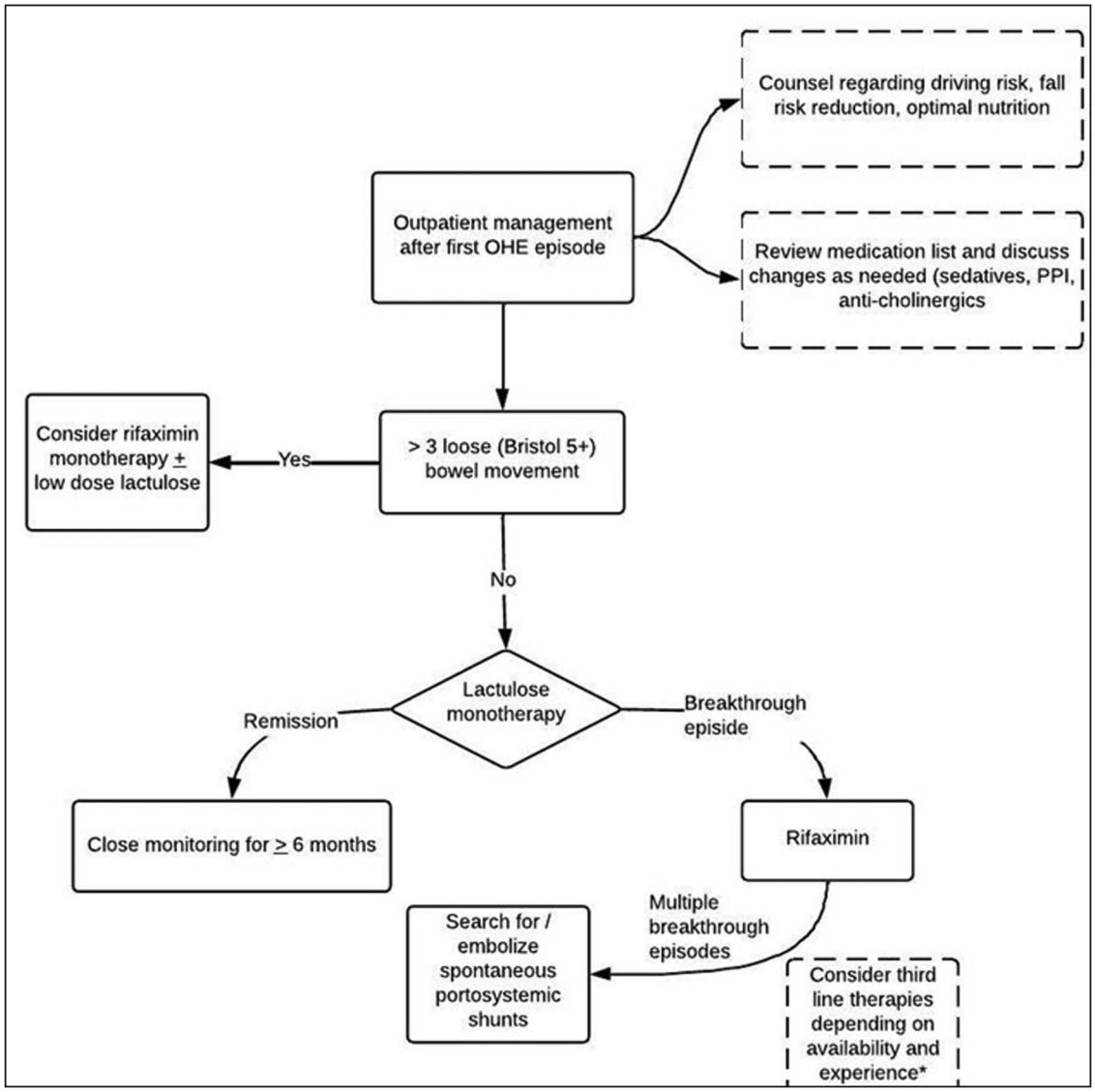

Figure 10. Proposed flowchart to prevent HE-related recurrences. HE, hepatic encephalopathy.

The risk of recurrence of OHE after an index episode is significant, with approximately 40%–60% of patients experiencing a second episode within 1 year (153,177). Secondary prophylaxis is therefore indicated in all patients with cirrhosis who develop OHE. These include medication and supportive nonmedication approaches. It is important to consider the social infrastructure for HE or the fifth axis in this setting, to ensure adequate implementation of the medical plans (Figure 10).

