REVIEW

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A practical approach to the diagnosis and management of hepatic encephalopathy

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ABSTRACT

Hepatic encephalopathy (HE) is a common complication of decompensated cirrhosis that can be reversed with treatment. Frequent episodes of recurrence are common, impacting patients, caregivers and healthcare systems, increasing morbidity and mortality statistics and resulting in grave financial consequences. Uptake and adherence to formal recommendations for HE diagnosis and management are low. There is an unmet need to advocate for the use of these recommendations in a more pragmatic form. Clinicians from multiple disciplines, dedicated to raising liver disease awareness, convened in a roundtable format to review and discuss the latest HE guidelines and relevant peer-reviewed literature on HE. The result was this clinical care publication on the screening, diagnosis and management of HE which seeks to facilitate clinicians' recognition and diagnosis of HE, apply a pathway of care for HE that addresses steps for initial management, long-term maintenance and prevention; it also addresses practical recommendations concerning situations encountered in HE. Resources are provided to address the different needs of the three key players in HE: patients, caregivers, and healthcare professionals.

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KEYWORDS: Decompensated cirrhosis; Hepatic encephalopathy; Screening; Diagnosis; Management; Recurrence

Introduction

Hepatic encephalopathy (HE), a common complication of decompensated cirrhosis, presents as a wide spectrum of potentially reversible neuropsychiatric abnormalities, classified as subclinical covert (CHE) to clinically apparent overt HE (OHE).[1] Studies suggest that up to 70% of cirrhotic patients will experience HE at some point during their illness.[2-4] Following a diagnosis of HE, overall survival is decreased to 2 years in all patients regardless of disease etiology and, in patients older than 65 years of age, overall survival is approximately 1 year.[5,6] In addition to the increased morbidity and mortality, HE increases rates of hospitalizations and healthcare costs and decreases patient and caregiver quality-of-life (QoL). Changing trends in the etiology of chronic liver disease may affect the development and consequences of HE[7] such as increased rates of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease. [8,9]

Despite the growing prevalence of HE, clinical practice gaps exist. A 2025 analysis of insurance claims and encounters and Medicare files between 2007 and 2020 indicate that HE prevalence, liver transplantation rates and cirrhosis and HE-related healthcare costs are increasing while lactulose use is decreasing.[10] Provider practice patterns indicate that screening for HE is inconsistent and occurs approximately 40% of the time.[11,12] Over the last 30 years, the treatment of OHE, albeit effective if used correctly, has not evolved.[13] Although clinical practice guidelines are available,[1,14] they are "only as good as their uptake."[15] Data on clinical

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practice guideline adherence demonstrate that approximately 70% of healthcare professionals across disciplines are noncompliant with guideline recommendations.[16] When asked for feedback on guideline adherence, physicians indicate that improved implementation and uptake of guidelines would require more education and publications that promote and simplify the guidelines.[17]

Approach

Clinicians who are members of or work closely with the Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease hosted a clinical roundtable discussion to review and discuss the latest HE guidelines and relevant peer-reviewed literature regarding the diagnosis and management of HE. The panel, which consisted of hepatologists, a hospitalist, and an advanced practice provider, determined that a clinical care publication on the screening, diagnosis and management of HE would help to fill HE clinical practice gaps and benefit a wide audience of clinicians managing HE. This publication seeks to facilitate clinicians' recognition and diagnosis of HE, apply a pathway of care for HE that addresses steps for initial management, long-term maintenance and prevention, and addresses practical recommendations concerning situations encountered in HE.

CLINICAL SIGNIFICANCE

- Early recognition of HE, treatment, and reduction in risk of recurrence are imperative to minimize patient morbidity and mortality.
- Approximately 70% of healthcare professionals across disciplines are noncompliant with guideline recommendations.
- When asked for feedback on guideline adherence, physicians indicate that improved implementation and uptake of guidelines would require more education and publications that promote and simplify the guidelines.
- This publication seeks to simplify clinical guidelines for HE.

When to suspect hepatic encephalopathy

Data indicate that, at the time of diagnosis, 10% to 14% of patients with compensated cirrhosis and 16% to 21% of patients with decompensated cirrhosis will have OHE, and 10% to 50% of patients will be at risk after transjugular intrahepatic portosystemic shunt placement.[1,18] The prompt recognition and management of HE in all patients with advanced liver disease is essential for improving clinical outcomes, as failure to manage HE appropriately can result in progression of clinical symptoms, repeated episodes, increased hospitalizations, and worsened overall prognosis. This section will discuss when to suspect HE and introduce "The HE Cascade of Care" (Fig. 1) which provides practical clinical pearls from recognizing HE to preventing recurrence.

HE comes in different forms and flavors. It is easy to suspect HE in patients with advanced liver disease experiencing severe confusion or who are comatose, but HE is a spectrum that also includes more subtle presentations. CHE affects a large proportion of patients with cirrhosis and these patients "appear and perform well during the office visit" but are impaired.[19] In addition to impacting daily life (e.g., employment, vehicle accidents, diminished QoL, propensity to falls), a significant number of patients with CHE progress to OHE, an advanced complication of liver decompensation.[19] If a patient has a diagnosis of advanced liver disease, with or without a history of HE, an assessment for HE is recommended at every office visit (Fig. 1). Table 1 provides a checklist for the healthcare team to assist in the recognition and diagnosis of HE.

