
In the name of
God

CME

ACG Clinical Guideline: Hepatic Encephalopathy

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Definition

- Hepatic encephalopathy (HE) is brain dysfunction resulting from liver impairment or portosystemic shunting, presenting as a spectrum of neurological and psychiatric manifestations.

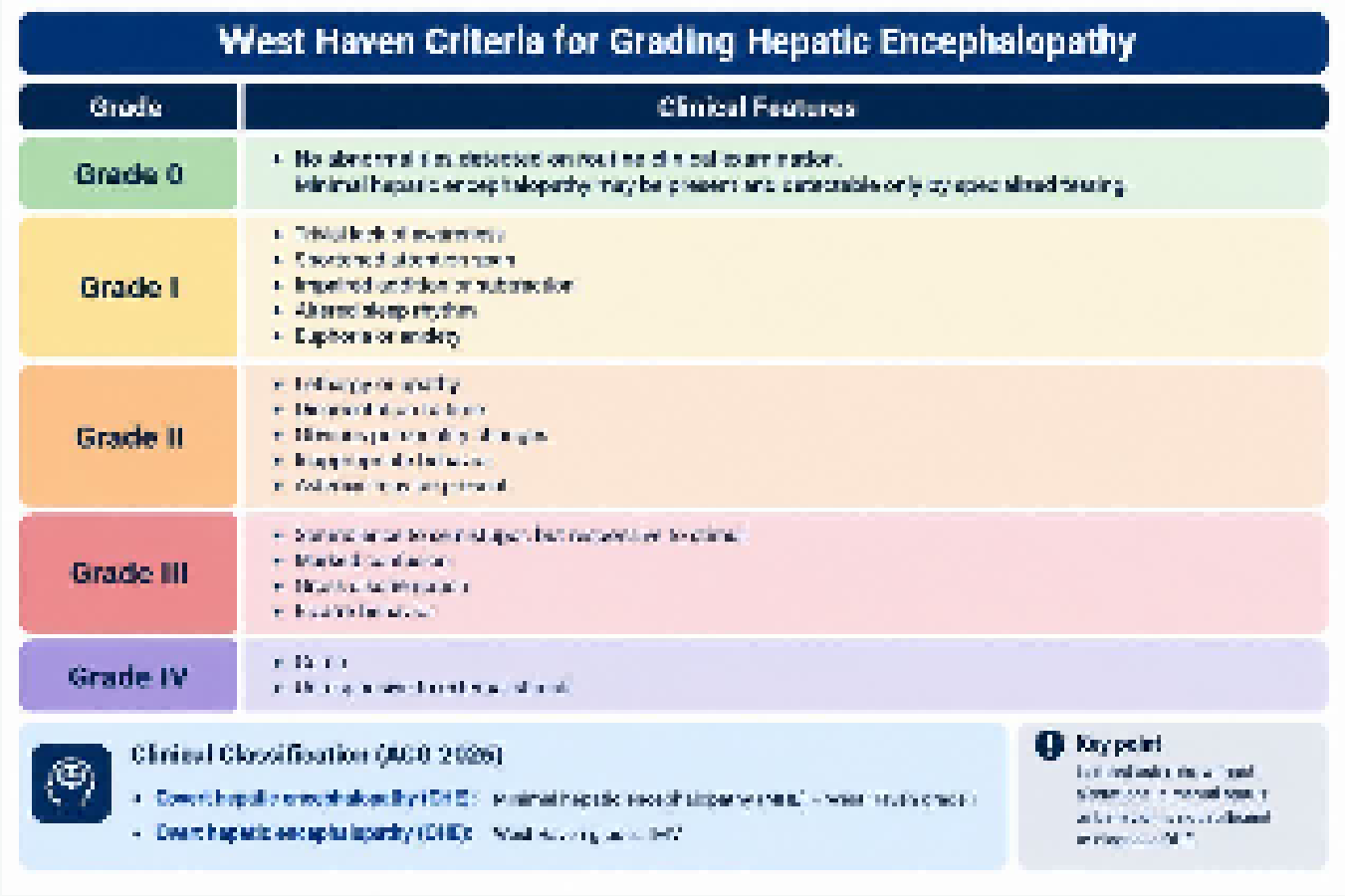
- Implicit in this definition, HE can occur without cirrhosis with simple portosystemic shunting and neuro-psychiatric and subclinical symptoms can occur as part of this syndrome.

