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Guideline

Chinese Guidelines on the Management of Hepatic Encephalopathy in Cirrhosis (2024)

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Abstract

With progress in basic and clinical research on hepatic encephalopathy in cirrhosis worldwide, the Chinese Society of Hepatology of the Chinese Medical Association has invited experts in relevant fields to revise the 2018 "Chinese Guidelines on the Management of Hepatic Encephalopathy in Cirrhosis." The updated guidelines provide recommendations for the clinical diagnosis, treatment, and both primary and secondary prevention of hepatic encephalopathy in cirrhosis.

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Introduction

Hepatic encephalopathy (HE), a common complication of end-stage liver disease, is a neuropsychiatric syndrome of varying clinical severity resulting from metabolic disorders caused by severe acute or chronic liver dysfunction, or various portosystemic shunts (PSS).

In 2018, the Chinese Society of Hepatology of the Chinese Medical Association published the first edition of the *Guidelines on the Management of Hepatic Encephalopathy in Cirrhosis*.[1] However, in recent years, significant advances have been made in basic and clinical research on HE, both in China and abroad. The introduction of concepts such as "minimal hepatic encephalopathy (MHE)," "subclinical cirrhosis," and "cirrhosis recompensation or reversal" provides valuable guidance for the diagnosis, treatment, and prognosis of HE. In 2023, the Hepatobiliary Disease Group of the Chinese Society of Gastroenterology issued the *Chinese Consensus on the Clinical Diagnosis and Management of Covert Hepatic Encephalopathy*.[2] Therefore, to facilitate the timely clinical application of recent findings in the prevention and treatment of HE, the Chinese Society of Hepatology of the Chinese Medical Association assembled experts in hepatology, infection, gastroenterology, surgery, Chinese medicine, interventional medicine, oncology, and clinical research methodology to jointly revise the *Guidelines on the Management of Hepatic Encephalopathy in Cirrhosis*.

These guidelines are not mandatory standards, nor do they address all issues related to the management of HE. Clinicians should follow the principles outlined in these guidelines when treating patients, thoroughly assess the patient's condition, and carefully consider the patient's views and wishes. Additionally, clinicians should account for local healthcare resources and practical experience to develop a comprehensive and reasonable individualized management plan.

The recommendations in these guidelines are categorized based on the level of evidence and strength of recommendations, following the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (Table 1).

Based on the type of underlying liver disease, HE can be classified into three types: A, B, and C.[3] Type A HE is caused by acute liver failure and exhibits rapid progression. Its key pathophysiological features include cerebral edema and intracranial hypertension. Type B HE is caused by PSS without significant liver dysfunction, with liver biopsy showing normal histological structure. Type C refers to HE caused by chronic liver damage, such as cirrhosis (Table 2).

These guidelines primarily focus on cirrhosis-induced HE, specifically type C HE, and do not address type A or type B HE caused by acute or acute-on-chronic liver failure or PSS due to other causes.

Keywords: Liver cirrhosis; Hepatic encephalopathy; Minimal hepatic encephalopathy; Diagnosis; Therapy; Prevention; Guidelines.
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Table 1. Quality of evidence and strength of recommendations

Quality of evidence	
High (A)	Further research is unlikely to alter the confidence in the estimation of efficacy
Moderate (B)	Moderate confidence in the observed values: the true values are probably close to the observed values, but it is possible that they may be different
Low (C)	Limited confidence in the observed values: the true values may be different from the observed values
Very low (D)	Low confidence in the observed values: the true values are most likely different from the observed values
Strength of recommendations	
Strong (1)	Advantages of an intervention clearly outweigh its disadvantages or its disadvantages clearly outweigh its advantages
Weak (2)	Uncertainty about the advantages and disadvantages or evidence of comparable advantages and disadvantages regardless of the quality of evidence

Epidemiology and pathogenesis

Epidemiology

Different incidence rates of HE in cirrhosis have been reported in China and abroad, which may be attributed to a lack of uniform diagnostic standards for HE among clinicians, particularly with significant variations in diagnostic methods for MHE. The majority of patients with cirrhosis will experience MHE to some extent at some point during the course of their disease. MHE is very common in clinical settings, with an incidence of 30% to 84% throughout the course of cirrhosis.[4] According to data from other countries, the incidence of cirrhosis with concurrent HE is 30–45% and may be even higher during the progressive stage of the disease. Furthermore, studies have demonstrated that HE is an independent risk factor for mortality in patients with cirrhosis.[5]

In China, hepatitis B-induced cirrhosis remains the primary cause of HE, followed by liver diseases induced by alcohol, drugs, and autoimmune conditions, particularly primary biliary cirrhosis. However, there has been a gradual increase in cases of cirrhosis caused by non-infectious liver diseases, such as metabolic-associated fatty liver disease (MAFLD).[6] In the Yangtze River Basin, schistosomiasis was once the leading cause of cirrhosis. In cases of hepatitis B-induced cirrhosis, the incidence of recompensation or reversal following effective antiviral therapy is approximately 56.2%.[7]

The occurrence of MHE is not significantly associated with etiology, but its incidence does increase with the severity of decompensated cirrhosis. Even patients with Child-Pugh class A cirrhosis have an MHE incidence of up to 24.8%.[4] Approximately 40% of hospitalized cirrhotic patients have MHE, and 30–45% of patients with cirrhosis and 10–50% of patients who underwent transjugular intrahepatic portosystemic shunt (TIPS) placement develop overt hepatic encephalopathy (OHE).[6]

Pathogenesis

The pathogenesis of HE is still poorly understood. The main hypotheses include the ammonia hypothesis and the inflammatory mediator hypothesis, while the role of other neurotoxic substances is also garnering increasing attention.[8]

The 2022 European Association for the Study of the Liver guidelines on the management of HE state that etiologies such as alcohol, viral hepatitis, and MAFLD may affect brain function through different mechanisms. Alcohol itself is neurotoxic; viruses can infect astrocytes and microglia in the brain; and MAFLD patients may exhibit impaired neurocognitive function, reduced brain volume, hyperammonemia, and astrocytic and microglial activation in the absence of cirrhosis. Additionally, diabetes, medications, aging, and comorbidities may all impact brain function, thereby increasing the risk of HE. However, it is difficult to distinguish between the contributions of these factors and liver dysfunction itself regarding their impact on brain function. Moreover, etiology is not an independent risk factor for predicting OHE in patients with cirrhosis.[9]

Ammonia hypothesis: Dietary protein is decomposed by gut bacteria, leading to increased production of ammonia. Increased intestinal permeability can result in a higher influx of ammonia into the portal vein, while liver dysfunction can hinder the effective detoxification of blood ammonia via the urea cycle.[10] In addition, PSS can allow portal blood containing ammonia to enter the systemic circulation directly. The entry of blood ammonia into brain tissue stimulates increased synthesis of glutamine by astrocytes, resulting in cellular atypia, swelling, and degeneration, thereby triggering acute neurocognitive impairments. Ammonia also contributes directly to an imbalance in the ratio of excitatory to inhibitory neurotransmitters, which can lead to clinical symptoms.