The early signs of HE can be subtle (e.g., forgetfulness, irritability) and the patient may not recognize the symptoms. Simple questions should be asked to assess their cognitive status (Table 1) or a specific tool can be used at each visit (e.g., the Stroop Test, Continuous Reaction Time Test, or the Inhibitory Control Test).[1] Caregivers play an important role in the HE screening process. With the patient's consent, caregivers should be engaged during the visit in identifying and reporting symptoms uch as insomnia, forgetfulness, difficulty with word retrieval, changes in driving patterns, difficulty with simple math, idleness and personality changes (e.g., irritability). HE can also present in various clinical scenarios and different healthcare settings where underlying liver disease status is unknown, making early diagnosis and treatment of HE crucial.

How to detect hepatic encephalopathy

HE diagnosis will be explored in this section and in Fig. 1.

Exclude alternative causes of altered cognition

The differential diagnosis of HE should consider alternative causes of brain dysfunction, especially on the first presentation (Table 1). Metabolic encephalopathy and dementia/Alzheimer's disease are the most difficult to rule out, particularly if the status of the liver is unknown in a patient with confusion on presentation. Table 2 provides factors to consider when making the differential diagnosis. Marked motor signs, asterixis, and response to HE treatments are good indicators that the patient is experiencing HE. Patients also should be screened for depression.[20]

Detecting HE and investigating potential precipitating factors

Detecting HE and investigating precipitating factors involves obtaining a patient history, performing a medication review and physical exam, and obtaining laboratory tests (Table 1). The history should investigate when the onset of mental status changes occurred, recent alcohol or

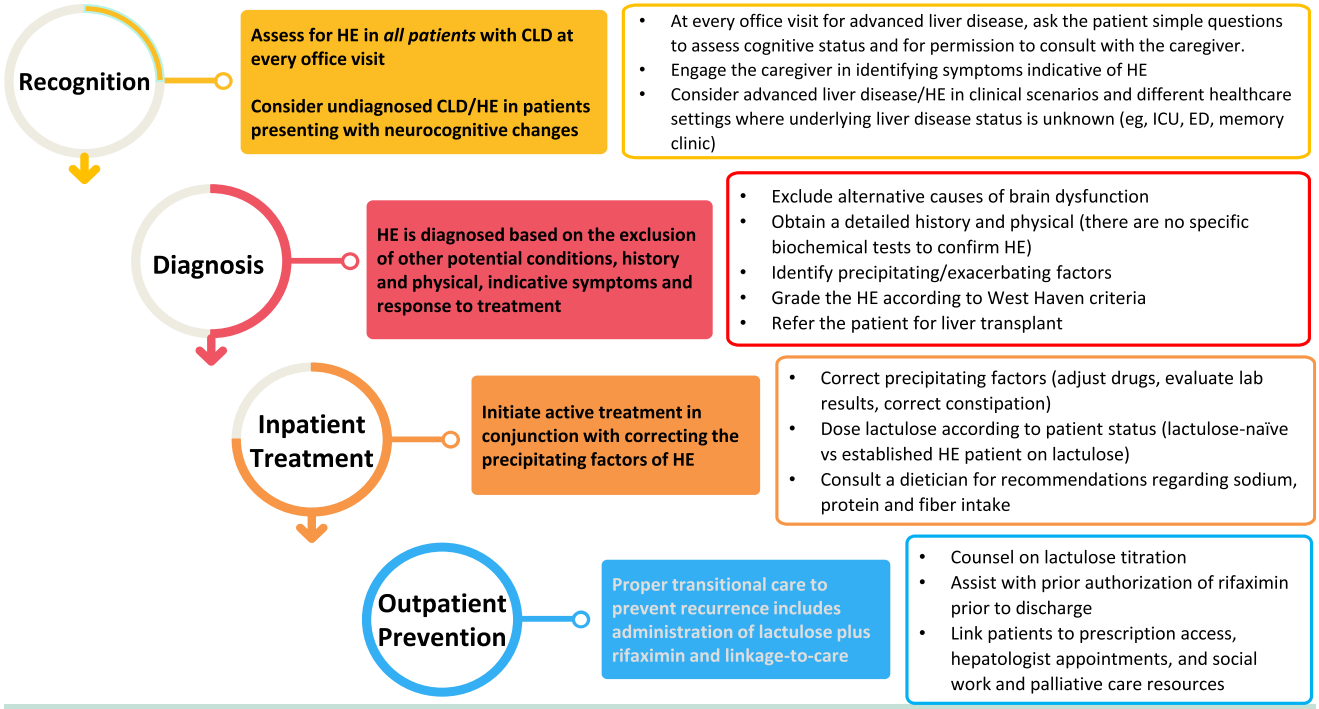


Fig. 1 The hepatic encephalopathy cascade of care.
CLD = chronic liver; ED = emergency department; HE = hepatic encephalopathy; ICU = intensive care unit.

drug intake, recent medication changes, medication adherence, and the number and size of bowel movements (BMs) in the past 24 h. Constipation or excessive BMs could suggest dehydration or electrolyte abnormalities. Day/night sleep reversal should also be addressed in the history as this often an early sign of HE. An initial evaluation of recently added or adjusted medications should be investigated, especially benzodiazepines, opiates, or other sedating neuroleptics or psychotropics. Clinicians should also look for changes in dosages or newly added/stopped medications. The last upper endoscopy should also be reviewed for the presence of gastroesophageal varices and portal hypertensive gastropathy.

