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Review Article

Reducing the Risk of Overt Hepatic Encephalopathy Recurrence: A Narrative Review

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Abstract

Hepatic encephalopathy (HE) is a neurologic complication of advanced liver disease (e.g., cirrhosis) resulting in impaired functioning and reduced quality of life. This condition is associated with a substantial burden for patients and their caregivers and carries a poor prognosis and increased risk of hospitalization and mortality. This narrative review discusses the burden of HE, precipitating risk factors, and clinical considerations for reducing the risk of overt HE (OHE) recurrence in adults with cirrhosis. Key precipitating factors include certain medications, constipation, dehydration, uncontrolled diabetes mellitus, electrolyte imbalances, gastrointestinal bleeding, infection, and sarcopenia, among others. Identification and treatment of precipitating factors are critical steps in the management of HE. Components of ongoing care include patient and caregiver education, nutritional supplementation and sleep management, pharmacotherapy, and nonpharmacologic interventions (e.g., spontaneous portosystemic shunt embolization and liver transplantation in appropriate patients). Clinical guidelines recommend lactulose therapy as secondary prophylaxis after an initial episode of OHE. Rifaximin is recommended as add-on therapy to lactulose when an additional OHE episode occurs. Polyethylene glycol has been investigated as an alternative to lactulose in patients with acute HE and in those with chronic HE and a poor response to lactulose. Oral L-ornithine-L-aspartate may reduce the risk of OHE recurrence in patients with cirrhosis. Investigational agents include nitazoxanide, fecal microbiota transplantation, and the use of artificial intelligence, app-based technology, and wearable devices to facilitate acute and prophylactic management of HE.

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Introduction

Hepatic encephalopathy (HE) is a neurologic complication of chronic liver disease and/or portosystemic shunting[1–3] with a prevalence of approximately one in five adults with cirrhosis (2020 US data).[4] In the United States, projections indicate that in 2030, the prevalence of HE among adults with cirrhosis will be approximately 697,000.[4] Clinical practice guidelines recommend classifying HE based on the underlying liver disease, symptom severity, and time course.[1,3] HE is categorized as type A if caused by acute liver failure, type B if caused by portosystemic shunting without significant liver disease, or type C if caused by cirrhosis with or without portosystemic shunting.[1,3] West Haven (WH) criteria are used to classify HE as covert or overt based on symptoms and associated intensity.[2,3] Covert HE (WH minimal or grade I) is defined by subtle neurocognitive abnormalities that may not be apparent during routine clinical examination but are detectable with neurophysiological and/or neuropsychological testing.[1,3] In contrast, overt HE (OHE; WH grades II–IV) is characterized by clinically apparent neurocognitive, motor, and psychiatric alterations, such as lethargy, apathy, temporal disorientation, personality changes or unusual or inappropriate behaviors, altered sleep–wake cycle, confusion, asterixis (hepatic tremor), and, in the most severe cases, coma.[3] The course of HE can be characterized as episodic, recurrent (≥2 episodes within six months), or persistent (lack of return to baseline neuropsychiatric performance).[1,3]

Diagnosis of HE is based on clinical signs and symptoms in the presence of severe liver insufficiency and/or portosystemic shunting in patients without an identified alternative cause of neurocognitive dysfunction.[3] A broad range of conditions should be considered in the differential diagnosis of HE, including mild cognitive impairment, dementia, cerebrovascular events (e.g., stroke), obstructive sleep apnea, electrolyte imbalances, infection, and alcohol use or withdrawal.[1,3,5,6] The differential diagnosis of HE is complicated by shared risk factors for HE and other conditions that may present with similar clinical features (e.g., older age and cirrhosis as shared risk factors for dementia and HE) and HE occurrence in the setting of pre-existing neurocognitive dysfunction (e.g., dementia).[1,6] For further guidance on the differential diagnosis of HE, the reader is referred to the European Association for the Study of the Liver (EASL)[1] and the American Association for the Study of the Liver Diseases (AASLD)/EASL guidelines[3] and reviews on this topic.[5,6]

HE is associated with considerable impairment in qual-

ity of life (QOL), including potentially irreversible cognitive dysfunction, as well as an economic burden for patients and caregivers, poor prognosis, and an increased risk of hospitalization and mortality.[3,4,7–12] The stigma associated with HE can further exacerbate the challenges faced by patients and their caregivers.[11,12] Thus, reduction in the risk of HE recurrence is paramount. This narrative review discusses the burden of HE, precipitating risk factors, and key clinical considerations for reducing the risk of OHE recurrence in adults with cirrhosis.

For this narrative review, a PubMed and Google Scholar search of English-language articles published between January 1, 2009, and January 20, 2026, was conducted. Search terms included "hepatic encephalopathy," "recurrent," "cirrhosis," "sarcopenia," "epidemiology," "quality of life," "health care resource utilization," "barriers," "burden," "risk factors," "prevention," "prophylaxis," and "treatment."

Burden of HE

HE can have a profound negative impact on the QOL of patients and their caregivers, largely related to its negative effects on the patient's ability to carry out daily activities, such as driving and adequate work performance.[13] Functional impairments related to HE result in a loss of independence, feelings of anxiety and frustration, and detrimental changes in relationships, including social isolation.[11] Alterations in sleep patterns and reduced mobility, including an increased risk of falls, also contribute to the functional and QOL burden of HE.[13,14] Multiple prospective studies have demonstrated a negative impact on QOL measures in patients with HE versus those without.[14] A systematic review identified HE as the only decompensating event consistently associated with poor health-related QOL, and this relationship persisted after controlling for severity of liver disease.[15] Among 24 studies (n = 4,510) that evaluated the relationship between OHE and health-related QOL, 18 (75%) supported that a history of OHE was associated with poor health-related QOL.[15] The adverse impact of HE on caregivers was highlighted in a study (n = 106) that showed a history of HE was a significant predictor of psychosocial burden in caregivers.[16]

The economic impact and loss of independence resulting from cognitive impairment and reduced functional capacity can also contribute to the burden of disease in both patients and their caregivers. In a study of 104 patients with cirrhosis (46 with a history of HE) and their informal caregivers, 13% of patients with a history of HE were employed versus 81% of those without a history of HE ($P = 0.001$).[7] Further, patients with a history of HE were significantly more likely than those without a history of HE to report having to decrease their work schedule (71% vs. 39%, $P = 0.02$) and being worse off regarding their job (74% vs. 47%, $P < 0.01$) and their financial status (85% vs. 61%, $P = 0.02$). In the overall cirrhosis population (including those with and without a history of HE), financial difficulties affected treatment adherence as well as daily activities, such as being able to afford basic necessities (e.g., food and housing). Beck Depression Inventory and Beck Anxiety Inventory scores indicated mild to severe depression and anxiety in 28% and 39% of caregivers, respectively, and were correlated with Perceived Caregiver Burden scores. The burden was significantly higher in caregivers of patients with a history of HE versus those without (Zarit Burden Interview, 19 vs. 12; $P = 0.005$; Perceived Caregiver Burden, 85 vs. 68; $P = 0.008$).

