

Minimal Hepatic Encephalopathy



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KEYWORDS

- Encephalopathy • Ammonia • Cirrhosis • Minimal • Covert • Cognitive • Attention • Confusion

KEY POINTS

- Minimal hepatic encephalopathy (MHE) is a frequent complication of cirrhosis characterized by subtle mental dysfunction.
- MHE nonetheless causes diminished quality of life and impairs driving motor vehicles to a variable extent.
- Smartphone applications such as EncephalApp-Stroop test are able to detect attention and cognitive defects associated with MHE.
- Therapy with lactulose can improve the psychometric abnormalities of MHE but the therapy can cause gastrointestinal symptoms such as diarrhea, flatulence, and abdominal discomfort.
- More research is needed to determine when and how MHE should be treated.

INTRODUCTION

Minimal hepatic encephalopathy (MHE) affects a large proportion of patients with cirrhosis, has demonstrated real and important consequences and impact on daily life, including impaired driving performance, increased vehicle accidents and traffic violations, diminished quality of life, unemployment, and propensity to falls, and predicts transition to overt HE, namely, decompensation of the cirrhosis (**Box 1**).

Given the absence of specific signs or symptoms associated with MHE, the study of its natural history has been particularly challenging and remains minimally understood. At present, it is clear that a significant proportion of patients with MHE go on to eventually develop overt hepatic encephalopathy (OHE). Known risk factors for such progression include male gender, prior history of OHE, alcohol etiology of the cirrhosis,

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Box 1**Impact of minimal hepatic encephalopathy^{a,b}**

Impaired ability to drive motor vehicles
 Increased risk of traffic accidents
 Impaired ability to operate machinery
 Impaired performance and fitness to work
 Decreased quality of life (HRQOL)
 Increased risk of falls
 Decreased home management skills
 Difficulties with emotional behavior
 Worse sleep quality

^aNote that not all the above consequences are present in every patient with MHE as its impact can markedly vary in individual patients. ^bFinancial impact of MHE on patient and society has not yet been estimated.

and those with esophagogastric varices. Likely but yet unproven factors affecting the natural history of MHE and progression to OHE include raising model for end stage liver disease (MELD) score, worsening of the underlying liver disease (eg, having a progressive and/or intractable etiology of the underlying cirrhosis such as metabolic-associated fatty liver disease, autoimmune liver disease resistant to current therapies, alcohol-associated cirrhosis with continued alcohol, and drinking), and onset of decompensation. However, more granular information on the natural history of MHE is not available, and several critical questions remain unanswered. Such questions include (1) whether MHE evolves with exacerbations and flares alternating with periods of remission? (2) what are the precipitating factors that temporarily worsen MHE? (3) are there significant interactions of MHE with concomitant neuropsychiatric entities such as depression, bipolar, substance use disorders, or the natural cognitive decline of aging? (4) is there potential modulation of MHE severity and evolution by environmental factors? (5) does MHE lead to irreversible subclinical cognitive deficits? and (6) is liver transplantation able to reverse the psychometric abnormalities of MHE? The answers to these and other equally relevant questions characterizing the natural history of MHE await clinical research that requires following up the MHE diagnostic tools over time while evaluating effect on outcomes by the above factors. Given the uncertainties about the natural history of MHE, it is suggested and seems reasonable to screen for MHE patients with cirrhosis every 6 to 12 months to be able to detect MHE and go over the need (or not) for therapeutic intervention.

The absence of verbal deficits, confusion, disorientation, and asterixis in MHE results in a patient who appears and performs well in the office visit. Thus, the diagnosis of MHE is currently only possible by performing specialized psychometric and neurophysiological testing, not fitted for routine clinical practice. The term “minimal” is misleading because of the effects of MHE on patients are not trivial. MHE is currently considered the earliest form of “covert” HE. Covert HE includes MHE but also stage I HE which may have already clinically detectable but subtle cognitive deficits (yet no asterixis, a marker of stage II overt HE), which may also be difficult to diagnose in a busy hepatology practice. Thus, the diagnosis of MHE still rests primarily on the ability to perform specialized testing, which fortunately has been gradually refined and shortened, getting closer to routine applicability in the office setting. Given the high

frequency of MHE in cirrhosis and its consequences, ideally all patients with cirrhosis should undergo screening tests for MHE. However, this is not yet pragmatic and the current guidelines suggest a focused approach, with MHE testing pursued in patients with cirrhosis who report employment difficulties, nonspecific neurologic symptoms, traffic violations, and motor vehicle accidents. The authors review the most commonly used tests to identify MHE, their performance, and limitation as follows.