The physical exam for an HE patient can be normal. Vital signs, including blood pressure and heart rate, should be assessed in the context of baseline readings to see if there is relative hypotension or tachycardia, which can indicate sepsis, bleeding, or dehydration. Many of these patients may be taking nonselective beta-blockers for variceal bleed prevention, which can inhibit a compensatory heart rate response. Other evaluations should include signs of gastrointestinal bleeding, neurological deficits to suggest intracranial hemorrhage, localized signs of infection (skin, abdomen, lungs) and urine output. Sarcopenia is also common in cirrhosis and associated with HE given the role that muscles play in ammonia clearance. An agitated patient should prompt immediate evaluations for HE and intoxication.

The physical examination should also look for clues that indicate HE. A musty or sweet breath odor, known as fetor hepaticus, can also be a unique clue. Asterixis, also called a flapping tremor, albeit observed in other diseases, is common in HE. Cognitive impairment can fluctuate greatly depending on the underlying liver disease status and the presence of precipitating factors. A study of 71,000 veterans with cirrhosis demonstrated that dementia is commonly diagnosed in patients with cirrhosis and correlates with a diagnosis of HE, but does not correlate with other decompensating events.[21]

With regard to laboratory tests, a complete blood count should be performed, including white blood cell counts to identify infection and red blood cell counts to identify bleeding. Thrombocytopenia is also a surrogate for portal hypertension. A decline from prior levels should be noted as this suggests progressive liver disease (and risk for HE). A complete metabolic panel should include electrolytes to identify hypo/hypernatremia, hypokalemia, hypomagnesemia and hypophosphatemia which can precipitate HE and can accompany diarrhea and the use of diuretics. Renal and liver function should also be assessed. Acute kidney injury can precipitate HE. Liver function tests, including bilirubin, may indicate signs of obstruction and should prompt right upper quadrant ultrasonography with doppler to evaluate for biliary tract disease as well as for the presence of portal vein thrombosis, a precipitator of HE. An INR should be obtained as it is an important assessment of liver function and, if highly deranged, could indicate a higher risk of bleeding. Point-of-care glucose should be checked for hypoglycemia.

The underlying pathophysiology of HE involves multiple metabolic abnormalities, with ammonia playing a central role in the neurotoxic cascade.[22] Serum ammonia levels can help suggest HE but are not reliable or specific, may be elevated in conditions other than liver disease[23] and do not always correlate with HE severity.[24] Per the guidelines of

Table 1 A healthcare team checklist for recognizing and diagnosing HE.

Screening Questions For Patients and Caregivers (YES or NO)
- ☐ Have you noticed a change in sleep pattern such as sleeping during the day and being awake all night?
- ☐ Have you noticed any recent changes in your memory or concentration?
- ☐ Are you able to perform simple tasks (simple math, writing bills, driving directions)?
- ☐ Have you experienced confusion or difficulty following conversations?
- ☐ Have others commented on personality or behavior changes?
- ☐ Do you notice hand tremors, flapping hand movements (asterixis), or difficulty with fine motor skills?

Simple Screening Tests
- ☐ Stroop test
- ☐ Animal naming

Differential Diagnosis
- ☐ CNS
  - ○ Intracranial hemorrhage
  - ○ Stroke
  - ○ Brain tumor
  - ○ Subdural hematoma
  - ○ Intracranial abscess
- ☐ Infectious conditions:
  - ○ Meningitis
  - ○ Encephalitis
  - ○ Systemic infection (sepsis)
- ☐ Metabolic disorders:
  - ○ Hypoglycemia
  - ○ Hyponatremia
  - ○ Hypercapnia
  - ○ Electrolyte imbalances
  - ○ Uremia
  - ○ Thiamine deficiency (Wernicke encephalopathy)
- ☐ Alzheimer's/Dementia
- ☐ Substance-related conditions:
  - ○ Alcohol intoxication
  - ○ Alcohol withdrawal
- ☐ Drug-induced encephalopathy (sedatives, antipsychotics)
- ☐ Psychiatric conditions:
  - ○ Depression
  - ○ Anxiety
  - ○ Psychosis

Medications
- ☐ Assess for any changes in dosages or newly added/stopped medications?
- ☐ Look for medications that may:
  - ○ Alter mental status and/or precipitate HE
    - ■ Sedatives
    - ■ Sedating neuroleptics
    - ■ Psychotropics
    - ■ Pain medications
    - ■ Antihistamines
  - ○ Precipitate upper gastrointestinal bleeding or acute kidney injury, which can precipitate HE
    - ■ Nonsteroidal anti-inflammatory agents
  - ○ Mask sepsis which can be a cause of altered mental status
    - ■ Blood pressure medications (alpha and beta blockers)
  - ○ Precipitate upper gastrointestinal bleeding which can cause altered mental status
    - ■ Warfarin
    - ■ Heparin
    - ■ Non-vitamin K antagonist, oral anticoagulants, and direct oral anticoagulants
  - ○ Cause electrolyte abnormalities, some of which can precipitate HE (specifically hypokalemia), other electrolyte abnormalities can also cause metabolic encephalopathy
    - ■ Diuretics

History and Physical
- ☐ Vital signs
- ☐ Timing of onset of mental status changes
- ☐ Recent alcohol or drug intake
- ☐ Recent medication change
- ☐ Medication adherence
- ☐ Number and size of bowel movements in the last 24 h
- ☐ Signs of HE (asterixis, fetor hepaticus)
- ☐ Signs of rectal bleeding
- ☐ Neurological deficits to suggest intracranial hemorrhage
- ☐ Localized signs of infection (skin, abdomen, lungs)
- ☐ Urine output