Minimal, covert and overt HE

MHE Minimal Hepatic Encephalopathy	The subclinical form of hepatic encephalopathy that can only be identified through specialized neuropsychological testing and is not detectable on standard clinical examination.
CHE Covert Hepatic Encephalopathy	Includes minimal hepatic encephalopathy and West Haven grade I hepatic encephalopathy. Given the low reproducibility of clinical diagnosis, CHE should be defined by excluding overt hepatic encephalopathy (grade II or higher) in the appropriate clinical context.
OHE Overt Hepatic Encephalopathy	Overt hepatic encephalopathy corresponds to West Haven grades II–IV and comprises forms of hepatic encephalopathy that can be diagnosed on standard clinical examination without specialized neuropsychological testing.

MHE and CHE are usually used interchangeably.

West Haven criteria for grading HE



West Haven Criteria for Grading Hepatic Encephalopathy	
Grade	Clinical Features
Grade 0	• No abnormal mental status detectable on routine clinical examination. Minimal hepatic encephalopathy may be present and detectable only by specialized testing.
Grade I	• [illegible]
Grade II	• [illegible]
Grade III	• [illegible]
Grade IV	• [illegible]

Clinical Classification (ACG 2026)

- [illegible]
- [illegible]

Key point

[illegible]

Asterixis and motor signs in CHE

- 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.
- 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.

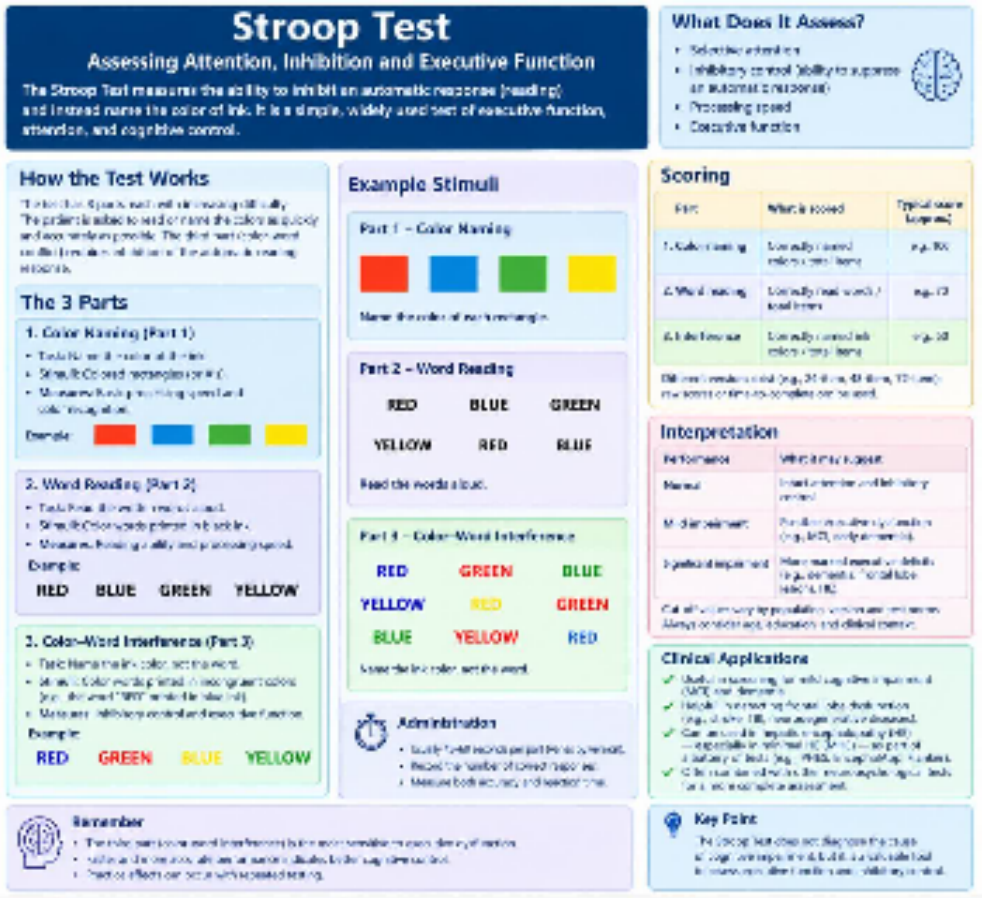
Cognitive tests for practical use in clinic