Inflammation-associated damage: Hyperammonemia interacts with inflammatory mediators to jointly promote the pathogenesis of HE. Inflammation can disrupt the blood-brain barrier, allowing toxic substances such as ammonia and inflammatory cytokines to enter brain tissue, inducing changes in brain parenchyma and impairing brain function. Additionally, hyperammonemia can lead to neutrophil dys-

Table 2. HE classification recommended by the 11th World Congress of Gastroenterology, 1998

HE type	Definition	Subcategory	Subdivision
Type A	HE associated with acute liver failure	None	None
Type B	HE associated with PSS and no liver disease associated with hepatocellular injury	None	None
Type C	HE associated with cirrhosis, accompanied by portal hypertension or PSS	Episodic HE	Precipitated

HE, hepatic encephalopathy; PSS portosystemic shunts.

function and promote oxidative stress and inflammation, while the cytokines generated by the inflammatory process can, in turn, exacerbate liver damage and contribute to the development of HE, creating a vicious cycle. The occurrence of HE is also associated with infections, with common infections in patients with cirrhosis including peritonitis, urinary tract infections, and pneumonia.[11,12]

Other hypotheses: *Amino acid imbalance hypothesis and false neurotransmitter hypothesis*: When liver dysfunction occurs in cirrhosis, the ability to degrade aromatic amino acids is reduced, resulting in increased blood levels of phenylalanine and tyrosine, which suppress normal neurotransmitter production. Elevated phenylalanine and tyrosine can lead to the production of phenylethanolamine and octopamine, which are false neurotransmitters that can replace normal neurotransmitters in large quantities, thereby contributing to the development of HE.[13]

γ-Aminobutyric acid (GABA)/benzodiazepine receptor complex hypothesis: GABA is the predominant inhibitory neurotransmitter in the central nervous system, and its receptor forms a complex with the benzodiazepine receptor in the brain. During HE, blood GABA levels are elevated, resulting in higher amounts crossing the blood-brain barrier, while the levels of endogenous benzodiazepines in the brain are also increased. Drugs that target the GABA/benzodiazepine receptor complex, such as phenobarbital and diazepam, can induce or exacerbate HE. In contrast, benzodiazepine receptor antagonists, such as flumazenil, can reduce the occurrence of HE.[14]

Manganese hypothesis,[15] brainstem reticular formation dysfunction,[16] and others.

Precipitating factors: Common precipitating factors of HE include infections (which may involve the abdominal cavity, bowel, urinary tract, respiratory tract, etc., but predominantly abdominal infections), followed by gastrointestinal bleeding, electrolyte and acid-base imbalances, large-volume paracentesis, high-protein diets, hypovolemia, diuresis, diarrhea, constipation, and the use of benzodiazepines and anesthetics. The incidence of HE increases after TIPS, while opting for TIPS placement in the left branch can decrease the incidence of HE.[17] Proton pump inhibitors may lead to small intestinal bacterial overgrowth, which can increase the risk of HE in patients with cirrhosis in a dose-dependent manner.[18]

Among cirrhotic patients with elevated blood ammonia, the presence of the aforementioned precipitants will further aggravate cerebral edema and oxidative stress, leading to a rapid decline in cognitive function.

Clinical Manifestations and Diagnosis

Patients with cirrhosis who develop HE, after excluding other possible causes, are considered to have decompensated cirrhosis. MHE is a subclinical manifestation of decompensated cirrhosis and does not fall under the decompensation phase.[19] Care should be taken in clinical practice to identify subclinical decompensation (MHE), first decompensation (HE), progressive decompensation/unstable decompensation (recurrent HE), and recompensation (when the etiology is controlled or eliminated after treatment, without the occurrence of HE following the discontinuation of lactulose or rifaximin for >12 months).

The mortality rate of progressive decompensation in cirrhosis is higher than that of first decompensation. Cirrhotic patients with HE are considered to have progressive decompensation in the following cases: (1) the onset of one or more of the following decompensation events caused by secondary portal hypertension: ascites, esophagogastric variceal bleeding, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome-acute kidney injury, and/or jaundice (after excluding other possible causes); and (2) recurrent HE.

Patients with decompensated cirrhosis who receive effective treatments targeting the underlying etiology and complications may experience a reversal to compensated cirrhosis, i.e., recompensation.[19]

Clinical symptoms and signs

HE is a continuum that ranges from normal cognitive function and intact consciousness to coma. Currently, the most widely adopted classification criteria for HE, both in China and abroad, remain the West Haven criteria, which divide HE into five grades from 0 to 4.[20] The main drawback of these classification criteria is that the differentiation between Grade 0 (possible MHE) and Grade 1 is highly subjective. MHE is characterized by the absence of noticeable personality or behavioral abnormalities, disorientation, asterixis, and other neurological signs, indicating normal cognitive function;[21,22] however, abnormalities may be present in neuropsychological tests. In Grade 1 HE, clinical manifestations such as euphoria, depression, or a shortened attention span can be difficult to identify. Only the most observant family members who are familiar with the patient's personality may detect mild cognitive impairment. Therefore, this classification demonstrates relatively poor repeatability and operability in clinical practice.

The International Society on Hepatic Encephalopathy and Nitrogen Metabolism collectively refers to MHE and West Haven Grades 1 and 0 as covert HE and has proposed the Spectrum of Neurocognitive Impairment in Cirrhosis classification. HE with clinical manifestations that include obvious mental abnormalities, such as personality and behavioral changes, or unconsciousness and coma, is referred to as OHE, which corresponds to West Haven Grades 2–4.[1,23] Notably, a minority of patients with Grade 1 HE may be positive for asterixis and are classified as OHE according to the Spectrum of Neurocognitive Impairment in Cirrhosis classification.

MHE is a highly covert phase in the pathogenesis of HE.[21,22] Its incidence is not associated with age, gender, smoking status, or education level but has a clear relationship with Child-Pugh class. The prevalence of MHE among patients with a Model for End-Stage Liver Disease score of ≥20 is 48%.[24] Despite the absence of apparent clinical symptoms and signs in patients with MHE, their clinical prognosis and quality of life are less favorable than those of cirrhotic patients with normal neuropsychological tests. Without prompt and effective treatment, MHE may progress to OHE in some cases. The three-year cumulative incidence of OHE in MHE is approximately 56%, along with significant increases in the incidence of other complications and mortality rates. MHE may persist even after the onset of OHE.[25] Additionally, patients with MHE experience a significant decline in their quality of life, driving safety, work efficiency, and socioeconomic status. Therefore, a key focus in clinical practice is to screen for MHE among patients with end-stage liver disease, such as cirrhosis.

The current guidelines have adopted the revised classification criteria for MHE and HE Grades 1–4, as described in the 2018 *Guidelines on the Management of Hepatic Encephalopathy in Cirrhosis* (Tables 3 and 4).[1] Patients with Grade 2–4 HE can be further assessed using the Glasgow Coma Scale to evaluate their level of consciousness.[1]

Laboratory tests

Liver function (bilirubin, alanine transaminase, aspartate transaminase, albumin, prothrombin activity), kidney function, and complete blood count are routinely tested in patients suspected of having HE.

Table 3. Revised HE classification criteria

Traditional West Haven classification	Grade 0		Grade 1 HE	Grade 2 HE	Grade 3 HE	Grade 4 HE
Recommended revised HE classification	Normal	MHE	Grade 1 HE	Grade 2 HE	Grade 3 HE	Grade 4 HE

HE, hepatic encephalopathy; MHE minimal hepatic encephalopathy.

Blood ammonia: Elevated blood ammonia levels are useful for diagnosing HE. However, the increase in blood ammonia is not entirely consistent with disease severity.[10,26] HE cannot be fully excluded in patients with normal blood ammonia levels.