Labs
- ☐ CBC (include platelets)
- ☐ CMP (electrolytes to identify hypo/hypernatremia, hypokalemia, hypomagnesaemia and hypophosphatemia, renal function, liver function)
- ☐ Blood cultures (to check for infection)
- ☐ Urinalysis with urine culture and sensitivity test (to check for infection)
- ☐ INR (if the patient is on blood thinners)
- ☐ Point-of-care glucose
- ☐ Alpha-fetoprotein
- ☐ Drug toxicity screen
- ☐ Phosphatidylethanol
- ☐ Second tier labs (not standard, but order as needed)
  - ○ Serum ammonia (although not diagnostic of HE)
  - ○ Vitamin B12
  - ○ Folate

Other Tests
- ☐ Ultrasound with doppler (to assess for portal vein thrombosis, ascites, hepatocellular carcinoma)
- ☐ Chest x-ray
- ☐ Paracentesis

CBC = complete blood count; CMP = complete metabolic panel; HE = hepatic encephalopathy; INR = international normalized ratio; RBC = red blood cell count; WBC = white blood cell count.

This comprehensive list was developed based on numerous discussions amongst the panel of authors, who recognize that these techniques are unvalidated, yet commonly used by specialists. By reviewing the items outlined in the checklist, healthcare providers can ensure a complete patient assessment, leading to a diagnosis of HE.

Table 2 Differentiating hepatic encephalopathy, metabolic encephalopathy and dementia/Alzheimer's disease.

	Hepatic Encephalopathy	Metabolic Encephalopathy	Dementia/ Alzheimer's Disease
Description	Associated with underlying advanced liver disease or a recent liver insult (e.g., infection, gastrointestinal bleeding, or alcohol use)	Presentations vary depending on the underlying cause (e.g., electrolyte disturbances, hypoglycemia, uremia, hypercapnia)	Associated with a gradual, progressive onset (months to years) and chronic and steady decline in memory and cognitive function
Symptoms	Fetor hepaticus is a unique clue. Confusion and asterixis are common. For additional information on HE symptoms, see Fig. 2.	Varied based on the cause. ME not classified by specific signs like asterixis (unless secondary to another cause).	Memory, language, visuospatial deficits. No tremor and gait disturbances appear later in the disease.
Precipitating Factors	Infections, electrolyte abnormalities, gastrointestinal bleeding, diuretic overdose, constipation, renal failure, dehydration, diet, medications (prescription, over-the-counter and illicit drugs), HE medication noncompliance	Kidney failure (uremia), sepsis, electrolyte disturbances (hyponatremia, hypercalcemia), diabetic complications (hypo/hyperglycemia), toxic ingestions	No specific precipitating factors lead to cognitive decline, although medical events like infections or surgical procedures can temporarily worsen confusion in patients with dementia (delirium superimposed on dementia)
Labs	Elevated ammonia in some cases, abnormal LFTs	Laboratory test abnormalities are dependent on the cause (e.g., electrolyte imbalances, hypoglycemia or hyperglycemia)	Normal
Imaging and other tests	MRI may show basal ganglia changes, but imaging is unlikely to be approved in the hospital setting. EEG often shows triphasic waves, which can help differentiate HE from dementia.	Nonspecific and dependent on the underlying cause	Brain MRI or CT in AD may show cortical atrophy, particularly in the temporal and parietal lobes. Hippocampal atrophy is particularly common in AD. EEG in AD is typically normal, unless in very advanced disease, where diffuse slowing may be seen.
Treatment	Improves with treatments such as lactulose or rifaximin. Successful treatment helps to confirm the diagnosis.	Correcting the underlying metabolic disturbance (e.g., glucose for hypoglycemia, electrolyte repletion) should lead to improvement	Cognitive decline persists despite management

AD = Alzheimer's disease; CT = computed tomography; EEG = electroencephalogram; HE = hepatic encephalopathy; LFTs = liver function tests; ME = metabolic encephalopathy; MRI = magnetic resonance imaging.

the American Association for the Study of Liver Diseases (AASLD), "high blood-ammonia levels alone do not add any diagnostic, staging, or prognostic value in patients with HE with advanced liver disease".[1] There are no specific biochemical tests that can confirm the diagnosis of HE. Furthermore, testing ammonia in an outpatient is notoriously inaccurate given delays in processing and the importance of keeping the sample on ice. If a patient has mild cognitive complaints, it is more useful to arrange psychomotor testing or a Mini-Mental State Examination.[25] Ammonia testing is most often recommended to exclude HE in a patient with confusion, as it is less common if the value is normal.

Grading hepatic encephalopathy is an important next step that is described in Fig. 2. Given the clinical implications for morbidity and mortality, patients with HE should also be followed closely and referred for liver transplant evaluation.

Steps for successful initial management and long-term prevention

Once the diagnosis of HE is suspected, the AASLD guidelines call for a multi-faceted approach to treatment, which will be discussed in this section.