Table 4. Cognitive tests for practical use in clinic

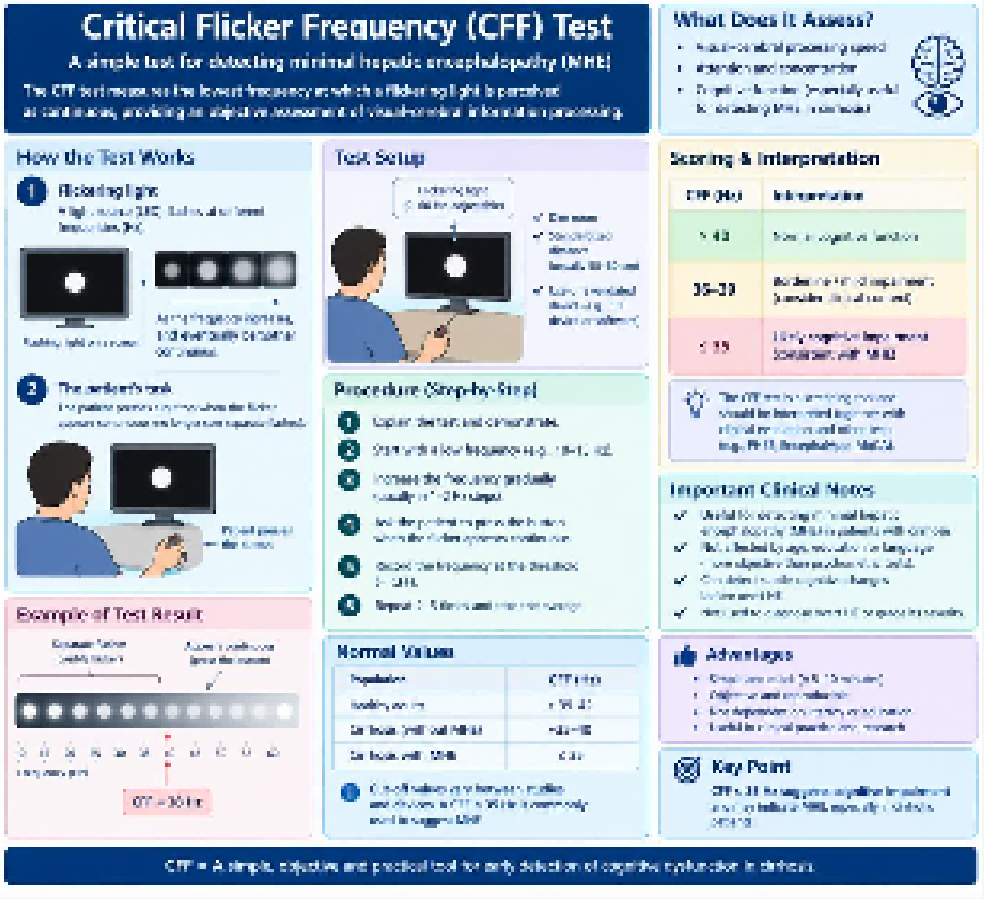
	Test description	Resources and time complete	Tested domains	Reported MHE or CHE prevalence	Clinical utility	Pros and cons
Stroop EncephalApp (Full) (61,70–72)	App-based version of Stroop test	Smartphone or tablet 5–15 min	Psychomotor speed, cognitive flexibility	45%–55%	Predicts OHE	Easy to apply, although 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.

Stroop test


Stroop Test
Assessing Attention, Inhibition and Executive Function
The Stroop Test measures the ability to inhibit an automatic response (reading) and instead name the color of ink. It is a simple, widely used test of executive function, attention, and cognitive control.
What Does It Assess?
Processing speed
Executive function
How the Test Works
The 3 Parts
1. Color Naming (Part 1)
2. Word Reading (Part 2)
Example:
RED BLUE GREEN YELLOW
3. Color–Word Interference (Part 3)
Example:
RED GREEN BLUE YELLOW
Example Stimuli
Part 1 – Color Naming
Part 2 – Word Reading
RED BLUE GREEN
YELLOW RED BLUE
Part 3 – Color–Word Interference
RED GREEN BLUE
YELLOW RED GREEN
BLUE YELLOW RED
Administration
Scoring
Interpretation
Clinical Applications
Remember
Key Point

Critical Flicker Frequency (CFF) test



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

Key concept

- 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.