Recurrence of HE episodes may result in persistent cognitive impairment, with a potential for residual deficits, even after perceived clinical resolution of symptoms. In a German study of 50 patients with cirrhosis and a history of ≥1 episode of OHE, the severity of cognitive impairment increased with the number of previous OHE episodes.[17] Impairment ranged from effects on executive function following an initial episode of OHE to deficits with repeated episodes across additional cognitive domains, such as psychomotor speed and divided attention. While the mechanisms underlying the residual cognitive dysfunction are unclear, it has been suggested that repeated episodes of HE may lead to potentially irreversible neurologic damage. Additionally, patients with a history of multiple OHE episodes may experience a loss of "cognitive reserve," thereby increasing patient vulnerability to cognitive and behavioral decline with subsequent changes in brain homeostasis. Lower levels of cognitive reserve have been associated with greater impairment in QOL in patients with covert HE, including after controlling for liver disease severity.[18] Together, the cognitive impairment and loss of cognitive reserve associated with recurrent episodes of HE may further compromise and contribute to decrements in QOL and a patient's ability to independently function.

Hospitalization and subsequent readmission of patients with HE are common and are associated with substantial mortality.[4,19–22] A German registry study of 78 individuals previously hospitalized for OHE (≤3 months) reported that 43.6% were rehospitalized for OHE during one year of follow-up.[9] In an Italian retrospective analysis that included 544 patients with a previous HE-related hospitalization, rates of mortality, all-cause hospitalization, and HE-related rehospitalization were 52.8%, 59.0%, and 31.2%, respectively.[20] The one-year mortality rate was significantly higher in patients with hospital readmission(s) versus those without (57% vs. 47%; $P < 0.001$).

Among patients hospitalized with complications of cirrhosis, development of HE is a key contributor to hospital readmission. Of 2,420 patients with cirrhosis in a North American cohort who were discharged without liver transplantation, readmission occurred in 41% during a 90-day follow-up period, with HE being the leading cause.[21] Likewise, a retrospective analysis of the 2014 Nationwide Readmission Database reported that 14,910 (25%) of 58,954 patients admitted to a US hospital (January to September 2014) with cirrhosis-related complications were readmitted within 90 days of discharge, with HE as the primary cause for 47% of the readmissions.[23] In a retrospective study of 402 individuals previously hospitalized in the United States for cirrhosis-related complications including HE, 37% of patients were readmitted within one month of initial discharge, and those with more frequent readmissions had a higher risk of mortality (hazard ratio [HR] = 1.08 per unit increase in hospitalization rate; $P < 0.001$).[22] Notably, HE and fluid imbalance were identified as the most common causes of possibly preventable hospital readmissions.

An international study in patients with cirrhosis admitted for acute decompensation followed 460 patients with a diagnosis of HE at study start and 888 patients without HE for one year.[8] Compared with patients without HE, those with HE had significantly higher rates of all-cause hospitalization (54% vs. 42%, $P < 0.001$) and HE-related hospitalizations (29% vs. 7%, $P < 0.001$) during the three months before study entry. Mortality during the one-year follow-up period was higher in patients with HE versus without HE and increased significantly when patients were subgrouped by HE severity ($P < 0.001$ across groups; no HE vs. WH grade I–II HE vs. WH grade III–IV HE).

Hospitalization because of HE imposes a considerable socioeconomic cost. According to a database analysis of com-

mercially insured US individuals with evidence of cirrhosis and HE, the cost per OHE hospitalization was $77,699 (2020 USD).[4] Based on an analysis of data from the 2010 to 2014 National Inpatient Sample, total annual inpatient charges associated with HE exceed $11 billion USD.[24]

Pathophysiology of HE

An understanding of the pathophysiology of OHE provides a framework for the rationale underlying various management strategies (Fig. 1).[25–32] OHE represents a complex neuropsychiatric syndrome arising from the convergence of multiple pathophysiologic mechanisms in patients with liver dysfunction. Such mechanisms may involve gut microbiome dysbiosis, hyperammonemia, systemic inflammation, oxidative stress, altered neurotransmission, elevated blood manganese levels, zinc deficiency, and increased levels of circulating bile acids and lactate.[26,33–36] In HE, the liver is unable to effectively remove toxins (e.g., ammonia, manganese, mercaptans, short-chain fatty acids, phenols, aromatic amino acids, neuroactive steroids) from the blood.[37–39] In addition, for patients with clinically significant portal hypertension, extensive portosystemic shunting redirects toxins into systemic circulation.[40] Consequently, toxins accumulate and cross the blood–brain barrier, leading to increased oxidative stress, neuroinflammation, astrocyte dysfunction, neurotransmitter imbalances, neuronal dysfunction, and cell death.[26,34–36] Additionally, deposition of manganese into the basal ganglia of the brain contributes to motor symptoms,[33,35] while zinc deficiency further compromises urea cycle enzymes and can damage the intestinal barrier.[26,34,35]

The ammonia burden is a key factor in the pathophysiology of HE.[26,34] Under normal conditions, the liver converts ammonia into urea via the urea cycle.[34] In cirrhosis, ammonia detoxification is impaired because of hepatocellular damage and portosystemic shunting, resulting in accumulation of ammonia-rich blood in the systemic circulation.[26,34] Blood ammonia readily crosses the blood–brain barrier and preferentially enters astrocytes, which attempt to compensate by converting ammonia to glutamine via glutamine synthetase.[34] Accumulation of glutamine leads to osmotic stress, causing astrocyte swelling and dysfunction and contributing to altered neurotransmission.[26,34] Additionally, ammonia triggers oxidative stress within astrocytes, further compromising their supportive functions for neurons.[34] Liver disease can negatively impact the gut microbiome, leading to dysbiosis, disruption of the intestinal barrier, and gastrointestinal (GI) and systemic inflammation.[26,34,36] Key contributing factors to dysbiosis include disease-related alterations in bile acid levels, changes in the gut acid–base balance, and compromised GI barrier integrity.[26] The gut microbiome undergoes substantial alterations in cirrhosis, characterized by reduced levels of beneficial bacteria and overgrowth of potentially pathogenic organisms.[25,34,36] Subsequent increases in levels of urease-producing bacteria result in amplified intestinal ammonia production.[34,36] In addition to increased ammonia levels, endotoxins (e.g., lipopolysaccharides) produced during dysbiosis can translocate across a disrupted intestinal barrier into the portal and systemic circulation, triggering inflammation.[36]

Systemic inflammation in cirrhosis can result not only from endotoxin exposure but also from other inciting events (e.g., infection, direct hepatocellular injury).[34] Proinflammatory cytokines enhance the neurotoxicity of ammonia through multiple mechanisms.[27,34,35] Systemically circulating cytokines can stimulate endothelial cells in the brain, leading to subsequent activation of astrocytes and microglia.[27] These activated cells, in turn, produce inflammatory mediators that exacerbate neuroinflammation and alter neurotransmitter signaling. Systemic inflammation also increases blood–brain barrier permeability, facilitating entry of additional inflammatory mediators into the brain.[27,35] Activated astrocytes and microglia further disrupt the blood–brain barrier, creating a positive feedback loop of inflammation, oxidative stress, and neuronal dysfunction.[27,34,35]