ASSESSMENT OF MINIMAL HEPATIC ENCEPHALOPATHY

The compilation of cognitive deficits found in MHE, known as SONIC (spectrum of neurocognitive impairment in cirrhosis), includes changes in attention, working memory, response inhibition, and executive function.¹ Performing specialized neuropsychiatric tests have been the traditional approach to diagnose these subtle cognitive disturbances.^{1,2} However, many of these tests are time-consuming, costly, and cannot realistically be implemented in clinical practice by providers taking care of a complex chronic diseases such as cirrhosis. The role of these tests is primarily for research purposes as the gold standard, and therefore, providers should be familiar with them.³

Patients with MHE are known to have poorer quality of life as well as risk of falls, impaired driving, and potentially danger operating heavy machinery.⁴⁻⁶ For this reason, it is important for a hepatology practice to implement routine diagnostic tools to better identify those patients experiencing MHE. In addition, patients with MHE are at high risk for transitioning to overt HE, considered one of the events that defines decompensation in cirrhosis.⁷ Traditionally thought to be reversible, there is emerging evidence that patients with a history of overt HE have persistent cognitive dysfunction even post-liver transplantation.⁸ As care for chronic liver disease patients shifts toward prevention of first decompensation event (overt HE, variceal bleed, ascites), it has become increasingly important to identify patients who may be at high risk for development of overt encephalopathy.⁹ Patients with cirrhosis and MHE are at risk for developing overt HE over time. Furthermore, there is an increased use of transjugular intrahepatic portosystemic shunt (TIPS) for its transplant-free survival benefit, but additional research is required to determine if pre-TIPS MHE is a risk factor for development of post-TIPS overt HE.¹⁰

Potentially primary prevention of overt HE will soon become standard of care. To do this, we need to understand the diagnostic tools available to diagnose MHE before the onset of overt HE. General intake questions include screening for sleep disturbances, falls, and irritability. These symptoms are more easily reported with recall by patients. Assessing for executive function, psychomotor speed, response inhibition, and working memory deficits require more invasive testing rather than self-assessment (**Box 2**).¹¹

The most recent AASLD practice guidelines regarding diagnosis of MHE, published in 2014, recommend that every patient with chronic liver disease be tested for minimal (or covert) HE.⁷ A consensus by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism reviewed the testing strategies for covert/minimal HE and discouraged the use of more than one test to diagnose minimal/covert HE to prevent excluding patients who may benefit from counseling or treatment.¹² This consensus also suggested that until there is broad validation of tests, diagnostic tools for MHE can be used after initial screening or self-reported symptoms raise concern. The authors agree that all patients with cirrhosis should be screened for MHE due to the MHE consequences outlined above. Furthermore, early diagnosis of MHE is important to improve quality of life and to identify patients who are at risk of developing OHE and decompensated cirrhosis. **Box 3** summarize the strengths and limitations of some of the commonly used tests to diagnoses MHE.

Box 2**Assessment and diagnostic tests for minimal hepatic encephalopathy**

Psychometric Hepatic Encephalopathy Score (PHES):

- Number connection test A and B
- Digital symbol test
- Line tracing test
- Serial dotting test

Inhibitory Control Test (ICT)

Smartphone Applications

- EncephalApp-Stroop Test
- QuickStroop

Animal Naming Tests

- ANT₁
- S-ANT₁

Predictors of Onset of Overt Hepatic Encephalopathy

- BABS
- MASQ: HE

PEN AND PAPER TESTS

The most frequently published test and considered the gold standard for identifying minimal cognitive dysfunction in chronic liver disease is the Psychometric Hepatic Encephalopathy Scores (PHESs), which is a series of five paper and pencil tests and is

Box 3**Strengths and limitations of tests used in the diagnosis of minimal hepatic encephalopathy**