Prolonged tourniquet placement, excessive delays in testing after blood collection, and transportation at high temperatures may all contribute to falsely elevated blood ammonia levels. Venous blood should be collected at room temperature and immediately transported at low temperatures for testing. The test should be completed within 30 m or within 2 h if the sample is centrifuged and refrigerated at 4°C.

Neuropsychological tests

Neuropsychological tests are the simplest approach for clinical screening and early diagnosis of MHE and Grade 1 HE. Guidelines from many countries recommend neuropsychological tests as the "gold standard" for screening or early diagnosis of MHE. Each test should be performed in combination with other examinations (Table 5).

Traditional paper-and-pencil neuropsychological tests: The Psychometric Hepatic Encephalopathy Score (PHES) consists of five subtests: the Number Connection Test (NCT) A and B, the Digit Symbol Test (DST), the Line-Tracing Test, and the Serial Dotting Test.[1] PHES is the preferred method for diagnosing MHE in China. Various factors can affect the results of this test, including the patient's age, education level, degree of cooperation, and learning effects. Currently, MHE can be diagnosed if both NCT-A and DST are positive, or if any two of the five subtests show abnormal results.[27] However, it should be noted that this test may not be sufficiently sensitive to detect all patients with early-stage MHE.

In recent years, computer software-assisted tools, such as the electronic Number Connection Test, have been developed for the self-monitoring and screening of cognitive impairment in patients with cirrhosis. These tools have demonstrated greater repeatability and reliability.[28] Additionally, computer-assisted psychometric tests have improved the convenience of testing to some extent.[29]

Stroop test and EncephalApp: The Stroop test[1,30] is an effective and direct tool that evaluates psychomotor speed and cognitive flexibility by recording the interference between the reaction time for recognizing a color field and a written color name. EncephalApp is an application based on the Stroop test (www.encephalapp.com) that has demonstrated good discriminative ability and promising prospects for distinguishing cognitive impairment in cirrhosis.[31,32] However, patients with color blindness are unable to use this instrument. Researchers have also developed the QuickStroop,[33] which can be completed in less than one minute and involves quickly matching digital symbols in red, green, or blue with their respective colors.

Critical flicker frequency (CFF) test: This test is used to detect the minimum stimulus frequency required to elicit the sensation of flicker fusion. It reflects impairments in brain nerve conduction and can serve as an auxiliary examination. A significantly smaller proportion of cirrhotic patients with a CFF < 39 Hz achieved five-year survival compared with those with a CFF ≥39 Hz. Thus, CFF is a simple, rapid, and non-invasive diagnostic test for MHE, demonstrating excellent accuracy below 39 Hz.[34]

Animal naming test (ANT1): The ANT1[35] is a simple, easy, and brief assessment[36]; however, it can be influenced by the patient's age, education level, and other factors. The ANT1 and the simplified ANT1 provide high diagnostic value for determining the onset of MHE, as well as for predicting OHE and prognosis in patients with cirrhosis. A simplified ANT1 score ≤20 demonstrated a sensitivity of 77.5% and a specificity of 58.3% for the diagnosis of MHE.[37]

Table 4. HE classification, symptoms, and signs

Revised HE classification	**Neuropsychiatric symptoms (i.e. cognitive manifestations)**	**Neurological signs**
Normal	Normal	Normal neurological signs, and normal neuropsychological tests
MHE	Potential HE, without noticeable personality or behavioral changes	Normal neurological signs, but with abnormalities in neuropsychological tests
Grade 1 HE	Presence of trivial clinical signs, such as mild cognitive impairment, decreased attention span, sleep disturbances (insomnia, sleep inversion), euphoria or depression	Asterixis can be elicited, abnormalities in neuropsychological tests
Grade 2 HE	Apparent behavioral and personality changes; lethargy or apathy; mild disorientation (time or place); impaired arithmetic ability, movement disorder, dysarthria	Asterixis can be readily elicited, neuropsychological tests not necessary
Grade 3 HE	Apparent disorientation (time or place), abnormal behavior, semi-stupor to stupor but responsive	Asterixis generally cannot be elicited; presence of ankle clonus, hypertonia and hyperreflexia; neuropsychological tests not necessary.
Grade 4 HE	Coma (unresponsive to verbal or external stimuli)	Hypertonia or positive central nervous system signs, neuropsychological tests not necessary

HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy.

Table 5. Commonly used neuropsychological/physiological tests in clinical practice

Test method	Purpose of test	Duration	Remarks
Psychometric tests			
Psychometric Hepatic Encephalopathy Score (PHES)	The "gold standard" for measuring cognitive impairment in patients with cirrhosis. Key indicator for diagnosing MHE	Consists of five subtests: Number Connection Test (NCT) A/B, Digit Symbol Test (DST), Serial Dotting Test (SDT), and Line-Tracing Test (LTT)	Paper-and pencil test. At least two subtests are needed for clinical diagnosis; all five subtests are needed for clinical research
NCT-A	Attention and psychomotor speed. It can be used for the rapid screening of MHE in outpatient clinics	30–120 s	Provides better accuracy after correcting for age and education level
NCT-B	Attention, psychomotor speed, divided attention. It can be used for the rapid screening of MHE in outpatient clinics	1–3 m	Requires physician or nurse
			More complex than NCT-A
DST	Attention and psychomotor speed. It can be used for the rapid screening of MHE in outpatient clinics	2 m	Requires physician or nurse
Stroop smartphone app (EncephalApp)	Attention. It can be used for the rapid screening of MHE in outpatient clinics.	10 m	Reliable and easy to use
Animal Naming Test (ANT)	Test of semantic fluency	1 m	Reliable and easy to use
Neurophysiological tests			
Critical flicker frequency (CFF)	Visual discrimination. It can be used for the auxiliary diagnosis of HE below Grade 2 in outpatient clinics but offers limited value	10 m	Requires the cooperation of more abled patients
EEG	Generalized brain activity, suitable for children	Variable	Requires physician or nurse, and professional equipment
Evoked potentials	Detects the time difference between electrical stimulation and response	Variable	Auditory P300 has been used to diagnose MHE

PHES, psychometric hepatic encephalopathy score; NCT, number connection test; DST, digit symbol test; SDT, serial dotting test, LTT, line-tracing test; ANT, animal naming test; CFF, critical flicker frequency; EEG, electroencephalogram; MHE, minimal hepatic encephalopathy.

Neurophysiological tests

The advantages of neurophysiological tests include relatively specific results that are not affected by learning effects. However, their disadvantages include poor sensitivity, the need for specialized equipment and personnel, and limited agreement with neuropsychological tests.

Electroencephalogram (EEG): Although EEG can reflect cerebral cortical function, typical EEG changes are typically observed only in patients with severe HE. Consequently, EEG is generally not employed for the early diagnosis of HE and is used primarily as an auxiliary diagnostic tool in pediatric HE cases.

Evoked potential tests: Evoked potentials include visual evoked potentials, auditory evoked potentials, and somatosensory evoked potentials. Patients with MHE may exhibit prolonged latency and reduced amplitude.

Imaging examinations

Neurological imaging examinations, such as magnetic resonance imaging (MRI) and computed tomography (CT) of the brain, cannot serve as a basis for diagnosing HE. However, they are useful for excluding or confirming organic neurological diseases.

CT: Brain CT scans cannot be used to diagnose or classify HE but can detect cerebral edema and exclude cerebrovascular accidents, intracranial tumors, and other conditions.