Sarcopenia can be considered a metabolic liability and is independently associated with the development of OHE.[41] Skeletal muscle serves as an alternative site for ammonia detoxification via glutamine synthetase activity.[26,34] In patients with sarcopenia, muscle protein catabolism releases amino acids that are deaminated to ammonia, while loss of muscle mass reduces the body's ammonia clearance capacity.[26] Accordingly, lower muscle mass has been shown to correlate with higher systemic ammonia levels in patients with cirrhosis.[41]

Precipitating and associated risk factors

Precipitating factors for HE include use of certain medications (e.g., nonselective beta-adrenergic receptor antagonists, sedatives, statins, and opioid analgesics) and symptoms such as constipation, dehydration, uncontrolled diabetes mellitus, electrolyte imbalances, GI bleeding, infection, and sarcopenia.[1,21,42–49] The presence of multiple precipitating factors was associated with an increased risk of mortality in a French retrospective study of 179 hospitalized patients with OHE.[50] Among the 77 patients who did not undergo liver transplantation and were discharged on secondary prophylaxis with lactulose or rifaximin, metabolic dysfunction–associated steatotic liver disease and Model for End-Stage Liver Disease (MELD) scores at admission were independently associated with an increased risk of HE recurrence.

Transjugular intrahepatic portosystemic shunt (TIPS) implantation is an effective treatment for complications of portal hypertension and is indicated both to prevent variceal rebleeding and as first-line treatment for refractory ascites.[51] In patients with cirrhosis and portal hypertension, TIPS has been shown to prevent further decompensation and improve overall survival.[52] However, 30% to 60% of patients develop HE following TIPS implantation.[53–57] Older age, higher MELD score, baseline ammonia and albumin levels, previous HE episodes, history of cardiac disease, sarcopenia, renal impairment, diabetes, proton pump inhibitor use, and stent diameter >10 mm have been associated with an increased risk of HE after TIPS implantation.[53,55,56,58–60] Recurrence of HE has been observed in patients with HE before TIPS implantation,[61] and 3% to 20% of patients may develop recurrent or persistent HE following TIPS implantation.[53,62]

Nonadherence to treatment is common among patients with HE and strongly associated with HE recurrence[63] and rehospitalization.[64] In an Italian study that included 544 patients with a previous HE-related hospitalization, the estimated probability of discontinuing rifaximin therapy during a one-year follow-up period was 38% at 90 days, 59% at 180 days, and 65% at one year.[20] Similarly, a prospective US study designed to investigate factors contributing to nonadherence in patients with cirrhosis taking lactulose as secondary prophylaxis for HE noted that only 35% of individuals were adherent to treatment.[65] In a retrospective US study of 137 patients prescribed lactulose after their first HE episode, 39 of 103 HE recurrences were related to treatment nonadherence.[63] All patients who were nonadherent to lactulose therapy developed recurrent HE, compared with 64% of patients who were adherent ($P < 0.0001$); nonadherence to

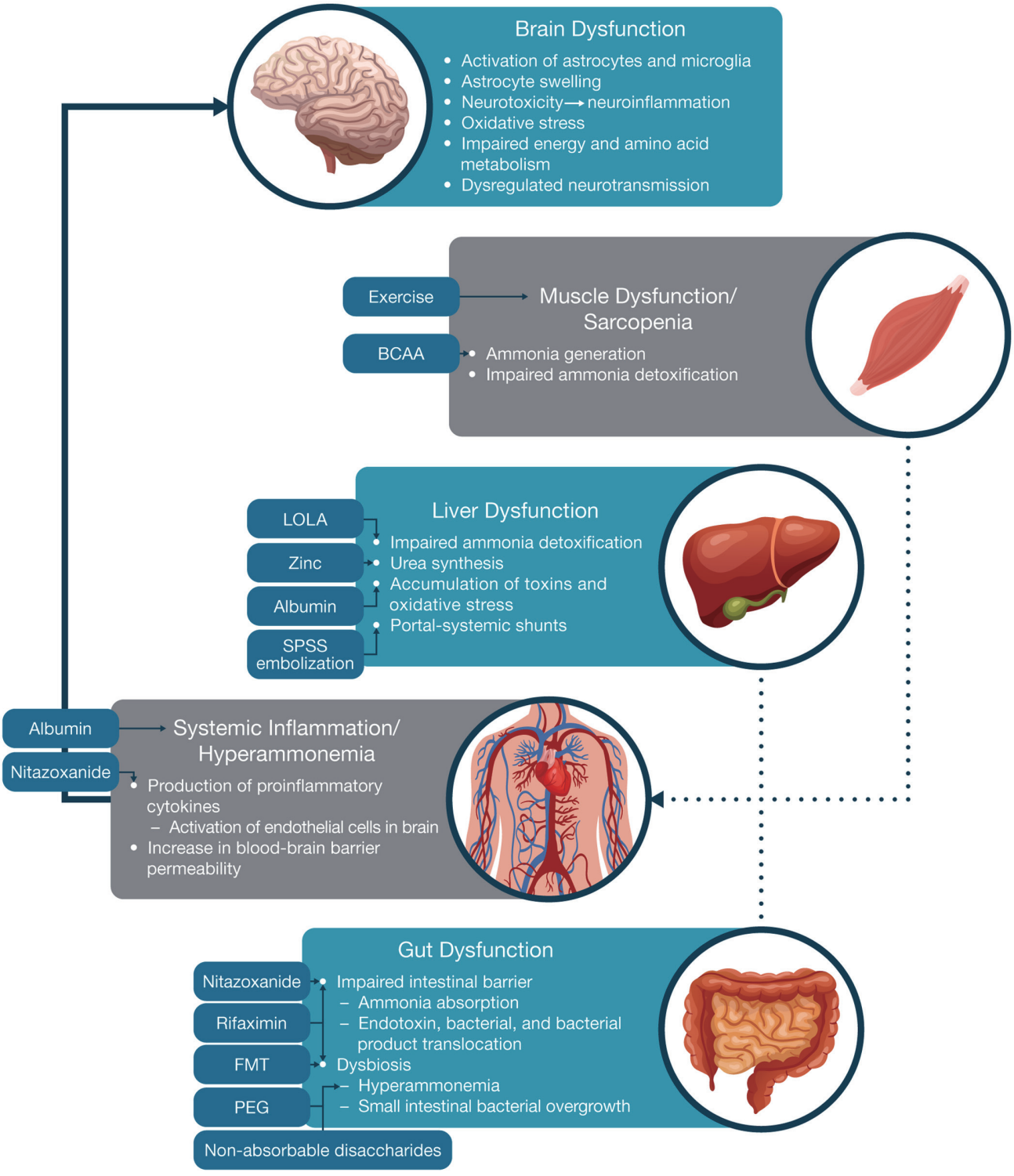

Fig. 1. Pathophysiology of HE and therapeutic targets.[25–32] BCAA, branched-chain amino acid; FMT, fecal microbiota transplantation; HE, hepatic encephalopathy; LOLA, L-ornithine-L-aspartate; PEG, polyethylene glycol; SPSS, spontaneous portosystemic shunt.