Medications

Lactulose has been demonstrated to significantly decrease the risk of recurrence of HE compared with placebo (150,153,177). To prevent recurrence, lactulose dosing and frequency are typically titrated to 2–3 soft bowel movements daily to ensure efficacy while avoiding diarrhea-associated hypovolemia. Adverse events in this setting are generally mild and include nausea, bloating, flatulence, and diarrhea. However, breakthrough episodes of HE in patients being prescribed lactulose are commonly attributed to nonadherence or dehydration (156). Incorporation of the Bristol Stool Scale (BSS) removes the focus from having the 2–3 daily bowel movement frequency to the characteristics of these bowel movements. Use of BSS has been shown to complement goal daily bowel movements in stabilizing lactulose regimens and improving patient adherence to therapy (154). There are apps that can assist with monitoring the number of daily bowel movements (178). Artificial intelligence-enabled apps using standardized assessment of stool target based on BSS can provide just-in-time feedback on lactulose dosing sufficiency (179,180). Typically, a score of 5 or more on the BSS would require cutting down on lactulose or suggest the need to add rifaximin in those already on lactulose. If BSS is ≥5 even before lactulose initiation, then these patients should be considered for alternative, nonlaxative therapies de novo to ensure adherence.

Rifaximin is a nonsystemic antibiotic that has broad activity against aerobic and anaerobic bacteria and thereby modulates the bacterial composition of the intestinal microbiota (162). It has been approved by the US Food and Drug Administration for the reduction in risk of OHE recurrence in adults at a dose of 550 mg

twice daily. A RCT compared rifaximin with placebo in 299 patients with cirrhosis and ≥2 episodes of OHE in the preceding 6 months who were in remission at trial entry, 91% of which were concomitantly taking lactulose. After 6 months of therapy, the rifaximin-treated patients had a 58% risk reduction (number needed to treat 4) in experiencing a breakthrough episode of OHE and a 50% risk reduction (number needed to treat of 9) in experiencing an HE-related hospitalization (161). A subsequent systematic review and meta-analysis that included 17 RCTs confirmed that rifaximin therapy was beneficial regarding secondary prevention of HE (181). In a recent post hoc subgroup analysis of a phase 3 RCT, rifaximin plus lactulose was more effective than lactulose alone in preventing the recurrence of OHE and HE-related hospitalization (182). Rifaximin monotherapy has been shown to effectively maintain remission from HE and has been associated with a lower risk of hospitalization compared with lactulose monotherapy in small or retrospective studies (22,183,184). However, the preponderance of available evidence supports the superior efficacy of rifaximin in combination with lactulose in patients who can tolerate dual therapy (163). Rifaximin is generally safe and well-tolerated compared with placebo in this population (161,163). A novel preparation of rifaximin soluble dispersion tablets is currently being investigated given its higher water solubility and less reliance on the presence of bile acids for action (137). The results of this RCT are currently pending.

We need better adherence to HE quality care measures such as appropriate lactulose titration and rifaximin use (185,186). In 2016, Tapper et al (187) published on the use of electronic order sets for spontaneous bacterial peritonitis management and appropriate lactulose titration and rifaximin use in 824 patients. Thirty-day readmissions were reduced by 40% as compared with the preintervention control period. A subsequent study by Louissaint et al evaluated a more active interruptive best practice alert-based strategy to advise rifaximin use for patients with HE on lactulose. Although rifaximin prescription rates remained high and stable (74%) on GI/hospitalist-based services, on non-GI/nonhospitalist services, the rifaximin prescriptions increased from 52.6% to 71.1%. The intervention was also associated with a significantly reduced readmission risk (subdistribution hazard ratio of 0.77, [95% CI 0.67–0.95]) (188).

Given the role of gut microbiota in the pathophysiology of HE, there is interest in the use of fecal microbiota transplant (FMT) for HE prevention. Enema-based FMT was evaluated in a 20-person phase 1 trial after antibiotics vs standard of care, which showed safety and a reduction in HE recurrence at 6 and 12 months (189). This was followed by a capsule-based FMT without pre-FMT antibiotics was evaluated in another 20-person phase 1 trial (190) and an open-label single-arm trial (191). Both of these confirmed potential safety and paved the way for larger trials. The THEMATIC trial, a larger phase 2a dose-ranging double-blind trial in patients on lactulose and rifaximin that tested capsule or enema routes, FMT was safe and associated with reduced HE recurrence compared with placebo (192). The specific route or dose was not contributory toward protection from recurrence. In general, results seem to suggest benefits; however, all FMT for HE should be confined to clinical trials at this time.

Zinc has been studied as a treatment for HE given its role as a cofactor in nitrogen metabolism. Zinc deficiency decreases the efficiency of the urea cycle and has been implicated in the pathogenesis of HE among affected patients with cirrhosis (139,193). Overall results regarding the efficacy of zinc treatment for HE have been conflicting. However, zinc seems to be a safe adjunctive therapy that may improve cognitive function when added to lactulose in HE (194,195).