Test	Strengths	Limitations
PHES	Considered gold standard Simple to administer Predicts OHE and survival Validated	Insensitive to early changes Expensive; copyrighted Influenced by age and educational level Learning effect
Inhibitory Control Test	Rapid, less expensive Extensive validation	Requires patient's familiarity with computers Requires high functional level
EEG	Validated for stage I covert HE	Requires specialized equipment; nonspecific
Smart Phone Stroop App Test	Rapid, simple, sensitive Validated, smart phone App	Influenced by age and educational level Training effect
SIP-CHE (Short Version)	High sensitivity, lower specificity Potentially suitable for office/POC use Able to predict onset of OHE Applicable to covert HE	Learning effect on repeat testing Calculators not yet readily available
Animal Naming Test	Rapid (1 minute to complete) Inexpensive, apt for office use Correlated with future OHE Associated also with frailty and disability	Requires further validation in MHE Influenced by age and educational level

Abbreviation: PHESs, Psychometric Hepatic Encephalopathy Scores; POC, point of care.^{2,13}

validated in several countries. PHES includes number connection test A (NCT-A), number connection test B (NCT-B), digit symbol test, line tracing test, and serial dotting test.² This series takes at least 15 minutes to complete and should ideally be administered and interpreted by a trained clinician. Although the PHES is not routinely used in clinical practice, it is important to be familiar with this battery of pen and paper tests as it is often used in publications to study MHE and validate newer diagnostic tools.¹³

Initial Screening for Minimal Hepatic Encephalopathy

Sickness impact profile covert hepatic encephalopathy

The importance of screening and diagnosing patients with MHE is that development of MHE significantly impacts health-related quality of life (HRQOL).¹⁴ The Sickness Impact Profile (SIP) is a 136-statement questionnaire measuring quality of life but difficult to realistically use in hepatology clinical practice due to its length.¹⁴ A proposed shortened version (SIP covert hepatic encephalopathy, SIP CHE) was developed by Nabi and colleagues to be readily integrated into a busy hepatology practice and includes four of the statements from SIP while also considering sex and age.¹⁵ Of note, the patient population studied did not have history of overt encephalopathy and included diverse etiologies of cirrhosis. The SIP covert hepatic encephalopathy (CHE) is not a test of cognition but could identify MHE with a sensitivity and specificity of 80% and 79%, respectively. Of note, the specificity of SIP CHE decreased on repeat testing at 6 and 12 months.¹⁵

$$\text{SIP CHE} = -0.6 + 0.1 \cdot \text{Age} + 0.9 \cdot \text{male gender} + 2.6 \cdot \text{BCM4} + 2.4 \cdot \text{EB7} + 1.9 \cdot \text{RP8} + 1.9 \cdot \text{E1}$$

BCM4: "I do not maintain balance"

EB7: "I act irritable or impatient with myself"

RP8: "I am not doing any of my usual physical recreation or activities"

E1: "I am eating much less than usual"

SIP CHE was then validated in 2020 with a Danish cross-sectional study of 110 outpatients and also used to determine future development of overt HE.¹⁴ The study used continuous reaction time computerized test and PHES as the gold standard for diagnosing MHE and found that SIP CHE had a high sensitivity (82%) but a relatively low specificity at 38%.¹⁴ The patients were then followed for an average of 2.7 years, during which time SIP CHE had an 87% sensitivity for predicting future development of overt HE. Currently, there are no readily accessible calculators to use the SIP CHE score in clinical practice/point of care. Thus, a suggested area of research is to evaluate the compliance and performance of SIP CHE calculator incorporation into current electronic medical record (EMR) systems.

Computerized Tests at the Point of Care

Point of care tests have become the most clinically relevant ways of diagnosing MHE in office.¹¹ The creation of cell phone and tablet applications has also improved availability and makes in-office evaluation and diagnosis more feasible.

Inhibitory control test

The inhibitory control test (ICT) is a computer-based test that takes 15 minutes to administer to assess attention and response inhibition.^{16,17} This is a computer-based test where the patient is exposed to flashing letters. Participants are instructed to press the spacebar after seeing the "target" which is when the letter Y follows the letter X or vice-versa. There are times where an X follows an X and Y follows a Y, called

“lures.” The software measures the response and reaction time for both targets and lures. High lure and low target response indicates poorer score and, in the appropriate setting (cirrhosis), MHE.