lactulose therapy increased the odds of HE recurrence 3.3-fold (95% confidence interval [CI]: 1.2–8.4).[63] Barriers to lactulose adherence include its unpleasant taste, ongoing dose titration requirements, and GI-related adverse effects (e.g., bloating, diarrhea, nausea, vomiting), which may subsequently precipitate HE recurrence due to risk of dehydration, hyponatremia, hypokalemia, and hypomagnesemia related to diarrhea.[65–68]

Table 1. Guideline-recommended treatments for reducing the risk of HE recurrence*[1,3,44,68,70,72–86]

Treatment	Mechanism/target	Key treatment considerations
Lactulose	Reduces ammonia production and absorption in the GI tract	Oral dose of 20 to 30 g, 3 to 4 times daily, titrated to achieve 2 to 3 bowel movements daily; Inadequate dose titration can lead to adverse effects and symptoms of overuse, which impact treatment adherence and, in some cases, can precipitate HE
Liver transplantation	Curative treatment for end-stage liver disease	Several preoperative and post-operative factors can complicate cognitive rehabilitation in patients with HE
Nutritional supplementation (e.g., zinc, BCAAs)	Supportive for malnutrition and/or vitamin deficiencies	Nutritional counseling from a multidisciplinary team can improve patient outcomes compared with nutritional supplementation alone
Rifaximin	Nonsystemic antibiotic that supports eubiosis and reduces GI-derived neurotoxins (e.g., ammonia) and promotes intestinal barrier repair	Indicated for reducing the risk of HE recurrence in adults; Administered as an oral dose of 550 mg BID; Recommended as an adjunct to lactulose as secondary prophylaxis after a breakthrough HE episode
SPSS embolization	Treats SPSS, a risk factor for HE	Recommended in patients with cirrhosis, recurrent or persistent HE, and MELD score < 11
TIPS reduction	May reduce HE risk by normalizing portal pressure	Can be considered in patients with recurrent or persistent HE refractory to pharmacologic therapy; May result in recurrence of portal hypertension complications

*Albumin dialysis and L-ornithine-L-aspartate may be considered for acute management but are not recommended by guidelines for reducing the risk of HE recurrence. BCAA, branched-chain amino acid; GI, gastrointestinal; HE, hepatic encephalopathy; MELD, Model for End-Stage Liver Disease; SPSS, spontaneous portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt.

Reducing the risk and management of HE recurrence

Identification and treatment of precipitating factors are key components in the treatment of HE.[1,3,69] Management of other decompensating cirrhosis-related complications (e.g., acute variceal bleeding) and efforts to delay further liver disease progression (e.g., alcohol cessation in patients with alcohol-related cirrhosis) are also paramount to improving prognosis in patients with HE.[1] In addition, a long-term management plan is important, and several evidence-based therapies are available for reducing the risk of HE recurrence (Table 1).[1,3,44,68,70–86] The AASLD quality measures for improving care include ensuring that hospitalized patients with cirrhosis are discharged on an appropriate therapy to reduce the risk of an additional HE episode(s).[82,87] However, in a North American study of 2,810 patients with cirrhosis, 790 (28.1%) were discharged without HE prophylaxis; this included 99 of 1,708 patients (5.8%) who were on HE therapy on admission (i.e., therapy not resumed post-hospitalization) and 691 of 1,102 patients (62.7%) who were not on HE therapy on admission (i.e., therapy not initiated post-hospitalization).[21]

A randomized prospective trial in Italy of 39 patients with cirrhosis determined that a 15-min educational intervention (i.e., describing HE pathophysiology and the names and mechanisms of action of HE pharmacotherapies and providing guidance for ensuring regular bowel movements during therapy) reduced the risk of HE-related hospitalizations during a 12-month follow-up period (HR = 0.14; 95% CI: 0.02–0.77; P = 0.02).[88] Treatment adherence may be improved via patient and caregiver education on the role and proper dosing of medication, strategies for medication reminders, and understanding and addressing potential adverse events (AEs).[69,89] As well, education should include early signs of HE recurrence and actions that should be taken upon symptom recurrence.[3]

Covert HE is recognized as a precursor and a significant risk factor for developing OHE.[1,3,90–92] Clinical guidelines recommend psychometric/neuropsychological testing to screen for covert HE, especially in patients with impaired QOL.[1,3] Testing may identify patients at increased risk of recurrent OHE,[3] although it should be noted that, in patients with a history of OHE episodes, the severity of liver dysfunction and/or portosystemic shunting is a more reliable predictor of subsequent OHE episodes.[1] The development of digital tools to detect covert HE may facilitate screening.[92,93] While the current AASLD/EASL practice guideline (2014), which is currently being updated by AASLD, does not specifically address treatment(s) for covert HE,[3] the 2022 EASL guidelines recommend that patients with covert HE be treated with non-absorbable disaccharides (e.g., lactulose).[1]

Identification and management of sarcopenia, a key precipitating factor for OHE,[94] is important to reduce the risk of recurrence. A range of standardized assessments for sarcopenia (e.g., anthropometry, bioelectrical impedance analysis, ultrasound, magnetic resonance imaging, computed tomography [considered the gold standard], and dual-energy x-ray absorptiometry) have been employed to evaluate muscle mass in patients with cirrhosis.[29,95] In addition to nutritional management, strategies to address malnutrition, frailty, and sarcopenia in patients with cirrhosis include liver disease–targeted approaches (e.g., management of disease etiology), physical activity/exercise, and addressing environmental/behavioral factors and other system-related factors, such as systemic inflammation and metabolic dysregulation.[29] For further information on the pathophysiology, assessment, and management of cirrhosis-related sarcopenia, please see the 2021 AASLD practice guideline.[29]

Nutritional supplementation and sleep management

A daily caloric intake of 35 to 40 kcal/kg of ideal body weight and a daily protein intake of 1.2 to 1.5 g/kg of ideal body weight are recommended.[73] For patients with cirrhosis and HE who require nutritional supplementation, diet enrichment with vegetarian protein sources should be considered.[78] Protein intake should not be restricted in patients with cirrhosis, including those with HE.[78] In a retrospective study of 234

patients in Japan with cirrhosis, nutritional counseling significantly improved survival rates versus nutritional supplementation alone (85.0% vs. 66.3%; $P < 0.05$).[77] A retrospective Japanese study of 211 patients with alcohol-associated liver disease reported that patients with ≥2 sessions of nutritional counseling had significantly lower OHE rates (16% vs. 27%) and higher survival rates (46% vs. 25%) at five years compared with patients who had a lower frequency of nutritional counseling.[96] Further, nutritional counseling remained associated with a significantly reduced risk of OHE or mortality, independent of liver function reserve and hepatocellular carcinoma after propensity score matching. Limitations of these studies include the retrospective study design and single-country participation (i.e., Japan). In a double-blind, randomized, controlled trial (RCT) in India, 150 patients with cirrhosis and a recent history of OHE were randomly assigned to receive nutrition therapy (diet providing 30–35 kcal/kg/day and 1.0–1.5 g/kg/day of protein, supplemented with high-protein powder) or no nutrition therapy and were followed for six months.[97] All patients were taking stable doses of lactulose. Nutrition therapy was associated with a lower risk of experiencing an OHE episode (13.3% vs. 48.0% of patients; $P < 0.001$) and an OHE-related hospitalization (10.7% vs. 32.0%; $P < 0.001$), as well as with a significantly longer time to first breakthrough OHE episode ($P < 0.001$) and first OHE-related hospitalization ($P < 0.001$). These findings support the dietary recommendations for nutritional management of patients with cirrhosis and HE.