Acute treatment of the HE episode in the inpatient

When HE is suspected, lactulose should be started. If started in the outpatient setting for mild HE, it can be given at 20-30 cc two to three times a day with a goal of 2 to 4 soft stools every 24 h. Lactulose should be avoided in the evening to prevent nocturnal stooling. Close outpatient monitoring is also important. All patients with significant confusion should be hospitalized and lactulose initiated at 20 to 30 cc every 4 h. Patients that present obtunded should be managed in the intensive care unit. Once 2 to 4 soft

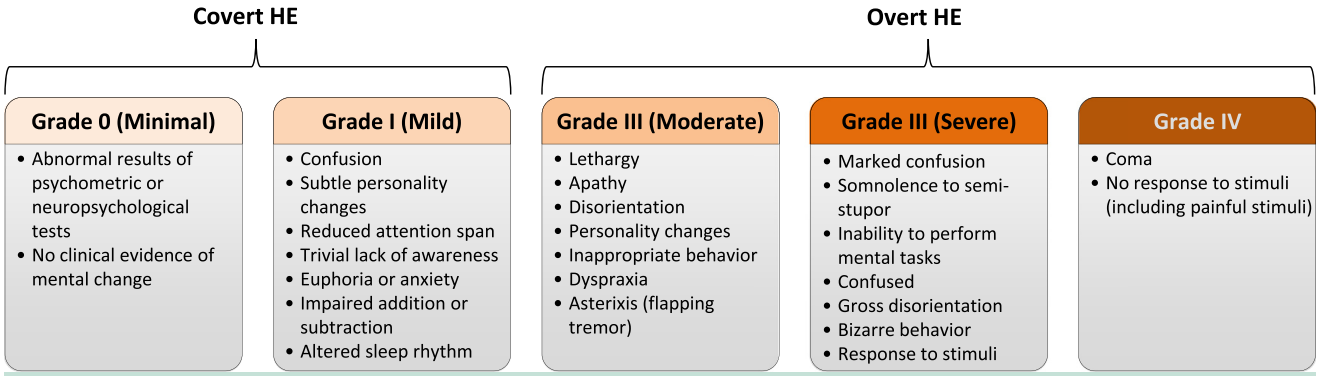


Fig. 2 The West Haven criteria and clinical manifestations of hepatic encephalopathy[1].

stools have been achieved, lactulose should be reduced to the lowest dose to maintain these results. Response to therapy is important to document. If there is no improvement after 24 h, rifaximin should be added and a thorough evaluation for exacerbating events revisited. If there is no alternative explanation, escalation of treatment should be considered every 12 to 24 h. A review of refractory HE is out of the scope of this paper but is addressed in the AASLD guidelines.[1] It is important to recognize that overuse of lactulose will lead to dehydration and electrolyte abnormalities which will exacerbate HE.[26]

Nutrition consult and dietary interventions for the inpatient

Sarcopenia is a poor prognostic factor in HE patients, so adequate protein intake is paramount. Daily energy intake should be 35 kcal/kg to 40 kcal/kg of the ideal body weight, with 1.2 g/kg to 1.5 g/kg/day of daily protein.[1] Sarcopenia and negative nitrogen metabolism can be a result of increased muscle protein breakdown and decreased muscle protein synthesis during periods of fasting. The American College of Gastroenterology's 2025 Clinical Guideline on Malnutrition and Nutritional Recommendations in Liver Disease recommends incorporating late evening snacks in patients with cirrhosis to improve body mass index, lean muscle tissue, and reduce the risk of ascites and HE.[27] Small meals or liquid nutritional supplements should be evenly distributed throughout the day and a late-night snack offered. Oral branched-chain amino acid supplementation may allow recommended protein intake to be achieved and maintained in patients intolerant of dietary protein,[1] but patient acceptance is limited because of their poor taste. Fiber is also recommended in those with excessive loose stools. However, lactulose may cause bloating and abdominal cramping, which can be exacerbated by fiber, so this should be discussed with the patient. A dietician may adjust the diet for low sodium in those with volume overload.

Transitional care for long-term maintenance and prevention in the outpatient

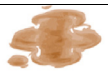
Despite appropriate treatment, patients with a previous history of OHE have a 42 % risk of recurrence within 1 year[28] andhigh hospital readmission rates.[29-36] One study identified HE as the leading cause of readmission in patients with cirrhosis.[36] This can be prevented with proper transitional care.

Outpatient lactulose use requires open communication with patients and caregivers on the nuances of proper titration. Patients should continue taking the lactulose dosing that was successful in eliciting 2 to 4 BMs in 24 h, adjusting the medication as necessary to achieve this. Use of the Bristol Stool Scale, a patient-reported characterization of BM consistency,[37] combined with the frequency of BMs, can assist in proper lactulose titration.[38] A visual aid to guide patients and caregivers on outpatient self-titration of lactulose is provided in Table 3.[37,38]

Patients and caregivers should also take note of any signs of sleep cycle reversal, mild confusion, excessive fatigue or asterixis, which should prompt an extra dose of lactulose that day. If these symptoms or constipation do not resolve within 24 h of the extra dose, symptoms become worse or bleeding occurs, patients should contact their GI/hepatologist or primary care physician for evaluation or be directed to the emergency department. Evaluation should rule out other precipitants, as discussed above, that may lead to decreased efficacy of the stable lactulose dose.