MRI: MRI findings in patients with cirrhosis and HE are characterized by significantly elevated mean diffusivity in brain white matter, which is associated with the stage of HE, blood ammonia levels, and the extent of other neuropsychological and neurophysiological damage. A typical brain MRI finding in HE is bilateral basal ganglia hyperintensity.[38] Additionally, MR radiomics can predict the presence of chronic HE and grade its severity.[39]

Functional MRI (fMRI): Resting-state fMRI can serve as a non-invasive examination method. Patients with MHE exhibit abnormal functional connectivity across multiple brain areas, and the degree centrality values of certain brain regions are associated with cognitive impairment in these patients. Therefore, degree centrality value may serve as a potential neuroimaging marker for quantifying the severity of cognitive functional changes in MHE patients.[40]

Brain MRI is not recommended for the routine diagnosis of HE in patients with delirium. However, it can be employed in the differential diagnosis of patients with delirium or encephalopathy when the diagnosis is uncertain or when the patient does not respond to treatment.

Diagnosis and differential diagnosis

OHE: OHE can be diagnosed fairly straightforwardly based on the patient's clinical manifestations and signs in accord-

ance with the West Haven classification criteria.[41,42] There is no need for the PHES, neuropsychological tests, neurophysiological tests, or imaging examinations. Diagnostic points:

1. Presence of underlying disease, severe liver disease, and/or extensive PSS causing HE.
2. Presence of clinically identifiable neuropsychiatric symptoms and signs.
3. Exclusion of other diseases that may cause neuropsychiatric abnormalities, such as metabolic encephalopathy, toxic encephalopathy, neurological diseases (e.g., intracranial hemorrhage, intracranial infection, intracranial space-occupying lesion), mental disorders, etc.
4. Special attention should be paid to identifying the precipitants of HE (Type C and Type B), such as infection, gastrointestinal bleeding, large-volume paracentesis, etc.
5. Elevated blood ammonia offers crucial diagnostic value.

MHE: Since patients do not exhibit marked cognitive abnormalities, special tests are often needed to confirm a diagnosis, which warrants special clinical attention.[43,44] MHE can be diagnosed if key diagnostic points (1) and (2), and any one or more of (3)–(6) are met. Key diagnostic points:

1. Presence of underlying disease, severe liver disease, and/or extensive PSS causing HE.
2. Abnormalities in at least two traditional neuropsychological tests.
3. Abnormalities in at least one novel neuropsychological test (ANT1, CFF).
4. Abnormalities in CFF test.
5. EEG abnormalities, brain electrical activity mapping, visual evoked potentials, and brainstem auditory evoked potentials — only suitable for pediatric patients.
6. fMRI abnormalities.

Key points of differential diagnosis: HE should be differentiated from the following diseases:

1. Mental disorder: HE with mental symptoms, such as personality changes, abnormal behaviors, insomnia, and delirium, as the only prominent manifestations, can be easily misdiagnosed as a mental disorder. Therefore, clinicians should remain vigilant to the possibility of HE in patients with severe liver disease or a history of PSS who develop neurological or psychiatric abnormalities.
2. Intracranial lesions: These include subarachnoid, epidural, or intracerebral hemorrhage, cerebral infarction, brain tumors, intracranial infections, and epilepsy. An appropriate diagnosis can be made by performing physical examinations to test for localizing neurological signs or meningeal irritation, combined with CT/MRI, lumbar puncture, arteriography, EEG, virological assays, and other relevant tests.
3. Other metabolic encephalopathies: These include ketoacidosis, hypoglycemia, hyponatremia, uremic encephalopathy, and pulmonary encephalopathy. A differential diagnosis can be established based on the corresponding primary disease and the characteristics of its blood biochemistry analysis.
4. Wernicke encephalopathy: This condition is commonly found in patients with severe alcohol-related liver disease and is caused by vitamin B1 deficiency. Supplementation with vitamin B1 should significantly improve the patient's symptoms.[45–47]
5. Toxic encephalopathies: These include alcoholic encephalopathy,[40] acute poisoning, withdrawal syndrome, heavy metal (mercury, manganese, etc.) encephalopathy, and toxic reactions to psychotropic drugs or salicylates. A differential diagnosis can be established by tracing the patient's medical history and/or performing appropriate toxicology tests.
6. Cirrhosis-related Parkinsonism: This condition is commonly found among the elderly and is primarily characterized by bradykinesia, tremors, involuntary movements, and cognitive impairment. Careful differentiation is necessary in elderly patients with liver disease.
7. Hepatic myelopathy: This condition commonly arises from liver cirrhosis, and its hallmark pathology involves the symmetrical demyelination of the lateral corticospinal tract. Clinical manifestations include gradually progressive symmetrical spastic quadriplegia, muscle weakness, hypertonia, spastic rigidity, and tendon hyperreflexia, often accompanied by positive pathological reflexes. Some patients may present with elevated blood ammonia levels.
8. Acquired hepatocerebral degeneration: This is a rare clinical syndrome characterized by mostly irreversible neurological impairments. It is an irreversible extrapyramidal syndrome caused by chronic liver disease. Manifestations include movement disorders such as Parkinsonism, ataxia, intention tremor, and chorea, as well as neuropsychological changes such as mental and behavioral abnormalities and intellectual deficits. fMRI is useful for its differential diagnosis.
9. Acute encephalopathy: This condition refers to the central nervous system manifestations of the pathophysiological process of acute-on-chronic liver failure. Depending on symptom severity, its clinical manifestations can include mild delirium, mental confusion, or even coma. This condition can be caused by various factors, including the loss of liver synthetic functions (e.g., clotting factor deficiency), accumulation of metabolic waste (e.g., ammonia), inflammatory response, and cerebral edema. The main difference between acute encephalopathy and HE lies in their etiology and severity. Acute encephalopathy causes a rapid loss of consciousness, accompanied by severe cerebral edema and intracranial hypertension, exhibiting fast progression and slow recovery. In contrast, HE is usually associated with severe chronic liver disease, exhibiting slow progression and fast recovery. Once liver failure is controlled to a certain extent, acute encephalopathy may evolve into HE.[9]
10. Cognitive impairment: A proportion of elderly individuals aged over 60 years have already developed cognitive impairment, which can easily lead to declines in memory, attention, learning, and sensorimotor function. Some of its manifestations may overlap with those of HE. Therefore, care should be taken during differential diagnosis in clinical practice.

Recommendation 1: HE is a neuropsychiatric disorder of varying clinical severity that encompasses a broad spectrum of manifestations. HE in cirrhosis can be clinically classified as MHE and Grade 1–4 HE (C1).

Recommendation 2: Patients with cirrhosis who develop HE (after excluding other possible causes) are considered to have decompensated cirrhosis. MHE is a subclinical manifestation of decompensated cirrhosis and does not fall under the decompensation phase (B1). Care should be taken in clinical practice to identify MHE, as well as first HE and recurrent HE (B1).

Recommendation 3: The manifestations of progressive decompensation in cirrhotic patients with HE are as follows: (1) the new onset of another decompensation event caused by secondary portal hypertension, including ascites, esophagogastric variceal bleeding,

SBP, hepatorenal syndrome-acute kidney injury, and/or jaundice (after excluding other possible causes); (2) recurrent HE (B1).

Recommendation 4: HE recompensation in cirrhosis implies that the etiology has been controlled or eliminated after treatment, with no occurrence of HE after discontinuation of lactulose/rifaximin for >12 months (B1).