Vitamin and nutrient deficiencies should be identified and addressed in patients with HE,[1,3] including those with sarcopenia, and nutritional counseling by a multidisciplinary team can support this objective.[72,98] Zinc deficiency has been implicated in the pathogenesis of HE,[99,100] and the 2025 American College of Gastroenterology (ACG) guideline on nutritional intervention in liver disease conditionally recommends that supplementation be considered for any patient with liver disease and hypozincemia/signs of zinc deficiency.[78] A meta-analysis of four randomized, double-blind, placebo-controlled trials (n = 233 patients with HE) concluded that zinc supplementation significantly improved performance on the number connection test versus placebo or no supplementation (standardized mean difference = −0.62; 95% CI: −1.12 to −0.11; $P = 0.02$) but did not reduce the rate of HE recurrence (relative risk [RR] = 0.64; 95% CI: 0.26–1.59; $P = 0.34$).[101] Another meta-analysis (3 studies; 227 patients) showed that zinc supplementation plus lactulose significantly improved the number connection test performance compared with lactulose alone (standardized mean difference = −0.97; 95% CI: −1.75 to −0.19; $P = 0.01$).[74]

The 2025 ACG guideline recommends branched-chain amino acid (BCAA) supplementation, when available, in addition to standard of care, in patients with cirrhosis and HE.[78] A meta-analysis of RCTs in patients with recurrent HE (7 studies; 382 patients) determined that supplementation with oral BCAAs significantly improved HE symptoms compared with placebo or a control diet (RR = 1.71; 95% CI: 1.17–2.51), although no significant benefit on mortality risk was observed.[102] Additionally, another meta-analysis (7 studies; 550 patients with cirrhosis) demonstrated a significant benefit of oral BCAA supplementation for preventing HE (RR = 0.68; 95% CI: 0.50–0.94; $P = 0.019$).[103] In a meta-analysis of interventional or observational studies examining the effect of BCAA supplementation on measures of sarcopenia in individuals with cirrhosis (11 studies; 1,215 participants), skeletal muscle index (2 studies; mean change from baseline = −0.35; 95% CI: −0.63–0.07; $P = 0.015$) and mid-arm muscle circumference (2 studies; mean change from baseline = −1.27; 95% CI: −2.25–0.29; $P = 0.011$) were significantly improved after BCAA supplementation compared with baseline.[104] Given the very low quality of published trials, there is no evidence supporting the use of probiotics compared with lactulose for treating OHE.[1,105]

Sleep disturbances are both a consequence and a pathophysiologic mechanism of HE, and their correction may improve patient QOL.[81] Recommended nonpharmacologic sleep management strategies include sleep hygiene (e.g., regular sleep–wake schedule, morning exposure and evening avoidance of bright light) and mindfulness-based stress reduction therapy.[81,83] In a study of 20 patients with cirrhosis, weekly mindfulness-based stress reduction group therapy sessions were associated with significant improvements in sleep quality and health-related QOL.[82] Pharmacologic sleep aids should be avoided, given impaired drug metabolism by the liver and the potential for sedative drugs to precipitate HE.[44,46,81]

Pharmacotherapy

Guidelines recommend lactulose (titrated to produce 2 to 3 bowel movements daily) as secondary prophylaxis after an initial episode of OHE.[1,3] Lactulose is a nonabsorbable disaccharide that is hypothesized to lower systemic ammonia levels and, indirectly, its production by the gut microbiota.[86] In an open-label RCT in India of 140 patients with cirrhosis who had recovered from an episode of HE within the previous week, recurrence was reported in 19.6% of those treated with lactulose prophylaxis compared with 46.8% of those not treated with lactulose (median follow-up, 14 months; $P = 0.001$).[106] The most frequently reported AEs in patients treated with lactulose were diarrhea (23%), distaste for lactulose (13%), and bloating (10%). Another open-label RCT in India also examining secondary prophylaxis noted that the incidence of HE recurrence during a 12-month follow-up period was significantly reduced following lactulose therapy (n = 68) versus no therapy (n = 68; 26.5% vs. 56.9%, $P = 0.001$).[80] Similarly, the most frequently reported AEs in lactulose-treated patients were diarrhea (26.4%), distaste for lactulose (17.6%), and bloating (16.2%). The open-label nature of these studies and the lack of RCTs evaluating lactulose for secondary prophylaxis of OHE outside of India are major limitations.

Rifaximin is a nonsystemic, GI-targeted antibiotic that modulates the gut microbiota to support eubiosis and reduce the production of GI-derived neurotoxins, including ammonia.[107,108] Twice-daily rifaximin 550 mg is indicated for reducing the risk of OHE recurrence in adults, and guidelines recommend rifaximin as add-on therapy to lactulose prophylaxis when an additional OHE episode occurs (e.g., within six months).[1,3] An industry-sponsored, phase 3, randomized, double-blind, placebo-controlled trial (n = 299) conducted at 70 sites in the United States, Canada, and Russia evaluated the efficacy and safety of rifaximin 550 mg BID in patients with a history of OHE who were in remission.[79] Rifaximin significantly reduced the risk of a breakthrough HE episode by 58% (HR = 0.42; 95% CI: 0.28–0.64; $P < 0.001$) and HE-related hospitalization by 50% (HR = 0.50; 95% CI: 0.29–0.87; $P = 0.01$) during six months of treatment compared with placebo (concomitant lactulose was administered in 91% of patients in each arm).[79] The most frequently reported AEs with rifaximin versus placebo were peripheral edema (15.0% vs. 8.2%), nausea (14.3% vs. 13.2%), dizziness (12.9% vs. 8.2%), fatigue (12.1% vs. 11.3%), and diarrhea (10.7% vs. 13.2%). Two rifaximin-treated patients, with multiple risk factors (e.g., recent hospitalizations involving several courses of antibiotics; proton pump inhibitor use), developed *Clostridioides difficile* colitis; both patients were treated and

fully recovered without rifaximin discontinuation.[79]