- Isolated asterixis without alterations in behavior or alertness is not enough to diagnose OHE

Who to test for MHE

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 (particularly if > 8 mm)

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

Alternative diagnoses and benefits of testing

- 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

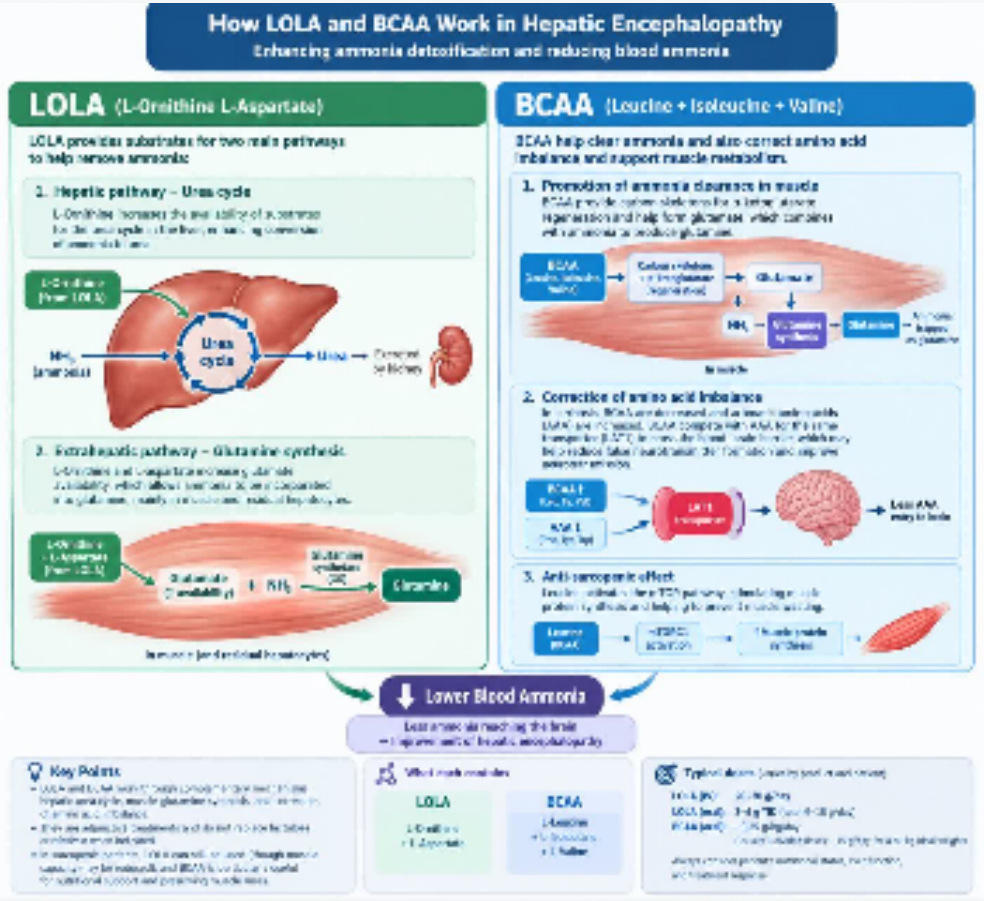
- Cognitive testing for CHE/MHE and subsequent therapy with lactulose or rifaximin may improve health-related quality of life.

Second-line agents and follow-up

- 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)

- 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

How LOLA and BCAA work in HE



Inpatient management of HE

1. In patients with HE, we suggest against routine testing of serum ammonia to guide HE treatment decisions
   Conditional recommendation, very low certainty of evidence

2. 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

3. 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

Inpatient management of HE (continued)