Several medications have been identified as precipitants of HE events or as increasing the risk of HE (196). Central nervous system depressant medications may exacerbate the neurotoxicity of ammonia (140). Opioids also impair intestinal motility, enabling more ammonia to be absorbed into the bloodstream, and have been shown to increase the risk of HE in patients with cirrhosis (197,198). Benzodiazepine use has been associated with HE-related hospitalization and increased healthcare utilization among patients with cirrhosis (196,199). Gabapentin and its related medications that act through the gamma aminobutyric acid (GABA) neurotransmitter pathway are similarly expected to increase this risk of HE (196). The sleep aid zolpidem, a nonbenzodiazepine that also acts through GABAergic neurotransmission, has been associated with HE as well as falls in patients with HE (200,201). Beyond sedating medications, numerous studies have demonstrated that proton pump inhibitor use increases the risk of HE (202–205). This consequence of proton pump inhibitor therapy in cirrhosis is likely related to alterations in gut microbiota resulting from gastric acid suppression (206). Deprescribing exacerbating medications should be approached in a coordinated and multidisciplinary fashion by all relevant providers in conjunction with an informed discussion with the patient with HE (207).

Although rare, certain decompensated cirrhosis patients who fully recompensate with cure or suppression of the underlying etiology of their cirrhosis may no longer require secondary prophylaxis against HE (208,209). Recompensation outside of HE involves resolution of ascites off diuretics and the absence of variceal bleeding for 12 months in addition to demonstrated improvement of liver function including serum albumin, international normalized ratio, and total bilirubin (210). If such a patient has no signs of symptoms of HE while on therapy, HE-directed medications may be discontinued sequentially while monitoring closely for recurrence.

Adherence to an HE regimen depends in large part on social determinants of health and patient access to prescribed medications (211) given that the cost of rifaximin remains significant. Providers should therefore assess affordability of HE therapy on a per patient basis, particularly as even brief lapses in rifaximin therapy have been associated with readmissions for HE after an initial HE hospitalization (22). In addition to adequate medications, other approaches to prevent HE recurrence need to be instituted. There are multiple forms of psychosocial interventions, checklists, and App-based interventions (178,186,188,212,213). These include the Patient Buddy App, which has been used in clinical trials to increase adherence and reduce HE-related readmissions through increasing communication between the study team and the patients and their families (178,213).

Caregivers should be engaged and educated. Patient and caregiver knowledge of HE has been found to be low across multiple studies (214–219). There is improvement in this knowledge using educational interventions ranging from booklets to multimedia material (216–218,220,221). Most patients and caregivers are interested in receiving educational interventions (222,223). Caregiver burden is considerable, which is identified using methods such as Zarit Burden Interview short and long forms (24,224–231). HE-based educational materials should be provided to all patients with HE and their caregivers. The patient codeveloped HE educational material can be found at https://cirrhosiscare.ca/confusion/ (212,232).

Screening results from these tools should guide additional evaluation and support requirements including consultation of palliative care and/or social work professionals (224). Deterioration of driving skills in patients with HE has a significant impact on both patients and caregivers; driving history should be obtained at clinic visits, and counseling and possible interventions should be discussed with patient/caregivers. As per a recent International Society for Hepatic Encephalopathy and Nitrogen Metabolism consensus, oral and written advice to avoid driving should be given to patients and caregivers based on expert consensus only in patients with recent (<3 months) episodes of OHE (28).

Coping strategies are promising interventions to reduce the impact of HE on patient-reported and clinical outcomes. A pre-post study suggests that mindfulness meditation can improve sleep and depressive symptoms for patients and caregivers alike (233). Meditation was also associated with improved quality of life and cramp severity for patients with HE suffering from lower body cramps (234). However, in a trial of meditative journaling for caregivers of patients with cirrhosis, there were inconsistent effects on caregiver burden (235). Thirty patients with CHE were recruited for a trial of cognitive training using video games to assess the impact on cognitive function, health-related quality of life (HRQoL), and MRI features of brain injury. The effects observed showed only partial improvements on functional MRI without positive effects on HRQoL or cognitive function (236). Additional trials of mind-body methods remain warranted (237).

SPSS investigation for nonresponse or multiple recurrences

SPSSs occur in up to 60% of people with cirrhosis. They are a marker of clinically significant portal hypertension and predict clinical decompensation as well as an increased risk of recurrent HE (50,238,239). The mechanism of action is a "flow steal" phenomenon where shunting of the blood into the systemic circulation occurs, bypassing the liver, thereby decreasing hepatic clearance of neurotoxins. This occurs in a stepwise fashion, where there is an early course (patients are asymptomatic with good hepatic reserve), and over time, a later course ensues (patients get OHE), and once it progresses to end stage (hepatic atrophy with poor hepatic reserve ± portal vein thrombosis), patients have recurrent HE readmissions while on optimal medical therapy. Therefore, in patients with refractory HE, evaluation for SPSS should be sought and in the right clinical setting (MELD usually <15), embolization should be considered (especially if shunts are ≥ 8 mm diameter) (240).