The ICT was validated in the United States by Bajaj and colleagues using a cutoff of ≥ 5 lures per person to diagnose MHE with a sensitivity of 88% and a specificity of 77%.¹⁶ A battery of pen and pencil tests and block design test (BDT) was used as the gold standard to diagnose MHE in this cohort. The ICT test does not require trained psychologist or personnel to administer but requires the computer program to be downloaded. In addition, ICT requires patients to be comfortable with computer-based tests and takes longer to administer than other point of care tests discussed above.¹⁸

The smartphone application EncephalApp-Stroop test

The Stroop test is often used in attention-deficit disorders and cognitive impairment to assess psychomotor speed, attention, and impulse inhibition (executive function).¹⁹ Impaired attention and cognitive functions are the hallmark abnormalities found in MHE. These deficits can be detected via assessment of response to auditory trigger events or Stroop-based tasks.²⁰ A free smart phone and tablet version (EncephalApp-Stroop) was developed making this a nearly ideal point of care tool to use in the assessment of MHE.^{21,22}

The EncephalApp-Stroop test also does not need a trained clinician to interpret the results and can be completed before clinic visits or at home in less than 5 minutes. There are five runs in the “Off state” followed by five runs in the “On state.” In the “Off state,” the Stroop test requires patients to focus on visually presented stimulus (hashtag) to determine its color and then respond with a timed motor action (clicking the correct color). The second part of the Stroop test, “On state,” requires attention on the words red, blue, and green which are presented in incongruent colors. For example, the word “red” will be written in a green color. Patients must correctly identify the color of the letters and not the color of the letters that is spelled. The total time in seconds to complete five series correctly is recorded.

The US-based multicenter study by Allampati and colleagues validated the EncephalApp-Stroop tests using two gold standards, PHES (score ≤ -4) and ICT (lures > 1 stand deviation).²³ Healthy controls ($n = 308$) completed the Off and On state an average of 138 seconds, whereas patients with MHE completed the task an average of 198 seconds. When using PHES, the EncephalApp had sensitivity and specificity of 80% and 61%, respectively. Of note, the studies of EncephalApp excluded patients with alcohol use in the past 3 to 6 months as well as those on psychoactive drugs that were not on stable antidepressants.

Despite the ease of EncephalApp-Stroop test, the use outside of clinical trials in real-world settings has been low at nearly 32%,²⁴ suggesting that the onus of screening and monitoring of MHE cannot solely rely on the patient or caregiver. More recently and even shorter version of the EncephalApp-Stroop test, the Quick-Stroop found that decreasing the test time to just two runs (which can be accomplished in less than 1 minute), in the “Off state” was statistically equivalent to the entire EncephalApp-Stroop test, using PHES as the gold standard for diagnosis.²⁵ This ultra-short version may be easier for patients to complete during a clinic visit, but the barriers of downloading a smartphone application still exist.

The animal naming test

Part of the original Repeatable Battery for Assessment of Neuropsychological Status, the animal naming test is a shortened version taking 1 minute to complete without any

tools needed. The animal naming test also does not require a trained clinician to score or interpret. It was initially studied and validated in Italy by Campagna and colleagues using patients admitted to two hospitals compared with healthy individuals and patients with inflammatory bowel disease also admitted to the hospital.²⁶ The PHES test (score ≤ -4) was used as the gold standard for diagnosis of MHE. The test requires simply asking a subject to name as many animals as they can in 1-minute animal naming test 1 (ANT₁). The test is influenced negatively by age (>80 year old) and education (<8 years) and was therefore adjusted to take into account these factors (S-ANT₁). The scores were correlated with PHES and EEG. In patients with cirrhosis, a simplified animal naming test 1 (S-ANTI₁) score of less than 10 animals was associated with future development of overt encephalopathy.²⁶ Furthermore, a recent prospective cohort study in the United States using the S-ANT₁ animal naming test found increased frailty and disability in patients who scored poorly, strengthening the concept that this is a clinically relevant test.²⁷

Potential use of risk scores and predictive modeling for minimal hepatic encephalopathy

Because diagnosing MHE can be quite challenging, a shift to developing risk scores for development of overt HE may be a valid alternative approach. Risk scores and predictive modeling have become an integral part of health care in multiple settings.