Recommendation 5: In the presence of severe liver disease, Grade 2–4 HE can be diagnosed based on clinical manifestations and neurological examinations. PHES, neuropsychological tests, and neurophysiological tests are not recommended. MRI and other imaging examinations can be performed to exclude or confirm organic neurological diseases (B1).

Recommendation 6: MHE can be diagnosed in the absence of noticeable cognitive impairment, with the patient exhibiting normal neurological signs but displaying abnormalities in neuropsychological tests such as traditional paper-and-pencil PHES, the Stroop test, or the ANT (B1).

Recommendation 7: Grade 1 HE refers to mild cognitive impairment that can only be detected by relatives who have close contact with the patient, or to mild neurological abnormalities. Neuropsychological tests such as traditional paper-and-pencil PHES, the Stroop test, or the ANT can assist in the diagnosis (B1).

Recommendation 8: MHE is common in patients with cirrhosis, especially those with Child-Pugh class C cirrhosis or those who have undergone TIPS placement. MHE can impact the patient's prognosis and quality of life, necessitating careful screening (A1). Routine screening for MHE should be performed for patients with cirrhosis who engage in activities with high safety requirements, such as driving (B1).

Recommendation 9: Elevated blood ammonia is not an indicator of disease severity, prognosis, or HE grade. However, it has a high negative predictive value for HE diagnosis (C1). For the detection of blood ammonia, venous blood should be collected at room temperature and immediately sent for testing. The test should be completed within 30 m or within 2 h if the sample is centrifuged and refrigerated at 4°C (B1).

Recommendation 10: MHE and Grade 1 HE should be differentiated from cognitive impairment that is already present to some extent in a proportion of elderly individuals, which involves a decline in memory, attention, sensorimotor function, and other cognitive domains. Grade 3–4 HE should be differentiated from cerebrovascular accidents, alcohol poisoning, and metabolic encephalopathies (C1).

HE Treatment

Treatment for HE depends on its severity and is subject to stratified management (Fig. 1). The treatment principles include the elimination of precipitants, rapid restoration of acute neuropsychiatric abnormalities to baseline, and both primary and secondary prevention.[35,36]

Elimination of MHE/HE precipitants

Clinically, more than 90% of MHE/HE cases have precipitating factors, with the most common including infections, gastrointestinal bleeding, electrolyte and acid-base imbalances, high-protein diets, diuresis, large-volume paracentesis, and constipation. Eliminating these precipitants is the top priority in treatment, with infection being the most common precipitating factor.

For cirrhotic patients with HE, the source of infection should be actively identified. Even in the absence of apparent infection foci, increased intestinal bacterial translocation and elevated endotoxin levels can lead to a generalized inflammatory state, which can be mitigated by antibiotic treatment. Therefore, empirical antibiotic therapy should be initiated as early as possible when there are any signs of bacterial infection.

Gastrointestinal bleeding is another common precipitating factor for HE, often inducing HE on the day of or a few days after the onset of bleeding. Occult gastrointestinal bleeding can also precipitate HE. Hemostasis should be achieved using pharmacological, endoscopic, or vascular interventions, and any accumulated blood should be removed from the gastrointestinal tract.

Contraction alkalosis and electrolyte imbalances caused by excessive diuresis can lead to HE. In such cases, diuretics should be temporarily discontinued, and supplementation with fluids and albumin should be administered. Electrolyte imbalances (such as hypokalemia, hyperkalemia, hyponatremia, or hypernatremia) should also be corrected. For hypovolemic hyponatremia (especially when blood sodium levels are <110 mmol/L), patients should receive intravenous supplementation with hypertonic saline. For hypervolemic or euvolemic hyponatremia, selective vasopressin V2-receptor antagonists can be administered. For patients with Grade 3–4 HE, cerebral edema should be actively managed using 20% mannitol (250–1,000 mL/day, two to six times/day) alone or in combination with furosemide (40–80 mg/day).

Drug therapy

Elevated blood ammonia remains a key factor in the management of HE: Therefore, reducing the production and absorption of blood ammonia is crucial. The main drugs for lowering blood ammonia include:

1. *Lactulose*: Lactulose is converted into low-molecular-weight organic acids by the gut microbiota in the colon, leading to a decrease in intestinal pH. It also increases stool volume by promoting water retention, stimulates colon peristalsis, maintains smooth bowel movements, relieves constipation, and exerts a laxative effect while restoring the physiological rhythm of the colon. During HE, lactulose promotes the growth of intestinal acidophilic bacteria (e.g., lactic acid bacteria), suppresses proteolytic bacteria, and induces the conversion of ammonia into ammonium ions. Additionally, lactulose can reduce intestinal bacterial translocation and prevent SBP. Multiple studies have shown that lactulose not only improves neuropsychological test results in patients with MHE and enhances their quality of life, but also impedes the progression of MHE to OHE and prevents the recurrence of HE.[48] The use of lactulose in combination with other drugs can further improve its efficacy.[49–51]

   The usual dosage of lactulose is 15–30 mL, administered two to three times/day (with the dosage adjusted according to the patient's response). Patients should ideally pass soft stools two to three times daily. If necessary, a retention enema can be administered. Studies have found that stool classification is closely associated with both preventive and treatment outcomes in HE.[48–52] For patients who are intolerant to lactulose, lactitol or other ammonia-lowering drugs can be prescribed. Lactitol and lactulose have shown similar efficacy when delivered through enemas.[53]
2. Rifaximin-α: Small intestinal bacterial overgrowth is com-