In patients with recurrent or persistent HE despite adequate medical treatment, cross-sectional imaging should be performed to evaluate for SPSS (241). Two retrospective cohort studies support a reduction in HE with obliteration of accessible portosystemic shunts, the earliest series noting that 59.4% remained HE free within 100 days after embolization (176,242). In that series, logistic regression identified the MELD score as the strongest predictive factor of HE recurrence, leading to a recommendation for a MELD cutoff of ≤11 for patient selection (176). Closure of shunts can be considered at the time of TIPS to reduce the risk of HE. A reduced risk HE was observed in a meta-analysis of small cohort studies and 2 small randomized trials of simultaneous shunt closure (243). This effect was also observed in a large retrospective cohort where 8 mm TIPS was used (244). It is unclear if these data can be generalized to patients for whom TIPS is considered for ascites. Postembolization, consideration should be given to re-evaluation of HE symptoms, laboratory test results and liver doppler ultrasound in 1 month (assess for thrombosis, development of ascites), repeat upper endoscopy in 6 months' time (assess for de novo or worsening esophageal varices), and repeat cross-sectional imaging in 1 year (assess for new SPSS development) (239). Embolization can also be performed using endoscopic ultrasound if needed (245). All decisions for embolization should be made in concert with a multidisciplinary team inclusive of hepatology and radiology because this could increase the formation of varices and ascites.

FRAILTY, SARCOPENIA, NUTRITION, AND HE

Recommendations

17. We recommend a protein intake target of 1.2–1.5 g/kg/d in outpatients with HE (strong recommendation, moderate certainty of evidence).
18. We recommend BCAA supplementation in individuals with HE if protein needs cannot be met by food alone (strong recommendation, moderate certainty of evidence).
19. We suggest a late-night snack for patients with cirrhosis to reduce frailty and HE (conditional recommendation, very low certainty of evidence).
20. We suggest against protein restriction in patients with HE because it increases muscle breakdown and does not reduce the duration of HE (conditional recommendation, very low certainty of evidence).
21. We suggest exercise interventions in patients with HE to reduce the risk for falls, lower portal pressure, and increase the capacity of skeletal muscle for ammonia metabolism (conditional recommendation, low certainty of evidence).

Key concepts

20. All patients with HE (including those with MHE/CHE) should be evaluated for impaired muscle health/physical fitness using available tools (e.g., sarcopenia/myosteatosis, skeletal muscle strength, physical function, and frailty or cardiorespiratory fitness) because these are all important targets of HE therapy.
21. Patients with impaired muscle health/physical fitness in any of its clinical presentations (i.e., sarcopenia, physical frailty, and deconditioning), and patients with myosteatosis (fat infiltration into muscle), have an increased risk for HE.
22. Critically ill patients with HE should receive up to 2 g/kg/d protein intake.
23. Although sarcopenia is not by itself an indication or a contraindication for TIPS, it could be associated with increased post-TIPS HE and post-TIPS mortality.
24. Increases in ammonia levels after anaerobiosis have not been associated with an elevated risk for HE and should not discourage clinicians from prescribing exercise for patients with cirrhosis.
25. Patients with any form of HE may experience an increased risk of exercise-induced injury. Supervision by exercise professionals, caregivers, or other surrogates is key to prevent exercise-related adverse events.

As a neuropsychiatric syndrome that considers motor skills and mobility function, it is not surprising to find that there is a strong association between HE and muscle health/physical fitness (246–249), and that physical and cognitive changes can

occur simultaneously and progress or regress in parallel (250–252). Approximately 40%–50% of patients with HE have either sarcopenia or frailty, significantly higher than expected by chance (253,254). Patients with cirrhosis and myosteatosis (fat infiltration into muscle) (255) are 2 times more likely to have a history of HE (32% vs 15% according to a systematic review of 6 studies) (255). Furthermore, there is a strong association between cognitive and physical decline at the MHE/CHE stage, and they follow parallel and interdependent trajectories (i.e., cognitive decline potentiates physical decline and vice versa). Multiple pathophysiologic mechanisms link impaired muscle health and HE (i.e., muscle-brain axis), discovered after initial observations 30 years ago (109,256). These include hyperammonemia-related changes, alterations in the microbiome (gut-muscle-brain axis), decreased glutamine synthetase scavenging of ammonia by skeletal muscle, chronic inflammation, and micronutrient deficiency (e.g., L-carnitine, thiamine, leucine, and zinc). Impaired muscle health leads to reductions in ammonia metabolism and hyperammonemia, which in turn can lead to further muscle loss (109).