Rifaximin, 550 mg orally twice daily[39] plus lactulose is the best-documented regimen to maintain remission in patients who have already experienced one or more OHE episodes.[1] Rifaximin is the only US Food and Drug Administration-approved treatment for the prevention of HE.[39] Rifaximin typically requires prior authorization, which can take time, so it is important to begin this process when the patient is still hospitalized, as opposed to when they are discharged. Prior authorization should be attempted in the hospital, and the facilitator of this depends on the institution (e.g., the hospitalist/primary team, inpatient case manager, or the hospital pharmacy). Be prepared to appeal to the insurance company with a letter of medical necessity and, if these attempts are unsuccessful, refer the patient to the manufacturer for assistance.[40] The rifaximin "copay savings program" can be accessed via https://xifaxan.copaysavingsprogram.com/ or 1-866-XIFAXAN.[41] A delay of 7 days in obtaining rifaximin is associated with recurrent HE and hospital readmission.[42] If prior authorization is not

Table 3 A visual aid to guide patients and caregivers on at-home titration of lactulose.

How My BM Looked Over the Last 24 Hours [37,38]	The Consistency of My BM Over the Last 24 Hours [37,38]	How Many BM's Have I Had Over the Last 24 Hours? [38]	How My Lactulose Should Be Titrated[38]
 	Separate lumps, hard to pass, nut-like *or* Lumpy, sausage-shaped	Regardless of the number	Increase total daily dose by 50%
	Cracked surface, sausage-shaped	<2	Increase total daily dose by 50%
		2 to > 4	Maintain current dose
 	Smooth, soft, sausage-shaped *or* Soft blobs with defined edges	<2	Increase total daily dose by 50%
		2 to 4	Maintain current dose
		>4	Decrease total daily dose by 50%
	Mushy, fluffy pieces with ragged edges	<2	Maintain current dose
		2 to 4	Decrease total daily dose by 50%
		>4	Stop lactulose for the day
	Entirely liquid, no solid pieces, watery	Regardless of the number	Stop lactulose for the day

A caveat to keep in mind when using this visual aid is that if the stool quality was abnormal prior to starting lactulose, the stool scale may be less useful (e.g., a patient with previous pancreatic insufficiency with baseline diarrhea or post-cholecystectomy with loose stools).

Table 4 Summary of practical tips in the HE cascade of care.

- HE ranges from subtle changes (forgetfulness, irritability) to severe confusion or coma, per the West Haven Criteria.
- Screening for HE in the outpatient setting (and identifying it at an earlier stage) will help facilitate treatment if a patient with HE goes to the emergency room with severe confusion or obtundation.
- Screening should include cognitive assessments and caregiver input to identify symptoms like sleep changes, forgetfulness, or personality changes.
- The differential diagnosis of HE should consider alternative causes of brain dysfunction (e.g., metabolic encephalopathy and dementia/Alzheimer's disease), especially on the first presentation.
- Detecting HE and investigating precipitating factors involves obtaining a patient history, performing a medication review and physical exam and laboratory testing.
- Testing ammonia is notoriously inaccurate for diagnosing HE; there are no specific biochemical tests that can confirm the diagnosis of HE. A low ammonia level can help to exclude HE in a patient with confusion.
- Nutrition is vital: adequate protein intake, late-night snacks, and branched-chain amino acids can help maintain muscle mass and reduce ammonia levels.
- Preventing recurrence involves using lactulose and rifaximin, alongside addressing social and logistical barriers (e.g., transportation, medication access).
- Outpatient follow-up with a provider trained in the care of HE within 2 weeks after discharge (or sooner in more severe HE cases) is recommended.
- Palliative care should be introduced to discuss goals of care and revisited as circumstances change.
- In patients with suspected HE, always evaluate for underlying liver disease.
- Liver transplantation evaluation is recommended for patients with documented episodes of overt HE.
- Patient and family education about treatment benefits of lactulose and rifaximin can improve compliance.

required or the patient is not insured, discerning the copay or cash amount can help the patient prepare for the costs to expect at the pharmacy. In preparation for any potential delays, inquire with your institution's pharmacy to provide the patient with a small supply of rifaximin to bridge the gap between discharge and the follow-up appointment.[40]

Outpatient access to a clinician with experience in liver disease . This is (usually a hepatologist or advanced practice provider specializing in hepatology) is important. Communication between the inpatient provider and hepatologist to help expedite the first appointment is needed, with the goal to have this appointment scheduled within 2 weeks after discharge or sooner in more severe HE cases. Transportation to appointments can be a barrier and may be covered by insurance. Social workers should be consulted as needed.

Palliative care is an important service that collaborates with the patient to focus on quality of life and goals of care and should be introduced. These patients will likely be hospitalized often and it is beneficial for them to consider their goals in a non-urgent setting. The goals of the advanced care directive may change over time (e.g., the patient becomes a transplant candidate), so this plan can and should be revisited as needed.

Identifying and addressing treatment failures, special considerations in HE and the future of HE are addressed in the Supplemental Online Materials.

Conclusions

Table 4 summarizes the practical tips presented throughout this paper. HE is common and finding it early will most effectively address morbidity and flag a patient at risk for future complications and the need for liver transplant. A thorough evaluation for exacerbating events is important. Most HE can be controlled with medications but there are many barriers in keeping a patient adherent to therapy. While providers await updated society guidelines and new data, multidisciplinary, practical, clinical strategies, like those presented in this publication, can help to improve the screening, diagnosis and management of HE.

The various clinical symptoms of HE range from subtle cognitive changes to coma and present based on HE severity. Symptoms may wax and wane over time, especially in chronic HE, where episodes of cognitive decline are followed by periods of nearly normal cognition. The West Haven criteria, described in the figure, remain the most widely accepted tool for grading the severity of HE based on clinical and neurocognitive signs.[1]

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2025.08.041.