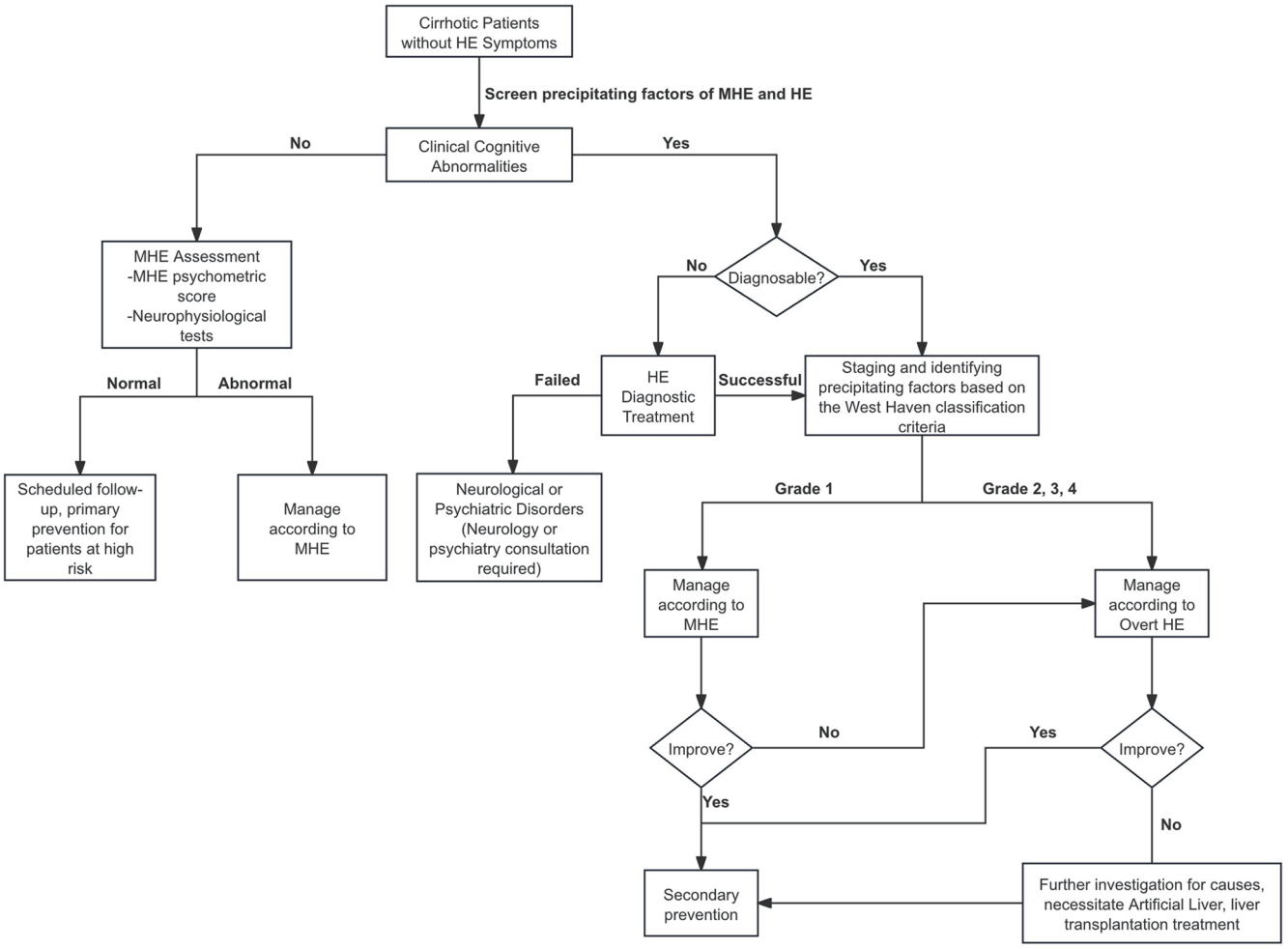

Fig. 1. Clinical diagnosis and treatment process of HE in cirrhosis. HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy.

mon among cirrhotic patients with MHE/HE. Compared to healthy controls and cirrhotic patients without HE, those with HE show higher abundances of Staphylococcaceae, Enterococcaceae, Porphyromonadaceae, and Lactobacillaceae.[54] Oral non-absorbable antibiotics can suppress the overgrowth of intestinal bacteria, reduce the quantity of ammonia-producing bacteria, and decrease the production and absorption of intestinal NH3. They can exert beneficial regulatory effects on the colon microbiota and promote the growth of beneficial bacteria such as bifidobacteria and lactic acid bacteria. Rifaximin-α has been shown to improve cognitive function in patients with cirrhosis, which is associated with intra- and inter-network functional connectivity in the brain.[55,56]

The dosage for rifaximin-α is 800–1,200 mg/day, three to four times/day, administered orally.[57] A meta-analysis revealed that 600 mg of rifaximin-α taken two times/day is more effective at preventing the progression from MHE to OHE. The treatment course generally lasts up to six months; further research is needed for treatment durations longer than one year.

Other antibiotics, such as neomycin, metronidazole, vancomycin, and paromomycin, are rarely administered due to their side effects and poor efficacy.

3. Ornithine aspartate: This drug can be administered orally or intravenously and is effective for both OHE and MHE. It can be given alone or in combination with lactulose. Ornithine aspartate reduces ammonia levels by promoting the hepatic urea cycle and glutamine synthesis,[58] thereby improving liver function. It can also prevent cirrhosis-associated sarcopenia, which enhances the ammonia removal capacity of skeletal muscles. This, in turn, can significantly decrease patients' fasting and postprandial blood ammonia levels, improve their HE grades and neuropsychological test results, shorten the length of hospital stay, and enhance their quality of life.[59,60]

Microecological preparations: These include probiotics, which can promote the growth of beneficial bacterial strains while inhibiting the growth of harmful bacteria such as urease-producing bacteria. They can also improve the nutritional status of intestinal epithelial cells, reduce intestinal permeability, decrease bacterial translocation and endotoxemia, and enhance hyperdynamic circulation. Additionally, these preparations can alleviate inflammation and oxidative stress in hepatocytes, thereby increasing ammonia clearance in the liver. Probiotics and lactulose have been shown to achieve comparable efficacy in improving MHE test results. The combined application of probiotics and lactulose can enhance the efficacy of lactulose in alleviating MHE.[55,61]

Application of sedatives: HE is associated with the

upregulation of inhibitory GABA receptors and excitatory aspartate-glutamate receptors, leading to an imbalance between inhibitory and excitatory signals. In theory, the use of flumazenil, bromocriptine, levodopa, and acetylcholinesterase inhibitors should all be feasible. For patients with HE precipitated by benzodiazepines or opioids, detoxification with flumazenil or naloxone can be attempted. However, due to limited evidence supporting the use of bromocriptine and levodopa in the treatment of HE, their use is not recommended.

Naloxone: A meta-analysis revealed that treating HE with a combination of ornithine aspartate and naloxone resulted in lower blood ammonia and total bilirubin levels compared to the control group, a shorter time to regain consciousness, significant improvements in NCT and DST, and no apparent adverse reactions. The administration of naloxone, either alone or in combination with drugs such as lactulose, has been shown to promote the recovery of consciousness in patients with hepatic encephalopathy.[62,63]

Propofol: A comparative study on the efficacy and adverse reactions of propofol involving 40 HE patients with mania demonstrated that propofol was safer and more effective than diazepam at controlling symptoms of HE with mania. Compared to midazolam, propofol resulted in a shorter recovery time and a faster recovery of cognitive function. The use of propofol during endoscopic procedures did not appear to exacerbate MHE or OHE.[64,65] However, it is worth noting that propofol has a short duration of action, and one of its adverse reactions is respiratory depression. Therefore, careful monitoring of oxygen saturation and respiratory rate is required when using propofol.

Benzodiazepine sedatives: Due to the high incidence of anxiety, depression, and painful conditions, as well as disruptions in their sleep-wake cycle, patients with cirrhosis often have a history of using sedatives, hypnotics, or analgesics, which can precipitate HE and carry the risk of aggravating liver damage. Flumazenil, a benzodiazepine antagonist, has been shown to have a short-term beneficial effect on hepatic encephalopathy in a randomized, double-blind, controlled trial involving patients with cirrhosis.

Other therapeutic drugs: *Arginine*: Arginine hydrochloride is weakly acidic and can be used to treat HE in patients with alkalosis (blood pH > 7.45). Clinicians should closely monitor blood gas analysis during its use and remain vigilant for acidosis caused by overdose. Arginine hydrochloride has limited efficacy in the treatment of HE and is not routinely administered in clinical practice.