Given the important connection between muscle and HE, it is recommended that all patients with HE undergo assessment of muscle health/physical fitness such as sarcopenia or physical frailty. The concepts of sarcopenia and frailty are blurred given their overlapping definitions and assessment tools (257). This overlap is particularly evident in composite metrics such as the European Working Group on Sarcopenia in Older People, the liver frailty index (LFI), or the short physical performance battery (258). Table 6 presents a practical toolbox for assessing muscle health and physical fitness, while Supplementary Table S2 (Supplementary Digital Content 1, http://links.lww.com/AJG/D846) has a comprehensive summary of all major testing strategies. It is important to repeat these measures throughout the clinical course. The delta or difference between measurements carries significant prognostic information (266,267) and can be more accurately captured using objective assessments as compared with subjectively scored frailty questionnaires. Objective measurement is also preferred over questionnaires about physical activity because patients tend to overestimate the activity performed (268,269). Protein needs are increased in patients with cirrhosis (270), studies identifying 1.2 g/kg of protein per day as a threshold for a positive nitrogen balance (271,272). Target protein intake alongside target caloric intake with dietitian support has been associated with improved muscle mass and less OHE and MHE (273–275) (Supplementary Table S3, Supplementary Digital Content 1, http://links.lww.com/AJG/D846). Increased protein intake and the provision of a late-evening snack (LES) are associated with improved muscle health and reduced HE (276–279).

Dietary counseling is key to achieve these goals (280,281). Cirrhosis results in a state of accelerated starvation because reductions in hepatic glycogen reserves force the body to rely on lipids and proteins for gluconeogenesis. As a result, fasting time should be minimized with frequent meals, LES, and early breakfast (273,276,277,282). Studies have associated a LES with improved nitrogen balance (276), total body protein stores (277), quality of life (277), and reduced HE compared with control conditions (relative risk 0.46, $P = 0.002$) (278). Although the composition of an LES is not uniform, a combination of complex carbohydrates and protein is suggested (279).

Branch-chained amino acids (BCAAs) (with or without agents to prevent cataplerosis, e.g., LOLA) and essential amino acids have been inconsistently linked to improvements in HE and muscle health/physical fitness (283). Across a systematic review of 16 RCT evaluating BCAA in HE (12 OHE, 4 trials MHE), a significant reduction in HE was seen over a follow-up duration ranging from 1 to 104 weeks (RR 0.73) (110,284). As BCAA are found in protein containing foods, long-term BCAA supplementation is not necessary unless needs cannot be met by food alone (284). However, a recent trial did not show a major impact of BCAAs (285).

Small studies (10 patients or less) have evaluated the impact of vegetable-based protein, the majority demonstrating improvements including in psychometric testing, beneficial EEG changes, and reduced serum ammonia (286–289). The substitution of a single meat-based meal with a vegan or vegetarian alternative was associated with decreased postprandial ammonia (290). Pathophysiologic rationale has included increased fiber and stool bulk, beneficial alterations in the composition and activity of the intestinal microbiota allowing for increased ammonia excretion, and increases in arginine that facilitate urea synthesis (286). Other amino acid-based supplements have also been evaluated, with evolving evidence for HE reduction, including β-hydroxy-β-methylbutyrate (291,292), acetyl-L-carnitine (108), and L-ornithine L-aspartate (107,293). Probiotics were also found to decrease the risk of falls along with betterment of cognitive and physical fitness metrics in one RCT (294).

Measures to improve sarcopenia and frailty for HE

Despite the multiple benefits that exercise can bring to patients with cirrhosis and portal hypertension (Supplementary Table S4, Supplementary Digital Content 1, http://links.lww.com/AJG/D846), incorporating exercise to the HE therapeutic armamentarium has been met with skepticism. Most of the exercise clinical trials have included diet as a cointervention (237). As an example, in a recent meta-analysis, 90% of studies included a dietary maneuver (295). As such, it is recommended to coprescribe exercise with a nutritional regimen, with close monitoring of adherence, ideally through specialized (p)rehabilitation clinics (296).

Regarding safety of exercise in patients with HE, hyperammonemia is an expected response to anaerobic exercising conditions (similarly to hyperlactatemia), but no OHE episodes were observed when studied systematically (297). Furthermore, exercise clinical trials have not reported on incidental OHE among exercisers—including a systematic review—even for patients with prior OHE or MHE at enrollment. Finally, narrative and systematic reviews have deemed exercise to be safe for patients with decompensated cirrhosis with no increased risk for exercise-related injuries (298,299). Notwithstanding, there is a potential risk of self-injury from the motor skills and response time limitations caused by any degree of HE (300). Thus, for patients with HE, it is of paramount importance for caregivers to make themselves available and provide support during exercise training. Their involvement increases adherence to an exercise/dietary prescription while decreasing the risk of self-injury/falls.