An open-label extension of the phase 3 trial demonstrated a continued reduction in the rate of HE-related hospitalizations during ≥24 months of rifaximin treatment.[109] Additionally, a subgroup analysis of individuals who had received placebo during the RCT, then received rifaximin during the open-label extension, identified a 79% reduction in the risk of OHE during six months of rifaximin treatment versus six months of placebo treatment (RR = 0.21; 95% CI: 0.10–0.44; $P < 0.0001$).[110] A 2025 meta-analysis (12 RCTs; n = 1,939) reported a reduced risk of HE recurrence (RR = 0.49; 95% CI: 0.40–0.61; $P < 0.0001$) in patients treated with rifaximin versus other treatments (placebo, nonabsorbable disaccharides, antibiotics, or L-ornithine–L-aspartate).[111]

Findings from a retrospective cohort study conducted at four hospitals in Japan suggest that the age–male–albumin–bilirubin (ALBI)–platelets (aMAP) risk score may predict recurrence in patients receiving rifaximin for secondary prophylaxis of cirrhosis-related OHE.[112] This score consists of age, male sex, ALBI score, and platelet count. Of 145 patients included in the analysis, 52 (35.9%) experienced recurrence of HE (defined as WH grade ≥ I) during a median follow-up period of 26.4 months. Although several baseline measures (ascites severity, ammonia level, MELD score, modified ALBI grade, fibrosis-4 index, and aMAP risk score) were significantly associated with HE recurrence risk in univariate analysis, the baseline aMAP risk score was the only significant independent predictor of HE recurrence in multivariate analysis, with a predictive cutoff value of 70.8 (sensitivity, 0.52; specificity, 0.70). Validation of these findings in a larger, prospective study with a more geographically and ethnically diverse population is needed to support the clinical utility of the aMAP risk score for risk stratification in patients receiving rifaximin for secondary prophylaxis of cirrhosis-related HE.

Rifaximin plus lactulose may also be effective for reducing the risk of HE recurrence after TIPS placement.[61] In 49 patients in Germany with a history of HE prior to TIPS, rifaximin plus lactulose (but not lactulose alone) significantly reduced the risk of HE recurrence at 1 ($P = 0.003$), 3 ($P = 0.003$), and 12 ($P = 0.006$) months after TIPS implantation.[61] At 12 months after TIPS placement, the rate of HE recurrence was 25.0% in those treated with rifaximin plus lactulose versus 64.7% for those treated with lactulose alone or no prophylaxis ($P = 0.007$).[61] Interpretation of this study is limited by its retrospective, open-label, non-randomized nature and small sample size.

Although rifaximin has traditionally been considered to pose a low risk of antimicrobial resistance due in part to its high fecal concentrations and minimal systemic absorption, additional investigations suggest that bacterial antibiotic resistance to certain antibiotics (e.g., daptomycin) could develop after prolonged exposure.[113–116] The clinical implications are unclear and warrant further study. Cost-effectiveness analyses of reducing the risk of OHE recurrence indicate that treatment is cost neutral, with cost savings associated with reductions in healthcare utilization (i.e., hospitalizations and outpatient/emergency department visits) offsetting rifaximin pharmacy costs.[117,118]

Polyethylene glycol (PEG) and L-ornithine–L-aspartate (LOLA) are not specifically recommended for prevention of HE recurrence but have been considered for treatment of an episode. PEG is a laxative that helps eliminate toxins in the GI tract, thus reducing systemic absorption.[26] A meta-analysis (5 RCTs; 288 patients with cirrhosis and HE) reported that PEG was more efficacious than lactulose for improving HE symptoms within 24 hours of administration (RR = 1.46; 95% CI: 1.26–1.68; $P < 0.001$), while the reduction in ammonia levels was similar.[119] Studies have not evaluated PEG as secondary prophylaxis for HE; however, it could be considered an alternative to lactulose in certain situations (e.g., patients with chronic HE and a poor response to lactulose) based on extrapolation from studies in acute HE.[119]

LOLA is a combination of two amino acids that reduce ammonia levels by serving as substrates for the urea cycle and promote glutamine synthesis in hepatocytes and myocytes via activation of glutamine synthetase.[26] The 2014 AASLD/EASL guidelines recommend considering use of intravenous LOLA as an alternative or add-on treatment for patients with HE who are unresponsive to conventional therapy; however, this guidance does not discuss its potential use as secondary prophylaxis.[3] A double-blind RCT in India compared oral LOLA with placebo in 150 patients with cirrhosis and a history of OHE within the previous 12 months.[120] During six months of treatment, patients receiving LOLA were significantly less likely than those in the placebo group to experience OHE recurrence (12.3% vs. 27.8%; HR = 0.39; 95% CI: 0.17–0.87; $P = 0.02$). The time to first HE breakthrough episode was slightly delayed in the LOLA versus the placebo group (170.9 vs. 157.8 days), and the probability of developing OHE was 57% lower among LOLA-treated patients compared with placebo-treated patients ($P = 0.02$). There was no significant difference between groups in the mortality rate ($P = 0.18$). Potential limitations included the relatively short follow-up duration (six months) and single-country participation (i.e., India). Adverse events reported with LOLA versus placebo included dyspepsia (2.7% vs. 0%), bloating (1.3% vs. 5.3%), flatulence (1.3% vs. 4.0%), and itching (0% vs. 4.0%). In the analysis of 49 patients with a history of HE prior to TIPS described previously, the addition of LOLA to rifaximin plus lactulose prophylaxis provided no significant additional benefit related to reduction in HE recurrence risk.[61]

Nonpharmacologic interventional management

The EASL guidelines recommend consideration of albumin dialysis in patients with liver failure and OHE, although its impact on patient prognosis is unclear.[1] In an RCT in the United States of 70 patients with grade 3 or 4 HE, albumin dialysis led to a significantly faster two-grade improvement in HE severity ($P = 0.045$) and a greater percentage of responders (62% vs. 40%; $P = 0.076$) compared with standard therapy (e.g., correction of precipitating factors; treatment with lactulose; treatment with neomycin or metronidazole; and daily zinc sulfate).[75] However, a European RCT of 189 patients with ≥ grade 2 HE demonstrated that albumin dialysis did not significantly improve HE severity or 28- or 90-day transplant-free survival rates compared with standard therapy.[70] Albumin dialysis is not currently considered for secondary prophylaxis.