Drugs for eradicating Helicobacter pylori (*Hp*): Studies have found that *Hp* infection may be associated with HE. Once HE has stabilized, *Hp* eradication should be performed at the appropriate time to facilitate the treatment and prevention of HE.[66,67]

Traditional Chinese medicine (TCM): In TCM, HE is thought to be predominantly caused by blazing heat-toxin, pericardial heat invasion, excessive internal phlegm turbidity, and phlegm-mist affecting the heart orifices. Therefore, HE should be treated using brain-awakening and orifice-opening methods. Chinese patent medicines or decoctions, such as Angong Niuhuang pills, Zixue pills, and Xingnaojing injection, are often used to achieve orifice-opening, brain-awakening, phlegm-resolving, heat-clearing, and detoxification effects.[68] In accordance with the ammonia hypothesis and the intestinal endotoxin hypothesis of HE, the "organ-dredging, orifice-opening" theory in TCM has been widely employed in the prevention and treatment of HE.[69,70] The most representative treatment is the retention enema using decoctions containing Da Huang (Radix et Rhizoma Rhei), which has shown effectiveness in relieving constipation, promoting the excretion of intestinal toxic substances, reducing blood ammonia levels, and shortening the duration of coma.

Nutritional support therapy: Conventionally, it has been believed that dietary protein intake should be limited in patients with cirrhosis, especially those with MHE and HE. However, recent findings suggest that approximately 80% of patients with cirrhosis suffer from malnutrition. Therefore, long-term protein-restricted diets may exacerbate malnutrition in cirrhosis, resulting in reduced muscle mass, which can increase patients' susceptibility to MHE and HE, while also affecting their prognosis and the occurrence of various complications.[71,72] Consequently, accurate assessment of patients' nutritional status and early nutritional intervention can improve their quality of life, reduce the incidence of various complications, and prolong survival. For patients with decompensated cirrhosis, especially those with sarcopenia, we recommend assessing their nutritional status every eight to twelve weeks.[73]

Energy intake and pattern: The ideal daily energy intake based on body weight should be 35–40 kcal/kg (1 kcal = 4.184 kJ). For patients with concomitant ascites, pleural effusion, and edema, assessment can be performed using estimations of pure body weight. Prolonged hunger should be avoided, and patients are encouraged to eat smaller, more frequent meals, with an extra meal at night containing at least 50 g of complex carbohydrates. Daytime fasting should be limited to no more than 3–6 h. Eating breakfast can improve attention and operational capacity in patients with MHE. Smaller, more frequent meals and an extra meal before bedtime can help increase muscle mass.[74] Based on each patient's condition, a personalized approach should be adopted to provide recommendations on the timing of additional snacks (early breakfast vs. late-night snacks) and the types of snacks (e.g., protein bars, rice balls, yogurt, etc.). For patients with concomitant diabetes, the onset of HE may affect their self-management of blood glucose levels[75]; therefore, more care should be taken to avoid prolonged fasting and the occurrence of hypoglycemia.

Protein: Intravenous infusion of albumin not only improves liver function but also enhances cognitive function and psychosocial quality of life.[76] The guidelines of the European Society of Parenteral and Enteral Nutrition recommend a daily protein intake of 1.2–1.5 g/kg. The daily dietary protein intake for obese or overweight patients with cirrhosis can be adjusted according to their individual condition. Plant protein contains less methionine and cysteine (sulfur-containing amino acids) and more ornithine and arginine. Therefore, it can promote ammonia removal through the urea cycle and is less likely to induce HE. Patients with recurrent or persistent HE can consume 30–40 g of plant protein per day.

Protein supplementation for patients with HE should follow these principles: Patients with Grade 3–4 HE should be prohibited from receiving enteral protein supplementation but can receive intravenous supplementation of human albumin. Patients with Grade 1–2 HE should limit oral protein intake to 20 g/day during the first few days, which can then be increased by 10–20 g every two to three days as their symptoms improve, until reaching 1 g/kg based on pure body weight. Plant protein is preferred over animal protein. Patients with recurrent HE should be encouraged to consume smaller, more frequent meals; protein intake should be tailored to each individual, and the amount of protein should be gradually increased.

Branched-chain amino acids (BCAAs): Patients with Grade 3–4 HE should receive parenteral nutritional supplements rich in BCAAs (valine, leucine, and isoleucine), which

improve HE outcomes.[77] Although many studies have found that BCAAs do not directly contribute to reducing mortality in HE, patients who can tolerate a normal protein diet or long-term BCAA supplementation may benefit from improved nutritional status over time. In addition to supporting glutamine synthesis in the brain and muscles and promoting ammonia detoxification and metabolism, BCAAs can also reduce the excessive influx of aromatic amino acids into the brain.[13,78,79] When administered in combination with lactulose, BCAAs can improve the prognosis of HE.

Other micronutrients: HE-induced mental symptoms may be related to deficiencies in trace elements and water-soluble vitamins, especially thiamine. Zinc deficiency can lead to elevated ammonia levels and malnutrition.[80]

Artificial liver therapy: When liver failure is complicated by HE, artificial liver therapies, such as blood purification, can be performed alongside medical treatments to remove inflammatory factors, endotoxins, blood ammonia, bilirubin, and other substances to some extent. Artificial liver modalities used to alleviate HE include the double plasma molecular adsorption system, plasma diafiltration, and the molecular adsorbent recirculating system.[81]

Liver transplant: Recurrent HE associated with liver failure or end-stage liver disease is an indication for liver transplantation.[82,83]

Full-course management: HE patients should undergo repeat examinations of blood ammonia, blood biochemistry, complete blood count, coagulation function, alpha-fetoprotein, abdominal ultrasound, and other relevant tests every three months. Long-term clinical management plans should be formulated for patients with recurrent HE.

HE nursing: The "Three preventions" involve preventing the patient from wandering and getting lost, preventing the patient from hurting others, and preventing the patient from self-harm. "Three protections" include the use of bed guard rails, restraint belts (after obtaining written informed consent from family members), and table tennis gloves. Care should be taken to assess the patient's frailty index and mobility to prevent secondary injuries due to falls. HE patients should be closely observed for changes in personality and behavior, consciousness and mental state, as well as neuropsychiatric symptoms and signs. The dietary structure of patients should be monitored, particularly their daily protein intake, with careful recording of both intake and excretion.

Recommendation 11: HE and MHE precipitants (such as infection, gastrointestinal bleeding, electrolyte imbalances, etc.) should be actively identified and eliminated (A1). For recurrent HE without clear precipitants, emphasis should be placed on screening for abnormal PSS (B1).

Recommendation 12: Lactulose can improve the quality of life and survival rate of cirrhotic patients with HE/MHE. The recommended dose is 15–30 mL, taken two to three times/day. Patients should ideally pass soft stools two to three times/day (A1).

Recommendation 13: Rifaximin-α shows good efficacy in the treatment of decompensated cirrhosis and can improve the quality of life and survival rate of cirrhotic patients with HE/MHE. The recommended dose is 800–1,200 mg/day, administered orally two to three times/day, with a treatment course of up to six months (B1).

Recommendation 14: Ornithine aspartate can reduce blood ammonia levels and shorten the hospital stay of HE patients, thereby exerting a therapeutic effect on HE (B1). BCAAs can serve as an alternative therapy or long-term nutritional intervention (B2).

Recommendation 15: For patients with severe mental abnormalities (e.g., those with mania, patients who pose a danger to others, and uncooperative patients), benzodiazepine sedatives or propofol can be administered to control symptoms after family members have been informed of the associated risks. Such medications should be given via slow intravenous infusion at reduced doses (B1).

Recommendation 16: Cirrhotic HE patients complicated by alkalosis can be treated with drugs such as arginine hydrochloride (C2).

Recommendation 17: Care should be taken to screen for malnutrition in patients with cirrhosis, and nutritional assessments should be performed every eight to twelve weeks. A reasonable diet and nutritional supplements (including smaller, more frequent meals and one extra meal before bedtime) can help improve patients' quality of life and prevent the recurrence of MHE/HE (B1).