Importantly, the 3 studies that assessed hepatic hemodynamics before and after an exercise ± dietary intervention showed a reduced hepatic venous pressure gradient (301–303). As such, lifestyle modification interventions focused on exercise/nutrition seem to stabilize portal hypertension and decrease its clinical burden. Exercise interventions also expose patients with HE to many comaneuvers that further support their cognitive health, such as mental engagement, attention shifts, social

Table 6. Practical strategies for testing skeletal muscle health and physical fitness

Test	Parameter description	Benefits	Caveats	Association with HE
Anatomic sarcopenia and myosteatosis				
CT/MRI from HCC surveillance studies	Cross-sectional area or volume of all muscles at L2 or L3 (skeletal muscle index), psoas (PMI), or thigh	Accurate SMI and psoas area are the most commonly studied	Radiation ++ (CT) Postprocessing Cost	Low SMI or PMI are associated with HE (259,260) and ↑ risk of incidental overt HE (246,261)
MAMC	Uses mid-arm circumference and triceps skinfold for calculation	Bedside test	Operator dependency Device cost +	Low handgrip associated with HE (262)
Skeletal muscle strength				
Handgrip	Isometric strength	Bedside test Easy to implement	Device cost +	Low handgrip associated with HE (262,263) and ↑ risk of incidental overt HE (264)
Measures of physical performance				
Gait speed	Usual walking speed over a specific distance	Bedside test Easy to implement	Requires walking	Slower gait associated with HE (265)
Balance	Time (≤10 sec) able to stand with feet together, in tandem, and semitandem	Bedside test Easy to implement	Requires ability to stand up	Not studied
Chair stands	Time to execute x number of chair stands or number of chair stand per unit of time	Bedside test Easy to implement	Requires ability to stand up	Longer time ↑ risk of incidental overt HE (15)
TUG	Time needed to stand up from a chair, walk 3 m, come back, and sit down again	Bedside test Easy to implement	Requires ability to stand up	Prolonged TUG associated with HE (35)
Composite scores				
LFI	Handgrip + balance + chair stands	Bedside test Easy to implement Improves with exercise	Requires ability to stand up Device cost +	Low LFI ↑ risk of incidental overt HE (249)

CT, computed tomography; HCC, hepatocellular cancer; HE, hepatic encephalopathy; LFI, liver frailty index; MAMC, mid arm muscle circumference; PMI, psoas muscle index; SMI, skeletal muscle index; TUG, timed up and go.

contact, community exposure, and navigation. Furthermore, fatigue, which is associated with hyperammonemia, has been improved by exercise (302,304–306), along with vitality (303,307) and overall mental or physical health scores of SF-36 (308). However, this is not a consistent finding (301,309).

In an RCT of 101 men with cirrhosis (80.5% Child Pugh B/C) and low testosterone levels, intramuscular testosterone undeconoate replacement resulted in improved glucose metabolism and increased muscle mass and decreased fat mass as evaluated using dual-energy x-ray absorptiometry. There were no significant differences in the severity of HE during the study period, and mortality was also nonsignificant (310). A 2024 multicenter double-blind phase 2 trial evaluated the impact of 24 weeks of the oral androgen receptor agonist ARA-LPCN 1148 in 29 male participants with sarcopenia and cirrhosis awaiting liver transplant. Significant improvements were seen in sarcopenia as measured by the L3-skeletal muscle index, alongside less episodes of OHE as compared with placebo, but no change in the EncephalApp Stroop test as compared with placebo (311). Although these results are promising for muscle health and physical fitness, clinical trials addressing OHE as an endpoint are still lacking.

Medical treatments being tested or not currently approved for HE are summarized in Table 7.

HE IN THE CONTEXT OF TIPS

Recommendations

22. We recommend initiating rifaximin therapy 14 days before elective TIPS insertion and continuing for at least 6 months in patients with decompensated cirrhosis with or without a prior episode of OHE to decrease the risk of recurrent or de novo OHE (strong recommendation, moderate certainty of evidence).
23. We suggest embolizing extrahepatic collaterals at the time of TIPS to reduce post-TIPS HE (conditional recommendation, low certainty of evidence).

HE occurs in 30%–40% of patients after TIPS and is associated with poor HRQoL and prognosis (324,325). There is also refractory post-TIPS HE that occurs in 3%–7% of patients with most cases occurring when the portal-systemic gradient decreases by >60% post TIPS (326,327). There is no impact of systemic inflammation but some effect of sarcopenia and pre-TIPS cognitive performance