Supplemental Materials

Identifying and addressing HE treatment failures

The high number of hospital readmissions for HE[1-3] is indicative of the frequency and severity of HE recurrence. Patients, caregivers and healthcare systems carry the burden of HE recurrence. Morbidity and mortality statistics intensify, and the financial consequences are grave. This section will examine potential reasons why initial treatments fail and provide clinical pearls for the prevention and management of HE reoccurrence. HE recurrence can be subdivided into three overarching issues: medication issues, lack of coordinated care, and communication and disease-related factors. Suppoementary Table 1[4-5] provides a checklist for the healthcare team to use when recurrence occurs, which will be discussed in detail throughout this section.

Medication issues. The inability to access the necessary medications to both treat and prevent HE and lack of adherence to these medications are two separate and distinct issues that result in the same outcome: HE recurrence. As previously discussed, and covered in the checklist (Supplementary table 1), patients typically experience challenges accessing rifaximin as a result of high out-of-pocket costs, difficulties obtaining prior authorization and lack of insurance coverage, and low tolerance and adherence to lactulose.

Lack of coordinated care and disjointed communication. To prevent rehospitalizations due to HE, the AASLD guidelines encourage planning outpatient post-discharge consultations.[5] These consultations are essential for adjusting treatment and addressing precipitating factors to avoid recurrence of HE episodes. However, this does not always occur due to failure to provide clear patient education in the hospital, lack of patient understanding due to the presence of HE, delayed patient follow-up and lack of coordination of care. When scheduling post-discharge follow up appointments on their own, patients may wait months to be seen by a hepatologist. Assisting the patient with scheduling this appointment as an inpatient can help to expedite this process. In a setting with hepatology support, this would be the gastroenterologist/hepatologist and/or the gastroenterology/hepatology fellow. Advanced practice providers, patient consultants or medical residents can also arrange an outpatient visit to an appropriate office or clinic, with this appointment being available at discharge. In order to address any potentially necessary medication dose adjustments, the goal is to schedule a telephone follow-up 3 to 5 days after hospital discharge and an in-person appointment within 2 weeks after hospital discharge.[4]

As previously discussed, some patients may have unexpected barriers that prohibit them from keeping these appointments (e.g., transportation). Involvement of a social worker may help to overcome these barriers. Video visits/telehealth may help to circumvent transportation challenges. Disjointed communication may result in the patient not being aware that HE medications are available to be picked up at the pharmacy. While patients are still in the hospital, they should be advised about the availability of discharge prescriptions and given any additional information that has been obtained on costs and insurance coverage, as discussed above.

Disease-related factors. Initial management may fail despite access to rifaximin, compliance with lactulose and skilled specialty care. This requires re-evaluation of precipitating factors . In some cases, titrating lactulose in a constipated patient or adjusting nutrition can solve the problem. In other cases, the progression of decompensated liver disease is the cause of HE exacerbations. At this point, clinicians are limited in their treatment options. If patients have not already been referred for liver transplantation (recommended at the time of diagnosis) and provided a palliative care consultation (recommended after the first HE episode), these steps should be initiated at this point. Review of the medication list is imperative, and all sedating medications eliminated. Recurrent HE in advanced disease should also trigger consideration of spontaneous portosystemic shunts that require identification via an abdominal computed tomography scan or magnetic resonance imaging. If a spontaneous portosystemic shunt is found to be present, embolization may be an effective treatment.[6-7]

Special considerations in hepatic encephalopathy

The panel identified and addressed some special considerations that occur in HE, which are summarized in this section.

Alcohol use. The continued use of alcohol in a patient with HE is deleterious in every sense. Alcohol use worsens hepatocellular function and contributes to increased hepatocellular damage. It also increases shunting that may already be present. Therefore, the use of alcohol increases the risk of recurrent HE and leads to hospital readmissions.[4] Alcohol use is a hard “no” in the setting of advanced liver disease. Continued alcohol use by a patient with HE, despite the best advice, may require substance abuse treatment interventions with consideration for initiation of medicines to reduce alcohol use such as acomprasate or naltrexone, if appropriate. Depression is common in those with alcohol use disorder and a recent study found that patients with a history of depression were more likely to experience HE.[8]

Medications that contribute to HE. Data indicates that increasing medication burden results in increased HE-related hospitalizations.[9] In patients with difficult-to-manage HE, a review of concomitant medicines should be performed to assess for appropriateness. These medications may include opioids, benzodiazepines and other sedatives, gabapentin/pregabalin, and proton pump inhibitors. In addition, patients should be counseled on the use of use of cannabis. Although the effects of cannabis in HE remain unclear, patients with labile, difficult to control HE, should

Supplementary Table 1 A healthcare team checklist for HE recurrence [1,41]

Medication Issues

The patient is unable to access lactulose or rifaximin

- Check to see if the patient has insurance:
  - *No*: Ascertain the cash amount and communicate it to the patient
  - *Yes*: Proceed to the next question
- Consult the patient's insurance to see if prior authorization is required:
  - *No*: Ascertain the copay amount and communicate it to the patient
  - *Yes*:
    - Begin this process upon hospital admission
    - Prepare a letter of medical necessity for a potential appeal
    - If these attempts are unsuccessful, refer the patient to the manufacturer for assistance
    - Provide the inpatient with a small supply of rifaximin to bridge the gap between discharge and the follow-up appointment