BABS score

A retrospective cohort study over 5 years of veteran patients with cirrhosis was used to create the BABS score: Bilirubin, Albumin, nonselective Beta blocker use, Statin use.²⁸ The BABS score was created to risk stratify patients with cirrhosis for development of OHE. Patients were analyzed if they had diagnostic codes for cirrhosis or a portal hypertensive complication and were excluded if their chart revealed prior diagnosis of hepatic encephalopathy or use of medications such as rifaximin and lactulose. The primary outcome was development of overt HE over the 5-year period. Multivariate analysis showed the use of statin was associated with lower risk of developing overt HE, whereas the use of nonselective beta blockade was associated with higher risk of developing overt HE.

Baseline bilirubin and albumin also had significant hazard ratios and were included in the score. Using these four variables, a risk score was created. Patients can score in one of three categories based on their baseline risk score: ≤ -10 low risk, -9 to 20 intermediate risk, and ≥ 21 high risk.²⁸ For patients with baseline low-risk scores, their risk of developing overt HE in the next 5 years was 27%. Patients with intermediate- or high-risk scores had 49% risk of developing overt HE at 5 years. Although the population studied, 98% male and 74% white, is not inclusive, a high BABS could be a clinical tool to screen for MHE, in addition to help counsel patients regarding falls and driving.

MELD-Na-activity-chair stands-quality of life hepatic encephalopathy score

Another relevant study to MHE evaluated cirrhotic patient's health- HRQOL using the self-reported Short Form-8 and Work Productivity and Activity Impairment questionnaire.²⁹

The study also incorporated measurement of frailty using chair-stands within 30 seconds and combined these measurements with MELD-Na+ to create a new score, the MELD-Na-Activity-Chair Stands-Quality of Life Hepatic Encephalopathy (MASQ-HE).²⁹ The area under the receiver operating curve was 0.82 to predict overt HE development at 12 months. As the BABS score outlined above, The MASQ-HE and other risk scores for transition to overt HE require further validation, in particular regarding

stratification by presence/absence of MHE, a factor which likely has major modulatory influence in the performance of tests and scores to predict the development of overt HE.

Artificial intelligence and digital biomarkers: cognition

It has been over 20 years since PHES was initially published as a diagnostic tool for MHE. Despite advances over the past few decades, there remains a need for an easily accessible, minimally invasive, and low-cost tool to diagnose MHE. The tools described above still require active implementation and participation by providers and patients. With decreasing patient encounter time, it is becoming necessary to shift the burden of diagnostics away from the clinician, medical staff, caretakers, and patients.

The use of artificial intelligence (AI) has the potential to expedite clinical diagnosis and shift toward more personalized and precise medicine. This is an opportunity to use natural language processing to evaluate subtle changes in cognition during patient encounters.³⁰

Dickerson and colleagues published a retrospective pilot study on pretransplant and posttransplant individuals compared with control and found that patient-generated EMR messages to health care team had slight differences in lexical and syntactic domains that may capture MHE.³¹ There is increasing use of electronic medical record software that records patient encounters to aid in documentation and billing. The rate of speech has been evaluated as a biomarker and one study found that low psychometric scores using PHES were correlated with significantly slowed speech.³² Likely there will be rapid advancements in AI over the next decade to aid in diagnostics, perhaps making many of the current tools to assess MHE obsolete.

Management of Minimal Hepatic Encephalopathy

The management of MHE presents a challenge due to the difficulties in establishing a definitive diagnosis. As outlined above, evaluation and interpretation of a range of psychometric tests, changes in clinical symptoms, and laboratory data have been suggested to accurately recognize, identify, and ultimately diagnose MHE. Despite a lack of consensus on therapeutic strategies for MHE and controversies on potential benefits and risks, the pursuit of novel prevention or reversal strategies has sparked numerous clinical trials. Several studies have explored MHE treatment, primarily based on variations of established therapies for overt HE. The current options for managing MHE include interventions to alter the intestinal microbiota with nonabsorbable disaccharides such as lactulose, nonabsorbable antibiotics such as rifaximin, probiotics, fecal microbiota transplantation (FMT), L-ornithine L-aspartate (LOLA), and maintaining proper nutritional status while averting sarcopenia with branched-chain amino acids (BCAAs) and a high protein diet^{33–35} (**Box 4**).

Nonabsorbable disaccharides

Nonabsorbable disaccharides, including lactulose and lactitol, are currently the primary treatment for OHE (and covert stage I HE) and exert their effect through various mechanisms, including osmotic laxative effect, lowering of intraluminal pH levels, and modulation of gut microbiome.