Table 7. Medical therapies under investigation or previously tested for HE

Modality	Potential mechanism of action	Stages of HE tested	Current stage of development	More comments
Gut-brain axis				
Rifaximin solid soluble dispersion (137)	Altered microbial function and enhancement of bile acid profiles	Prevention of HE development Reduction in time spent confused inpatient HE	Phase 3 multicenter trial topline results show no significant effect on first HE prevention (360)	Trials in decompensated cirrhosis to prevent further decompensation and first HE episode are negative
Fecal microbiota transplant (189–192,312)	Microbial structure and function change	Prevention of HE recurrence	Phase 1 to phase 2a	Larger studies needed but signal for safety, cognitive improvement, and reduced HE recurrence
Defined bacterial consortium (313)	Microbial structure and function change	Prevention of HE recurrence	Phase 1	Larger studies needed
Rifamycin SV MMX (98)	Microbial structure and function change	Minimal HE	Phase 2	Improved sarcopenia, inflammation, and microbial profile but not cognitive testing
Probiotic mixtures (including mixtures known as VSL#3 before) (100,101,314–316)	Microbial structure and function change	Minimal/covert HE Prevention of overt HE	Phase 2	Not approved for HE; prevented readmissions
Lactobacillus GG (317)	Microbial structure and function change	Minimal HE	Phase 2	Improved endotoxemia and microbial profile but not cognitive testing
Sarcopenia prevention				
LPCN 1148 (313)	Androgen agonist	Prevention of HE recurrence	Phase 2	Only for men with reduced HE recurrence
Ammonia scavenger				
Ornithine phenylacetate (318)	Ammonia scavenger	Inpatients with HE to reduce time spent in confusional state	Phase 2	Not effective but if limited to those with true hyperammonemia would be successful
Glycerol phenylbutyrate (138)	Ammonia scavenger	Prevention of HE recurrence	Phase 2	Successful but not in those with concomitant rifaximin; not being developed further
Anti-inflammatory				
IV Albumin (167,319–322)	Anti-inflammatory Reduce endothelial dysfunction	Minimal/covert HE Inpatient HE Prevention of overt HE	Phases 2–3	Not specifically approved for HE prevention or treatment
Neuro-steroid alteration				
Golexanolone (323)	GABA-A receptor-modulating steroid antagonist	Minimal/covert HE	Phase 2	Reduced impact of sleepiness and fatigue

HE, hepatic encephalopathy.

in predicting the development of post-TIPS HE (328). There are multiple factors that influence the development of post-TIPS HE, including increased age, worse liver function, hyponatremia, pre-TIPS SPSSs, HE history, larger stent diameter, increased portal pressure gradient reduction, and sarcopenia (329). There is substantial literature evaluating the impact of sarcopenia on post-TIPS HE (330,331). TIPS can result in improvements in muscle mass (332) potentially on the basis of portal pressure reduction, ascites resolution, and improvements in dietary absorption. Those patients who improve their sarcopenia post-TIPS have a lower risk of HE postprocedure (333–336). Although further evaluation is required, body fat distribution may also play a role in post-TIPS HE with increased risk of HE seen in those with alterations in body fat distribution pre-TIPS (low visceral fat in males and low subcutaneous fat in females) (337), and a lower risk seen in those with improvements in the subcutaneous adipose tissue index (338).

Preventing post-TIPS HE using lactulose or lactitol in smaller studies was unsuccessful compared with placebo (339). Embolization of extrahepatic collaterals may also decrease post-TIPS HE (243,244,340). However, a larger RCT with rifaximin pre-TIPS

was able to reduce post-TIPS HE occurrence significantly over placebo (341). This study with prophylactic rifaximin involved mostly refractory ascites patients with alcohol use as the etiology. Once HE occurs, the treatment is similar to non-TIPS HE including lactulose and rifaximin. However, if unsuccessful or refractory, reducing the TIPS diameter through ballooning or placing a smaller TIPS within a TIPS can dramatically reduce the diameter and improve the cause of HE (326). Ultimately, liver tranplant (LT) should be considered in these patients if clinically appropriate.

LIVER TRANSPLANT AND HE

Recommendation

24. For patients with multiple HE episodes and MELD score <15, we suggest evaluating candidacy for living donor liver transplantation (conditional recommendation, low certainty of evidence).

Key concepts

26. Adding 4–5 MELD points regardless of the MELD score iteration used more accurately reflects the 90-day mortality of inpatient OHE and outpatient CHE.
27. As multiple HE episodes lead to persistent cognitive impairment which may not recover after LT, early LT could have additional benefits to improve brain function.
28. Early evaluation for liver transplantation should be considered in patients with high MELD3.0 scores, severe HE (grades III–IV), or frequent HE episodes, to improve long-term outcomes.
29. Persistent confusion in an inpatient setting is a relative contraindication to transplant

Since the changeover from the Child score to MELD and subsequent iterations for liver transplant priority in the United States, HE is not given extra priority points (342). The latest iteration of MELD, the MELD3.0, still does not take HE into account for organ allocation. This omission could lead to underestimation of the true illness of how chronic liver disease in patients with HE affects their prioritization on the transplant waitlist. Although the prior HE guidelines state that HE alone is not considered an indication for LT unless it is associated with poor liver function (11), severe HE (grades 3–4) has been shown to significantly increase 90-day waitlist mortality, independent of the MELD score (343,344). Further studies suggest that patients with MELD scores between 30 and 34 and severe HE have similar mortality rates to those with MELD scores ≥35 without HE, indicating that HE should be considered in the allocation system (343,345). Therefore, patients with HE should be referred for transplant evaluation.