Spontaneous portosystemic shunt (SPSS) embolization can be considered in patients with recurrent or persistent HE, MELD score < 11, and no known contraindications.[1] A retrospective German study of 301 patients with cirrhosis and SPSS found that those with an SPSS area > 83 mm^2 had a significantly higher risk of HE ($P < 0.01$) and mortality (HR = 1.66; 95% CI: 0.04–2.70; $P = 0.04$) compared with those with SPSS <83 mm^2.[84] In a retrospective European study of 37 patients with refractory, chronic HE and SPSS, 22 patients (59.5%) were free of HE at 100 days post-embolization, and 18 (48.6%) were free of HE during a mean follow-up of 697 days (both $P < 0.001$ vs. preembolization).[28] Additionally, a retrospective study in India of patients with recurrent or persistent HE and large SPSS showed that 75.0% of 20 in-

dividuals were free of HE after three months, 75.0% of 12 were free of HE after six months, and 71.4% of 7 were free of HE after nine months (all $P < 0.05$ vs. preembolization).[121]

In patients who develop HE following TIPS implantation, shunt diameter reduction can be considered.[1,3] Shunt reduction improves HE symptoms in up to 90% of patients with development or worsening of HE post-TIPS without increasing the likelihood of new variceal bleeding, although ascites often partially recurred.[55] A retrospective US study of 33 patients who underwent TIPS reduction identified statistically significant reductions in the rates of HE (91% post-TIPS to 55% after TIPS reduction, $P = 0.002$) and HE-related hospitalization (76% post-TIPS to 33% after TIPS reduction, $P = 0.001$).[122] The North American practice-based recommendations from the Advancing Liver Therapeutic Approaches Consensus Conference suggested that TIPS reduction should only be considered in patients with recurrent (e.g., ≥3 HE episodes requiring hospitalization during a three-month period) or persistent HE refractory to pharmacologic therapy.[85]

Guidelines strongly recommend that patients with recurrent or persistent HE despite adequate treatment be considered for liver transplantation.[1,3] However, post-transplant conditions (e.g., infection during intensive care unit stay, neurotoxicity due to immunosuppressant drugs, lack of social support) combined with pretransplant factors (e.g., severity of HE and underlying liver disease) may contribute to post-transplant cognitive dysfunction and/or impede cognitive rehabilitation after liver transplantation.[76] These challenges should thus be considered during the course of treatment for these patients.

Other approaches

Several modalities are being investigated as potential acute treatments or as prophylaxis for HE. The antiprotozoal agent nitazoxanide, which also has broad-spectrum activity against anaerobic bacteria in addition to anti-inflammatory effects, was evaluated in a double-blind RCT in 60 Egyptian patients with cirrhosis and HE.[30] Nitazoxanide reduced serum ammonia levels to a greater extent than rifaximin after six months of treatment and was associated with a longer time to HE recurrence (136 vs. 67 days with rifaximin; $P = 0.0001$).[30] Fecal microbiota transplantation (FMT) involves transferring stool from healthy donors to patients with gut dysbiosis with the aim of restoring eubiosis.[31] In HE, FMT may reduce ammonia production by shifting GI bacterial populations toward those with lower urease activity and reducing systemic ammonia uptake by restoring GI barrier integrity.[31,123] The EASL guidelines did not recommend FMT as a treatment option for patients with recurrent/persistent HE given the lack of adequately powered, randomized, placebo-controlled trials at the time of publication.[1]

A phase 2, randomized, double-blind, placebo-controlled US trial published in 2025 evaluated FMT in 60 patients with cirrhosis who were receiving treatment with lactulose and rifaximin for a confirmed episode of OHE.[123] Patients were divided into four groups and assigned to receive either 60-mL FMT enema/oral FMT capsules at baseline followed by oral FMT capsules at day 30; placebo enema/FMT capsules at baseline and FMT capsules at day 30; FMT enema/placebo capsules at baseline and placebo capsules at day 30; or placebo enema/placebo capsules at baseline and placebo capsules at day 30 and were followed for six months. Post hoc analysis revealed that, compared with the placebo enema/capsules group, patients receiving FMT (pooled across FMT enema or capsule groups) had lower rates of HE recurrence (9.1% vs. 40.0%; odds ratio = 0.15; 95% CI: 0.04–0.64). Rates of HE recurrence did not differ among treatment groups receiving different forms/doses of FMT, although the study was not powered for comparison between these subgroups. Beneficial changes in gut microbiota were demonstrated in the FMT treatment groups and related to absence of HE recurrence. The most commonly reported AEs among patients receiving any FMT treatment versus placebo were falls (17.8% vs. 13.3%), fractures (11.1% vs. 6.7%), abrasions/wounds (11.1% vs. 0%), abdominal pain (8.9% vs. 13.3%), constipation (8.9% vs. 6.7%), and rashes/blisters (8.9% vs. 0%); none required a change in trial participation. No AEs or serious AEs were considered related to FMT. While these results are promising, results from the post hoc analysis should be considered exploratory, and larger studies in patients with cirrhosis and HE are needed.

Artificial intelligence (AI), app-based technology, and wearable devices may facilitate management and prevention of HE. Wearable devices and home-based technologies can generate data to monitor patient adherence and health in real time, which may potentially allow for early detection of problems and timely intervention to prevent further decompensation.[124–126] For example, caregiver use of a remote data transmission app to monitor medication adherence, sodium intake, cognitive functioning, and fall risk was effective in reducing HE-related readmissions over 30 days.[126] An AI-enabled smartphone application has been used to accurately track bowel movement frequency and stool characteristics to allow self-titration of lactulose therapy for HE.[127] Other applications of AI and wearable technology include collection of biometric data, such as sleep quality, that may help detect, assess, and monitor HE,[128] or potentially facilitate assessment of the effectiveness of nonpharmacologic sleep management strategies and other interventions.

Recognition of barriers to care

Secondary prevention of OHE depends on the sustained efforts of patients and caregivers, underscoring the importance of identifying and addressing barriers to ongoing management and prevention. In two studies (one each in Germany and Sweden), the presence of covert HE was associated with poor health literacy in patients with cirrhosis, although both studies found no significant relationship between health literacy and a history of OHE.[129,130] Poor health literacy may adversely impact patients' understanding of their condition and ability to effectively communicate with healthcare providers and adhere to recommended management, including medication regimens.[129] Thus, assessment of health literacy (e.g., with the Health Literacy Questionnaire)[131] may help identify patients with low health literacy who may require extra support and closer follow-up.

The caregiver burden associated with HE is described above. Considering the risk of caregiver fatigue, there is a need for healthcare workers to be conscious of evaluating caregivers for exhaustion/burnout and psychological conditions, such as anxiety and depression.[7,12] A multidisciplinary treatment paradigm that includes social worker participation may be particularly important when caregiver-related barriers to patient management are present.[132]

Cost barriers and disparities in access to care may limit effective prevention of OHE recurrence. As described above, HE is associated with a substantial economic impact, related in part to employment limitations, and financial difficulty is associated with reduced treatment adherence.[7] The affordability of rifaximin may serve as a barrier to treatment for some patients, and racial/ethnic disparities have been observed. In an analysis of Medicare claims data from a popula-