4 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

5 In patients with acute OHE, we suggest adding rifaximin to lactulose therapy vs lactulose therapy alone

Conditional recommendation, low certainty of evidence

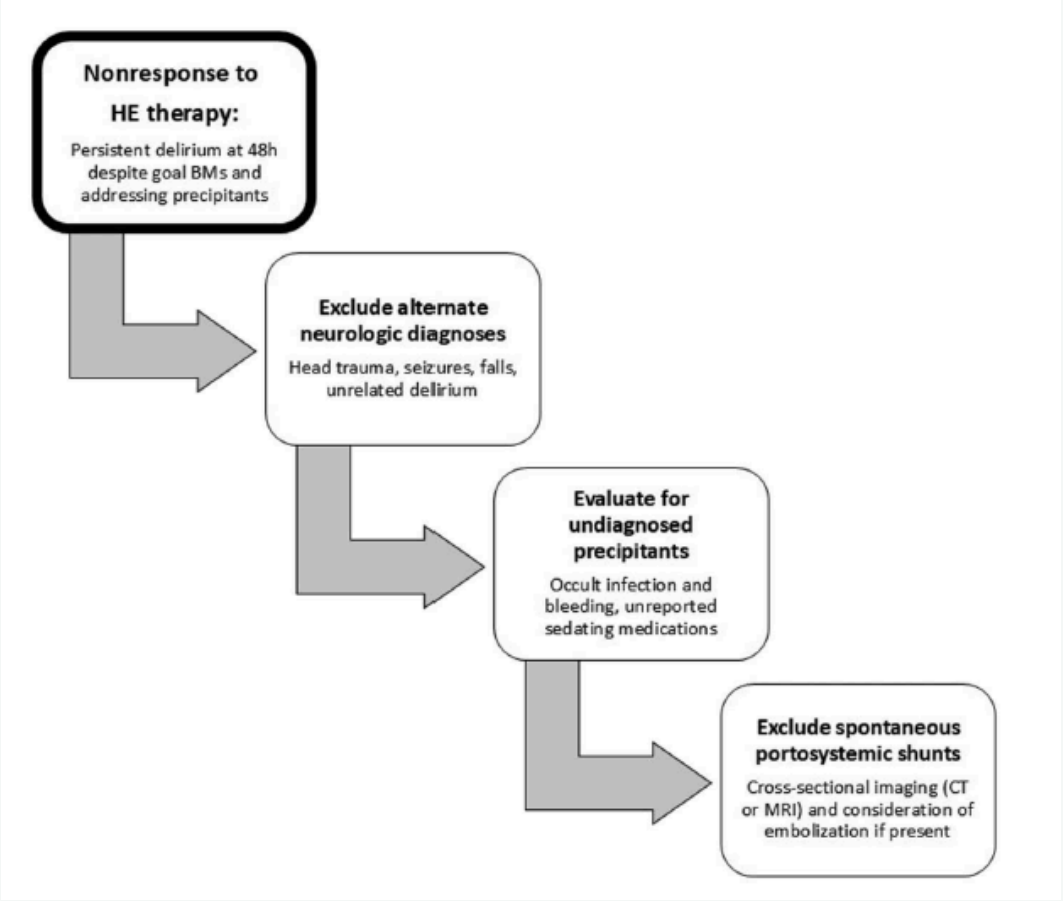
Key concept

- 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

- A normal blood ammonia level in patients with altered mental status should prompt consideration of other potential diagnoses in addition to OHE

- 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

Approach to nonresponse to HE therapy



Treatment of HE for patients in intensive care unit (ICU)

1

Lactulose in Intubated Patients:

- Titrate lactulose primarily according to bowel movement frequency and stool output when mental status cannot be assessed.
- Hold lactulose and other laxatives if stool output exceeds 300 mL/day in patients using a fecal management system.
- Monitor for hypernatremia and dehydration.
- Implement measures to prevent aspiration.

Treatment of HE in the ICU (continued)

2

Rifaximin in the ICU:

- Benefit may be limited, particularly in patients receiving broad-spectrum antibiotics.
- A randomized trial showed no significant improvement in OHE reversal with rifaximin plus antibiotics compared with antibiotics alone.

Treatment of HE in the ICU (continued)

3

Nontraditional Therapies for HE

- Renal replacement therapy (RRT): Consider early in acute liver failure with severe hyperammonemia (>100 µmol/L); evidence is insufficient for routine use in cirrhosis solely to lower ammonia.
- High-volume plasma exchange: May improve HE and survival in acute liver failure; benefit in cirrhosis remains unproven.
- Albumin dialysis (MARS): May reduce HE severity and serve as a bridge to liver transplantation; further studies are needed.

Prevention of HE recurrence

1. 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

2. 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

3. In patients with cirrhosis and OHE, we suggest rifaximin therapy in the outpatient setting to prevent HE recurrence
   Conditional recommendation, low certainty of evidence

Prevention of HE recurrence (continued)

4 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

5 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

Prevention of HE recurrence (continued)

6 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

7 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 concept

- 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

- 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

Medication review in HE

- 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)

De-escalation, driving and caregivers

- HE therapy may be deescalated and potentially discontinued in a stepwise fashion in patients who clinically recompensate

- 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.

- Caregivers should be screened for caregiver burnout and provided necessary support as appropriate

Sarcopenia and nutrition

1. We recommend a protein intake target of 1.2–1.5 g/kg/d in outpatients with HE
   Strong recommendation, moderate certainty of evidence

2. We recommend BCAA supplementation in individuals with HE if protein needs cannot be met by food alone
   Strong recommendation, moderate certainty of evidence

3. We suggest a late-night snack for patients with cirrhosis to reduce frailty and HE
   Conditional recommendation, very low certainty of evidence

Sarcopenia and nutrition (continued)

4 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

5 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 concept

- 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

- 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

Critical illness, sarcopenia and exercise

- Critically ill patients with HE should receive up to 2 g/kg/d protein intake
- 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
- 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
- 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

HE in the context of TIPS

1. 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

2. 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

1. 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 concept

- 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
- 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
- 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
- Persistent confusion in an inpatient setting is a relative contraindication to transplant


Hepatic Encephalopathy
Please...
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