By shortening colonic transit time, lactulose decreases the amount of time that gut bacteria are exposed to nutrients and substrates, thereby reducing ammonia production. In addition, lactulose can lower intraluminal pH levels, which in turn prevents the conversion of NH₄⁺ ammonium cation to NH₃ ammonia. As NH₄⁺ ammonium is not readily absorbed, it is excreted in the feces, further reducing the amount of

Box 4**Therapeutic interventions for patients with minimal hepatic encephalopathy and potential agents which require of additional evaluation**

Therapeutic Interventions for Patients with Minimal Hepatic Encephalopathy

- Lactulose and other nonabsorbable disaccharides
- Probiotics
- Rifaximin

Potential Agents which Require of Additional Evaluation

- Polyethylene glycol (PEG)
- Fecal microbiota transplantation (FMT)
- L-ornithine L-aspartate (LOLA)
- Branched-chain amino acids

ammonia produced. Another mechanism by which nonabsorbable disaccharides reduce ammonia production is through modulation of the gut microbiome. Disaccharides are metabolized by the gut microbiome, leading to a reduction in ammonia-producing microbiota due to the low pH acidic environment. As a result, there is a decrease in the amount of ammonia produced in the colon, which can be associated with lower blood ammonia levels.³⁶

Several clinical studies have explored the efficacy of lactulose in the management of MHE.^{37,38} In a pioneer clinical trial, McClain and colleagues demonstrated the effectiveness of lactulose in improving psychomotor performance in patients with alcohol-associated cirrhosis who did not exhibit overt HE.³⁹ The study comprised 32 patients who were randomly assigned to receive either lactulose or sucrose daily for a period of 3 months. Of note, patients treated with lactulose showed significant improvements in the Reitan trail test, writing speed, and digit symbol test, whereas no significant improvement was observed in the sucrose group.³⁹ Watanabe and colleagues also demonstrated the efficacy of lactulose treatment in improving psychometric tests, such as the NCT, symbol digit, and BDTs of the Wechsler adult intelligence scale, in patients with MHE.⁴⁰

The study included 22 MHE patients who received lactulose (45 mL/d) for 8 weeks, whereas 14 did not receive lactulose. The lactulose treatment group exhibited significant improvements in psychometric evaluations at 4 and 8 weeks, with 50% of patients experiencing resolution of MHE by week 8, compared with 85% of untreated patients who had persistent MHE.⁴⁰ Prasad and colleagues investigated the effect of lactulose treatment on HRQOL and cognitive functions in cirrhotic patients with MHE⁴¹; 61 patients with MHE were randomly assigned in a 1:1 ratio to receive treatment (lactulose) for 3 months or no treatment. The results showed that lactulose improved both cognitive function and HRQOL compared with the untreated group, and the improvement in HRQOL was related to the improvement in psychometry.⁴¹

Thus, a trial of lactulose should be considered in patients with cirrhosis who complain of falls, driving difficulties, experience traffic accidents or violations, or have a decreased quality of life and test positive for MHE (see **Boxes 2** and **3**).

Rifaximin

Rifaximin, a semisynthetic derivative of the naturally occurring antibiotic rifamycin exhibits a broad spectrum anti-microbial activity against both gram-positive and gram-negative bacterial intestinal flora. Rifaximin inhibits bacterial RNA synthesis via its binding to the beta subunit of bacterial DNA-dependent RNA polymerase ultimately suppressing bacterial protein synthesis.

It has minimal systemic absorption, acting locally within the intestinal tract, targeting bacterial overgrowth and lowering bacterial toxins production.^{42,43} Rifaximin also has anti-inflammatory activity, inhibiting the activation of pro-inflammatory cytokines and reducing intestinal permeability, thereby preventing translocation of harmful substances from the gut into the systemic compartments.^{44,45}

Multiple clinical trials, reviewed elsewhere in this Clinics in Liver Disease Issue, have established clear roles for rifaximin in the management of overt HE. Consequently, rifaximin has emerged as a potential treatment option for the management of MHE as well.^{33–35} Bajaj and colleagues showed that patients with MHE exhibited significant improvements in driving simulator performance following treatment with rifaximin, compared with those who received a placebo.⁴⁶ Rifaximin was associated with enhanced cognitive function and reduced endotoxemia in MHE patients in another study.⁴⁷ These findings were accompanied by changes in relationships between gut microbiome.^{46,47}