Recommendation 18: Patients with Grade 2–4 HE should avoid excessive enteral protein supplementation, particularly from animal sources, but can receive intravenous supplementation of human albumin. Patients with MHE and Grade 1 HE should limit oral protein intake to 20 g/day during the first few days, which can then be increased by 10–20 g every two to three days to a potentially tolerable amount as their symptoms improve (C2)**.**

Recommendation 19: The double plasma molecular adsorption system, plasma diafiltration, molecular adsorbent recirculating system, and other methods can reduce blood ammonia, inflammatory factors, bilirubin, etc., and improve the clinical symptoms of HE (B2). Liver transplant can be considered for recurrent HE with liver failure or end-stage liver disease (B1).

Prevention

Primary prevention

The primary prevention of HE applies to patients at risk of developing HE but who have not yet developed it. The goal is to prevent the onset of MHE/OHE, reduce hospital stays related to OHE, improve quality of life, and enhance survival rates. In addition to closely monitoring the condition of patients with cirrhosis, liver failure, and post-TIPS placement for any changes, regular MHE screening using neuropsychological and neurophysiological tests should also be performed. Patients diagnosed with MHE should be treated immediately to prevent progression to OHE.

The focus of primary prevention is on treating the underlying liver disease and administering nutritional interventions. Etiological treatment can alleviate liver inflammation and fibrosis, reduce portal vein pressure, and prevent or reverse the progression of cirrhosis, which is crucial for the prevention and control of HE and cirrhosis-related complications. This approach can reduce the incidence of cognitive impairment, improve liver function, and enhance quality of life. Elderly patients[84] with lower brain reserves, as well as those with baseline cognitive impairment, may derive greater benefits. Patients at risk of HE due to cirrhosis, liver failure, or post-TIPS placement should regularly

undergo neuropsychological and neurophysiological tests to screen MHE.

Precipitating factors of HE, including infection, gastrointestinal bleeding, electrolyte imbalances, acid-base imbalance, and constipation, should be actively treated and prevented. Large-volume paracentesis or diuresis should be avoided. Patients should consume smaller but more frequent meals and avoid excessive intake of high-protein foods. There is currently a lack of clinical evidence supporting the role of ammonia-lowering drugs in primary prevention.

Secondary prevention

After the first episode of OHE, patients are at high risk for recurrence and therefore require secondary prevention. The focus of secondary prevention is on enhancing health education for patients and their family members, controlling elevated blood ammonia levels, and regulating gut microecology.

Health education for patients and their family members should be strengthened. They should be informed about the potential hazards of MHE and made aware of the precipitants of HE. Under the guidance of a physician, patients should adjust their diets rationally according to their individual conditions. Large one-time intakes of high-protein foods should be avoided during HE episodes. Lactulose, rifaximin, and ornithine aspartate can be used as first-line prophylactic medications. Patients should be guided toward self-management of their health. Family members should be instructed to closely monitor the patient for behavioral and personality changes, as well as to identify any decline in the patient's attention, memory, and orientation. Every effort should be made to achieve the early discovery, diagnosis, and treatment of HE.[85]

TCM

Etiological treatment can alleviate liver fibrosis, lower portal vein pressure, and prevent or reverse the progression of liver fibrosis and cirrhosis. "Dual therapy," which combines etiological treatment with hepatic anti-fibrotic treatment, can lead to better outcomes.[58]

For patients with cirrhosis who cannot undergo etiological treatment, hepatic anti-fibrotic treatment, prevention and treatment of intestinal bacterial translocation, protection of endothelial cell function, and correction of coagulopathies can also help alleviate the progression of complications related to portal hypertension in cirrhosis.[59]

There are currently no Western hepatic anti-fibrotic drugs with clinically proven effectiveness. Therefore, this is an area where TCM plays a crucial role.[54,57,60,86] According to the results of major national infectious disease projects conducted during the 12th and 13th Five-Year Plans, "dual therapy" that combines anti-hepatitis B virus therapy with hepatic anti-fibrotic therapy can improve and reverse cirrhosis. TCM treatments, such as Fuzheng Huayu tablets/capsules, Anluo Huaxian pills, and Biejia Ruangan tablets, can strengthen the body, replenish deficiencies, activate blood circulation, and reduce stasis. This approach exerts hepatic anti-fibrotic effects, improves liver function, enhances immune function, reduces hepatic circulatory disorders, and alleviates portal hypertension. As a result, these medications can effectively alleviate and prevent HE in cirrhosis.[87–92]

Post-TIPS HE prevention

Owing to continuous advancements in TIPS management, there are significant variations in the incidence of postoperative HE (7–61%).[93] Strengthening pre-, intra-, and postoperative management can effectively reduce the incidence of post-TIPS HE.

HE is not an absolute contraindication for TIPS in cirrhotic patients at high risk of variceal bleeding.[94] The occurrence of post-TIPS HE is associated with factors such as advanced age (>70 years),[95] preoperative nutritional status, liver function,[96] spontaneous portal vein shunts,[97] hyponatremia,[98] comorbid diabetes, obesity,[99] renal insufficiency,[100] and medications. Pre-TIPS malnutrition or sarcopenia is an independent predictor of poor prognosis post-TIPS.[101]

Post-TIPS prevention: Patients are at high risk of HE in the first month to one year after surgery. The risk of HE appears to decrease as the patient's muscle mass improves and precipitating events diminish. The onset of HE can be prevented by administering lactulose, rifaximin, or ornithine aspartate.[86,102]

Recommendation 20: Primary prevention is essential for patients at high risk of MHE or HE (B1). The focus of MHE/HE primary prevention is on targeting disease etiology, controlling or reversing the course of cirrhosis, and providing nutritional interventions (C1).

Recommendation 21: "Dual therapy", which combines anti-hepatitis B virus therapy with hepatic anti-fibrotic therapy, can alleviate and reverse the course of cirrhosis. TCM products such as Fuzheng Huayu tablets/capsules, Anluo Huaxian pills, and Biejia Ruangan tablets can exert hepatic anti-fibrotic effects and improve liver function, thus proving effective in alleviating cirrhosis (A1).

Recommendation 22: Once HE is under control, secondary prevention becomes necessary (A1). The focus of secondary prevention is on providing health education to patients and their family members, offering appropriate nutritional support, and reducing recurrent HE episodes (B1). Family members should be instructed to closely monitor the patient for sleep disorders and decreased attention (C1). Lactulose, rifaximin, or ornithine aspartate can serve as first-line drugs (C1). The dose of rifaximin can be reduced, if needed, to 400–600 mg/day (B1).

Recommendation 23: Lactulose, rifaximin, or ornithine aspartate can reduce the risk of post-TIPS HE (C1).

Problems to be Resolved

(1) Research on the application of neuroimaging biomarkers and fMRI in the diagnosis and prognosis of MHE/HE. (2) Research and application of novel methods, such as serum biomarkers and neuropsychological tests, for the early diagnosis of MHE. (3) Safety and efficacy of low-dose (400–600 mg/day) long-term (>12 months) treatment with rifaximin-α in the primary and secondary prevention of MHE and Grade 1 HE. (4) Research on novel treatment methods for HE, including fecal microbiota transplantation for the prevention and treatment of HE, stem cell therapy for HE, and new therapeutic targets for HE.

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Conflict of interest

JJ and LW have been Executive Associate Editors of *Journal*

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