The patient is not compliant with lactulose

- Add an osmotic laxative if bloating is an issue (eg, polyethylene glycol)
- Educate patients and caregivers on:
  - Why these medications are being prescribed (use layman's terms such as, "They are used to keep your brain clear.")
  - The AEs associated with lactulose
  - Titration methods for lactulose; provide a visual aid similar to the one provided in Table 3
  - Arrange office follow-up or have RN check on the patient after education (frequent touch points)

Lack of Coordinated Care and Communication

Provide the inpatient with the following:

- Arrange a post-discharge telephone follow-up 3—5 days after discharge
- Verify that patients receive a follow-up appointment 2 weeks after discharge
- Access to a social worker, as needed, if there are barriers to keeping appointments (eg, transportation)
- Inform patients that outpatient prescriptions are ready to be picked up

Disease-Related Factors

- Identify and manage possible precipitating factors, which include:
  - Infections
  - Electrolyte abnormalities
  - GI bleeding
  - Constipation
  - Renal failure
  - Dehydration
  - Diet
  - Medications, especially sedatives and pain medications (prescription, over-the-counter and/or illicit drugs)
- Consider advanced decompensated disease
  - Confirm possible portosystemic shunts with abdominal CT scan and consider treatment with embolization
  - If this has not been done when the patient was diagnosed (as recommended), refer for liver transplant evaluation and palliative care consultation

AEs = adverse events; CT = computed tomography; GI = gastrointestinal.

be counseled to discontinue their use of cannabis, along with other substances associated with abuse.

Loss of autonomy and associated consequences. Patients with HE report that they experience "multiple losses," which are not limited to the loss of physical abilities alone (eg, memory, physical and communicative), but include the loss of autonomy as well.[10] For example, if a patient cannot drive, operate dangerous machinery, or make complex decisions, then they typically cannot work. Loss of employment and associated financial implications are significant issues. Although these feelings of loss should be respected, healthcare providers also need to provide appropriate advice, especially when the safety of the patient and others may be compromised. The goal is to balance autonomy and independence with safety.[11]

The ability to drive a motor vehicle needs to be considered in patients with HE. Advice on this topic is an individual decision between the patient, caregiver, and healthcare professional regarding the risks associated with driving, including impaired reaction time and unpredictability of OHE episode occurrence. Patients are often in denial about their driving ability, so it is important to ask pointed questions (eg, "Do you experience difficulties finding your way to the store?") and remind them that they could endanger not only themselves but others. Family members and other caregivers should be advised to closely monitor the patient regarding driving abilities. Patients with asterixis or repeated bouts of HE should be advised not to drive. The AASLD emphasizes that "a diagnosis of CHE or OHE does not automatically mean that the affected subject is a dangerous driver." The AASLD recognizes that providers are not

trained to formally evaluate fitness to drive and are not the legal representatives of the patient but does recommend that providers act in the best interests of both the patient and society by following local laws and counseling patients on consequences.[5] Each state has rules and regulations requiring medical providers to report their concerns to their respective Division of Motor Vehicles. Caregivers should be aware of these rules in their jurisdictions.

Firearm safety in HE is a topic that is discussed less frequently than driving, but should be considered in parallel with driving. If firearms are in the home, they should be kept locked away and access to the keys limited to caregivers or family members. Emphasize that this is not about confiscating their guns, but rather about having a conversation before an accident occurs.[11]

Caregivers. Caregivers play an important role in the well-being of an HE patient. Patients should be encouraged to have their caregivers attend every clinic visit and participate in the education provided by the healthcare team. Healthcare professionals rely on caregivers to identify underlying subtle changes that suggest that the person they are caring for is developing early stages of HE or are experiencing recurrence. This education should also include information on the importance of lactulose, the best methods to mitigate the adverse events of lactulose and the importance of medication compliance. These added responsibilities are important, but the burden that this places on caregivers should not be overlooked, as caregivers lose their autonomy as well. The American Liver Foundation has devoted a page to caregivers, providing tips, tools, and resources on this topic (https://liverfoundation.org/resource-center/caregiver-resources/).[12] Directing caregivers to these resources can be an important first step to relieving some of the strain.

Expecting disease-related setbacks. Despite following all the recommendations discussed in this article, patients with HE are likely to experience recurrence. This is part of the natural history of disease and medical management does not mean that HE is always going to be under good control. There are intercurrent cirrhosis complications that occur and contribute to episodes of HE regardless of optimal treatment with rifaximin, lactulose, protein restriction, etc. When a patient has a diagnosis of HE, additional education needs to be provided to emphasize the waxing and waning nature of the disease. Although healthcare professionals can intervene and make necessary treatment changes, patients will still have hospitalizations and other setbacks. Certain situations, however, can increase those risks, such as lack of medication compliance.

The Future of HE

Further research and development in this field can only improve risk reduction and prevention and management strategies. Newer HE diagnosis and treatment guidelines are available in Europe[13] and currently in the process of being updated in the United States. Artificial intelligence will eventually be important in identifying patients at risk of HE. Such applications, which track visual signals or speech patterns that are linked to HE, are being researched that. Plant-based diets are linked to a lower risk of the development of HE and sarcopenia,[14] and the role of this approach requires further investigation. Fecal microbial transplants have demonstrated safety, tolerability and efficacy at preventing HE recurrence in a phase 2 study, [15] and large phase 3 trials are warranted.

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