Unproven but Potentially Helpful Therapies for Minimal Hepatic Encephalopathy

Polyethylene glycol

Polyethylene glycol (PEG) is a water-soluble, nonabsorbable, nontoxic polymer which is used as an osmotic laxative to treat constipation or colon purge before colonoscopy. PEG is not absorbed and passes through the gastrointestinal tract unaltered, increasing the water content of the stools.⁴⁸ PEG has been extensively evaluated for overt HE,^{49–52} but to our knowledge, no clinical trial has investigated the efficacy and safety of PEG as a treatment for MHE. In the overt HE setting, PEG is used sometimes in conjunction with lower doses of lactulose, or without lactulose, in patients who are unable to tolerate lactulose.⁵² Because of its laxative effect, PEG could be a potentially useful agent in MHE. A prospective evaluation of PEG, which is available over the counter in the United States, as a possible therapeutic tool for MHE seems a reasonable research endeavor.

Probiotics

Probiotics are live bacteria beneficial to the gut microbiota which have been studied for a potential therapeutic role in the treatment of MHE. Dysbiosis, an imbalance in the gut microbiota, has been linked to the development and progression of hepatic encephalopathy in cirrhosis. Probiotics restore gut microbiota equilibrium, effectively reducing the production and absorption of various toxic molecules, including ammonia. Another notable benefit of probiotics is their ability to enhance gut barrier function. Bacterial translocation, a pathologic process involving migration of gut bacteria into the systemic circulation, can incite inflammation and endotoxemia, both of which are pathogenetic mechanisms for hepatic encephalopathy.

Furthermore, probiotics exhibit immunomodulatory effects within the gut by attenuating the activity of immune-mediated cells, thereby contributing to a reduction in inflammation. Given the role of inflammation in the pathogenesis of hepatic encephalopathy, this immunomodulatory action highlights the potential benefits of probiotics in the management of HE.^{53–55}

In a randomized controlled trial conducted by Malaguarnera and colleagues, the efficacy of *Bifidobacterium longum* with fructo-oligosaccharide was investigated in patients diagnosed with MHE.⁵⁶ Following a 90-day treatment period, the group receiving *Bifidobacterium* showed a significant decrease in serum ammonia levels, along with notable improvement in performance on both the Symbol Digit Modalities Test (SDMT) and BDT, indicative of enhanced cognitive function.³⁵ Bajaj and colleagues further demonstrated similar improvements in cognitive function using

surrogate markers of MHE reversal, including BDT, SDMT, and NCT-A, in addition to showing excellent adherence to probiotic yogurt supplementation compared to the placebo group among nonalcoholic cirrhotic patients.⁵⁷

In a small prospective, open-label, randomized study, Manzhali studied the safety and efficacy of *Escherichia coli* Nissle (EcN) 1917 strain compared with lactulose and rifaximin. EcN was found non-inferior to rifaximin; however, it outperformed lactulose in terms of ammonia and pro-inflammatory cytokines reduction, gut microbiota modulation and cognitive function improvement among patients with MHE.⁵⁸

In summary, probiotics for MHE seem promising and have excellent adherence but further studies are needed to identify their granular benefits, best type of probiotics, and optimal dose and administration program for MHE.

Fecal microbiota transplantation

FMT involves transferring fecal material from a healthy donor to a patient suffering from gut dysbiosis, using methods such as a nasoduodenal tube, enema, or colonoscopy. FMT is now integrated into mainstream medicine.^{59,60}

Cirrhotic patients with MHE have distinct changes in gut microbiota patterns, with reduced levels of certain short-chain fatty acid-producing Firmicutes, including Lachnospiraceae and Ruminococcaceae and abundance of proteobacteria, such as Enterobacteriaceae.⁶¹ Based on this information, Bajaj and colleagues conducted an open-label, randomized controlled trial involving a single stool donor with abundant Lachnospiraceae and Ruminococcaceae, identified by a machine learning technique⁶²; 10 participants received FMT via enema and 10 control subjects received lactulose and rifaximin as standard of care. The trial outcomes were favorable as FMT from the rationally selected donor reduced hospitalizations, improved cognition and dysbiosis in cirrhotic patients with recurrent HE.⁴⁶