Therefore, although HE is not currently prioritized adequately in the MELD system, there is substantial evidence supporting its inclusion to better reflect the severity of liver disease and improve outcomes for these patients by improving the allocation system. A study by Lucidi et al found that incorporating HE into the original MELD score by the addition of 7 points in patients with HE optimally predicted 6-month mortality (346). Silvey et al also supported the addition of 4–5 points to the MELD3.0 score for patients with documented inpatient OHE to enhance mortality prediction (347). Although CHE is less severe than OHE, it has independently been associated with poor survival and increased risk of hospitalization. Patidar et al found that patients with CHE had a higher risk of developing OHE, hospitalization, and death or transplant, even after controlling for MELD score and using critical flicker frequency additional MELD points would be needed to counter the impact of HE exclusion (40,79). Therefore, it could be suggested that CHE also contributes to the overall severity of liver disease and should be considered in the prognostic assessment in conjunction with the MELD score.

In addition to mortality, preserving brain function and daily function that would be lost with recurrent HE pre-LT, are major reasons for improving access to LT for patients with HE. Multiple HE episodes lead to cumulative and potentially irreversible cognitive deficits (348–352). Patients with severe pretransplant HE (grades 3–4) have been shown to have lower overall post-LT survival compared with those without HE. This increased mortality is primarily observed within the first year post-LT and is largely attributed to higher rates of infection-related deaths among patients with severe HE (353). Furthermore, severe pretransplant HE is associated with longer hospital stays post-LT, independent of other factors including the MELD score due to higher postoperative complications and morbidity (354). Neurological complications are also more common in these patients with higher risk for perioperative neurological events, such as altered mental status and seizures, which can further complicate recovery and prolong hospital stays (355,356). Despite overall improvements, a persistent deficit can remain in patients with a history of OHE pre-LT particularly in domains such as attention, executive function, and psychomotor speed (355,356). It may also be observed that overall brain volume and function in pretransplant HE is associated with reduced brain volume and neuronal markers, which may not fully normalize post-LT (356). Hence, severe pre-LT HE could potentially lead to cognitive inflexibility and learning deficits post LT. In one study, patients with HE showed impaired learning and cognitive flexibility, which can improve post-LT but may not reach the levels seen in patients without HE (357). As transplantation is the only definitive treatment for HE, patients who are candidates should be promptly evaluated and consideration of transplant urgently discussed (8) because LT improves cognitive function (349). With early evaluation and listing in patients with frequent HE episodes, we could mitigate the high morbidity and healthcare burden (QoL) associated with recurrent HE, ultimately improving long-term outcomes (8,11).

Operationalization of HE diagnosis is difficult because of the subjective nature of the diagnosis. Studies have used cognitive testing and evidence of hospitalizations for inpatient HE management as benchmarks (79,346,347). However, more data are needed to address potential gaming of the system if additional points are awarded. Validated and reproducible inpatient diagnosis of HE is needed to ensure objectivity for transplant prioritization, and a recent study of natural language processing has shown promise (358). In addition, as recommended in the ACG ACLF guidelines, patients whose confusion does not get better despite adequate treatment are likely not appropriate candidates for LT due to a high potential of persistently poor brain recovery post-LT (171).

An alternative to extra points for deceased donor liver transplant is living donor LT (LDLT), which could offer a survival benefit for patients with low MELD scores (359). This survival benefit is particularly relevant for patients with recurrent HE

because timely transplantation can prevent further cognitive decline and improve overall prognosis. Moreover, early transplantation in patients with frequent HE episodes can mitigate the high morbidity associated with recurrent HE, leading to better long-term cognitive outcomes and quality of life. Therefore, incorporating LDLT as a viable option for these patients can significantly enhance their chances of survival and recovery. LDLT could be considered for patients with multiple episodes of HE and low MELD scores to improve long-term outcomes, reduce mortality, and enhance quality of life.

CONCLUSIONS

HE in cirrhosis is a multiorgan disorder of gut-brain axis that has a major negative impact on patients, caregivers, medical systems, and society. The pathogenesis, symptoms, effect on clinical and psychosocial function, and need for a multidisciplinary approach to manage this condition, are highlighted. Although current diagnostic and management strategies have made major strides, gaps remain in the appropriate identification of HE and to treat patients who are not responsive to currently available therapies. In addition, the impact of HE on liver transplant eligibility needs further elucidation. Novel targets focused on the gut-brain axis, sarcopenia, ammonia, and brain neuro-steroids are being investigated.

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CONFLICTS OF INTEREST

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