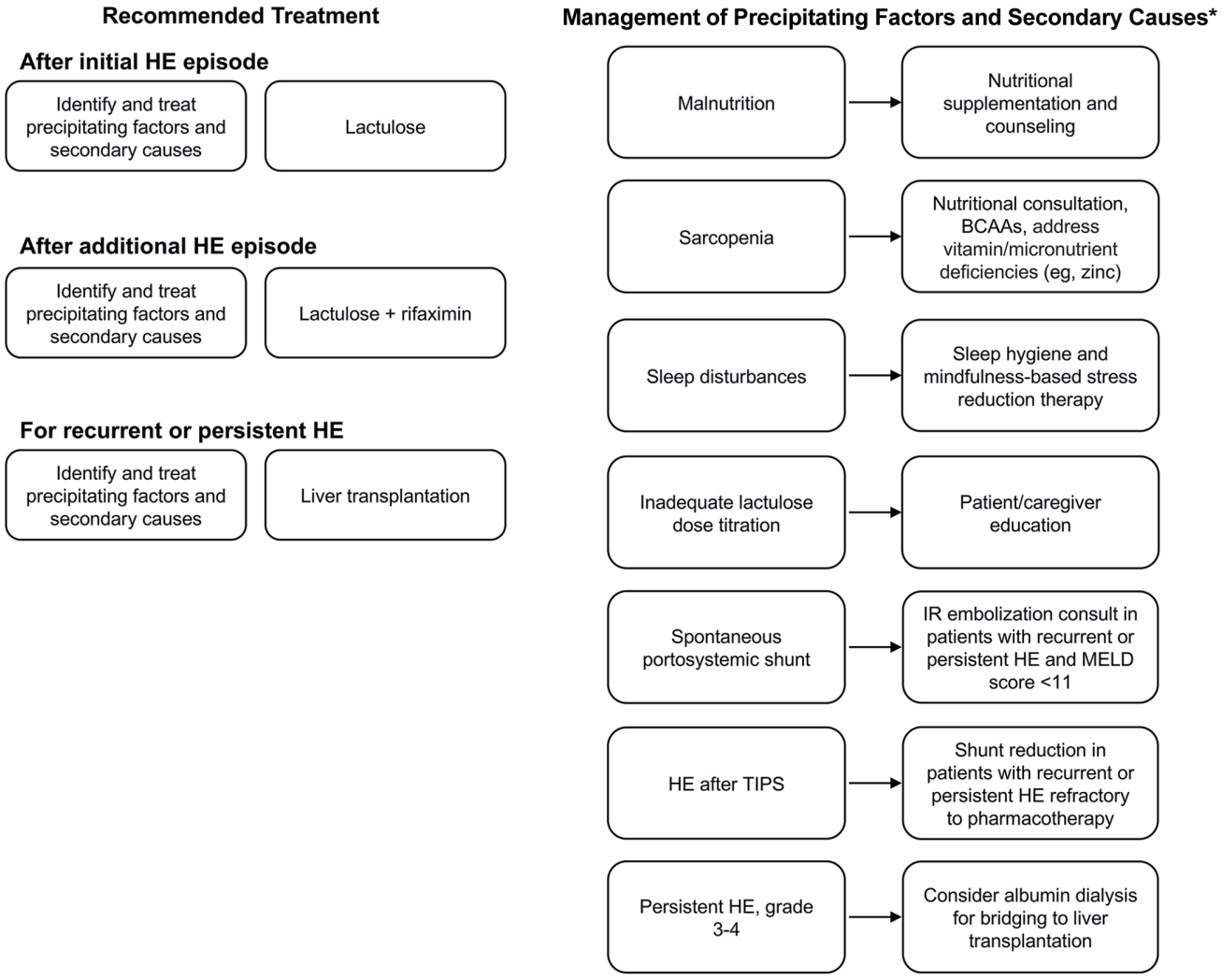

Fig. 2. Proposed algorithm for reducing the risk of overt HE and treating HE recurrence. *Select list of potential precipitating factors and secondary causes of HE. BCAA, branched-chain amino acid; HE, hepatic encephalopathy; IR, interventional radiotherapy; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

tion-based cohort of enrollees with cirrhosis and incident HE (identified via both diagnosis code and lactulose use), Black, Asian, and Hispanic patients were significantly less likely than White patients to receive a rifaximin prescription.[133] Additionally, Black and Hispanic patients were significantly less likely than White patients to receive subspecialty consultation both before and after HE diagnosis, which may have contributed to the lower rifaximin prescribing rates in these minority populations. Insulin-related spending was associated with a reduced likelihood of filling an initial rifaximin prescription among Black patients only, suggesting that spending on essential medications may pose a financial barrier in this population. An analysis of claims data from commercially insured US adults prescribed rifaximin for HE found that 95% of patients experienced ≥1 treatment gap—either an initial delay, interruption, or cessation of treatment—within a one-year period.[134] Prescription claim rejections accounted for 20% of all treatment gaps, including nearly 80% of initiation gaps. These gaps in rifaximin treatment were significantly associated with both an increased risk of OHE hospitalizations and higher total healthcare costs. These results highlight the importance of preventing treatment gaps through interventions such as patient assistance with the insurance authorization process.

Conclusions

A proposed algorithm for reducing the risk of OHE and treating HE recurrence is provided and based on hepatology society guidelines and a review of the literature (Fig. 2). In all situations, correction of known precipitating factors and/or secondary causes and avoidance of sedatives and narcotics are imperative. Lactulose is considered first-line therapy after an initial episode of HE. Lifestyle interventions, including nutritional supplementation and counseling, sleep hygiene, and mindfulness-based stress reduction therapy, may also be beneficial. Rifaximin plus lactulose therapy is recommended when additional HE episode(s) occur. Patients with recurrent or persistent HE should be evaluated for a shunt; SPSS embolization should be considered for those with an SPSS and MELD score < 11. In situations of recurrent or persistent HE refractory to pharmacologic therapy following TIPS implan-

tation, evaluation for shunt reduction may be appropriate. Liver transplantation should be considered for patients with recurrent or persistent HE despite adequate treatment. Albumin dialysis for bridging to liver transplantation may be considered in patients with persistent, grade 3–4 HE. In addition, patient and caregiver education on HE symptoms and treatments, including the importance of long-term adherence, is advised for receptive individuals. Overall, the burden of HE is substantial and includes patient and caregiver QOL impairment and increased risk of patient hospitalization and mortality. Reducing the risk of HE recurrence is imperative given associated morbidity and mortality risks.

Future research priorities include identifying patients most likely to benefit from specific treatment approaches for secondary prevention of OHE. Additionally, primary prevention of OHE in patients with early decompensated cirrhosis remains an unmet need. The development of predictive models for OHE risk in patients with cirrhosis (e.g., the AMMON-OHE model, which incorporates ammonia level, sex, diabetes, albumin, and creatinine)[135,136] may facilitate patient selection in clinical trials of primary prophylaxis and help identify patients with cirrhosis who would benefit from more intensive monitoring and intervention to prevent encephalopathic decompensation. Many studies included herein are limited by study design (e.g., open-label trials), small sample sizes, and geographic clustering (predominantly in the US, India, and Europe). Large, prospective international RCTs will be important to enhance the interpretation and generalizability of future study results.

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Conflict of interest

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Author contributions

Conceptualization and drafting of the manuscript (NTP) and critical review and editing of the manuscript (NTP, NG, PKJ, GEC). All authors have approved the final version and publication of the manuscript.

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