Safety and improvements in clinical and cognitive function parameters among patients treated with FMT enemas were sustained in the long term (>12 months).^{62,63} These investigators also found that patients preferred FMT capsules over enema.⁶⁴

To our knowledge, FMT has not been studied specifically in the management of MHE. The progress in FMT formulation (capsules), coupled with the recent FDA approval of a commercially available, rectally administered FMT agent in 2022, is expected to enhance accessibility to FMT therapy. Given the unmet needs in MHE therapy, further evaluation of FMT as a potential intervention for patients with MHE seems warranted.

L-ornithine L-aspartate

LOLA is a combination of two amino acids with potential therapeutic use in the management of hepatic encephalopathy and other metabolic disorders characterized by hyperammonemia. L-ornithine activates glutamine synthetase activity and promotes glutamine synthesis and because glutamine is the main reservoir of ammonia in the liver, it ameliorates hyperammonemia. On the other hand, L-aspartate is converted to urea in the liver. Thus, LOLA alleviates hepatic encephalopathy by lowering ammonia production by multiple mechanisms,^{65,66} and indeed, numerous randomized controlled trials have documented the efficacy of LOLA in the management of overt episodic or chronic HE.^{67,68}

Mittal and colleagues studied the efficacy of LOLA (6g three times daily) in the management of 160 patients with MHE.⁶⁹ LOLA significantly improved HRQOL and lowered arterial ammonia level in patients with MHE compared with no treatment.⁶⁹ Similarly, another study found that MHE patients who received LOLA treatment exhibited notable enhancement in neuropsychometric tests and critical flicker frequency results, in comparison to those who were administered placebo.⁷⁰ LOLA

and lactulose were most effective in preventing transition to overt HE in patients with MHE on a recent systematic review of various treatment options for MHE³⁸ despite a prior Cochrane review of 36 randomized clinical trials in which subgroup analyses showed no differences in MHE outcomes associated with LOLA therapy.⁷¹

Branched-chain amino acids

The BCAAs, valine, leucine, and isoleucine play an important role in nitrogen metabolism and muscle protein synthesis. A Cochrane database systematic review of 16 randomized clinical trials concluded that BCAAs were beneficial in patients with overt HE.⁷² However, as with other potential interventions outlined above, BCAAs have had very limited evaluation in the setting of MHE.^{38,73}

In conclusion, multiple agents have been found to reverse the neurophysiological abnormalities of MHE, particularly lactulose and rifaximin, whereas others (lactulose, LOLA) seem to have the capability of decreasing transition to overt HE in patients with MHE. However, the adverse events of lactulose and the cost of rifaximin prevent recommending therapy for every patient with MHE. Current guidance suggests considering therapy for MHE on a case-by-case basis.⁷ We interpret this to suggest a therapeutic trial in cirrhotic patients with falls, motor vehicle accidents, machine operators, subjective feelings of neurologic deficits, or employment difficulties. Lactulose seems the first-line treatment for MHE due to its strong evidence of effectiveness in improving both MHE and HRQOL. A trial of lactulose is reasonable in patients with cirrhosis who complain of falls, driving difficulties, experience traffic accidents and violations, or have a decreased quality of life and test positive for MHE (see **Boxes 2** and **3**). In cases of MHE recurrence or patients unresponsive to lactulose, rifaximin may serve as the second-line treatment, if financially feasible. For patients experiencing lactulose intolerance, an alternative option is the use of PEG, either as a substitute for lactulose or in combination with a reduced lactulose dose, understanding that PEG has not been evaluated in, or is formally indicated in MHE. A trial with probiotics is also an attractive option. Third-line agents, such as FMT, LOLA, and BCAAs, while generally safe in other settings, should be considered experimental and require the appropriate clinical trials to establish their role, if any, in the management of MHE.

CLINICS CARE POINTS

- Minimal hepatic encephalopathy is common in patients with cirrhosis.
- The standard neurological examination is normal in patients with minimal encephalopathy.
- The Animal Naming Test and EncephalApp-Stroop tests are useful to screen for minimal encephalopathy in the office or bedside settings.
- A trial of lactulose or probiotics can be considered for patients with minimal encephalopathy.

DISCLOSURE

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