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Review Article

Comprehensive Insights into hepatic encephalopathy pathophysiology, epidemiology, diagnosis, and management

Manar M. Esmail[a*], Noha M. Saeed[a], Diana M.F. Hanna[b], Haidy E. Michel[b], Reem N. El-Naga[b], Samar S. Azab[b]

[a]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt*
[b]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt*

ABSTRACT

Hepatic encephalopathy (HE) is a prevalent and potentially fatal complication arising from both chronic liver disease and acute liver failure, significantly impacting patient outcomes. This condition encompasses a wide spectrum of neuropsychiatric disorders, ranging from mild cognitive impairment to severe manifestations such as disorientation, confusion, and even coma. The clinical implications of HE are profound, as it not only contributes to increased morbidity and mortality rates but also imposes a substantial economic burden on healthcare systems due to frequent hospitalizations and prolonged treatment courses. This review aims to provide a comprehensive analysis of the latest classifications of HE, elucidating the underlying mechanisms and physiological processes that lead to neurological deterioration in patients with advanced liver disease. Furthermore, it will explore current diagnostic methodologies and management strategies, including established therapeutic options such as lactulose and rifaximin, as well as emerging treatment modalities that show promise in improving patient outcomes. By synthesizing recent findings and clinical practices, this article seeks to enhance understanding of HE and inform future research directions aimed at optimizing care for affected individuals.

Keywords: *Ammonia; Hepatic encephalopathy; Experimental models; Inflammation; Oxidative stress; Treatment strategies.*

***Correspondence** | Manar M. Esmail; Department of Pharmacology and Toxicology, Faculty of Pharmacy, Egyptian Russian University, Cairo, Egypt. Email: manar-esmail@eru.edu.eg

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1. Introduction

Hepatic encephalopathy (HE) is a medical disorder where the brain's functioning is disrupted as a result of inadequate liver function. This condition presents with a range of neurological or mental abnormalities, varying from mild changes to a state of coma **[1]**. It is commonly classified into three types: type A, which results from acute liver failure (ALF); type B, which results from portosystemic bypass or shunting; and type C, which results from cirrhosis **[2]**. From an epidemiological standpoint, HE is likely the most common consequence of cirrhosis that results in hospitalization and recurrent readmission **[3]**. Consequently, the healthcare burden and expenses related to the management of HE are substantial and growing. Studies have shown that ammonia continues to play a crucial role in the development of HE. Nevertheless, it is well-established that both systemic and neuro-inflammation, together with oxidative stress and

cellular senescence, play a significant role in this context. This is in addition to the disruption in the permeability and function of the blood-brain barrier (BBB). These abnormalities lead to neurological dysfunction and offer prospective targets for therapeutic intervention **[4]**.

2. Classification

According to (AASLD/EASL) standards, the classification of HE should be based on four primary factors: (1) the disease cause, (2) the severity of symptoms, (3) the disease's development over time, (4) the presence of triggering events, (5). The use of this four-axis hierarchical classification system guarantees appropriate patient care and uniform execution of observational research and clinical trials **[5, 6]**.

2.1. The underlying etiology of HE

Regarding etiology, there are three classifications for HE: A, B, and C. Type A, which occurs as a result of ALF, type B, which occurs as a result of portosystemic bypass or shunting, and type C, which occurs as a result of cirrhosis, which is the predominant risk factor for HE **[2]**.

2.2. The degree of severity of the disease symptoms

The intensity of HE symptoms affects both the prognosis of the condition and the therapeutic strategies pursued **[7]**. The severity of HE is classified using two types: the International Society of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) grade and the West Haven criterion (WHC). The ISHEN grade **(Fig. 1B)** differentiates between two categories, covert and overt. Covert HE is distinguished by changes in executive functioning resulting from brain damage. Patients exhibiting covert HE display minimal to no discernible clinical manifestations, and hospitalization is unnecessary for those affected **[8]**. On the other hand, overt HE is marked by disruptions in temporal and spatial perception or the asterixis' presence **[9]**.The clinical manifestations of overt HE are easily noticeable and lead to the need for hospitalization **[8]**. The classification by the WHC Organization includes six phases, which are unimpaired, minimum, and grades I to IV **(Fig. 1A).** Individuals who have an unimpaired grade do not exhibit any clinical or subclinical symptoms of HE **[5, 9]**. Minimal hepatic encephalopathy (MHE) is the least severe kind. The disease begins has a specific form and it reveals modest changes in cognitive capabilities that can be recognized by psychometric testing **[10]**. Grade I HE is characterized by cognitive and/or behavioral decline in patients' performance on clinical assessments. Grades II to IV categorize overt HE, with increasing severity from asterixis, to gross disorientation, and coma in grade IV **[5]**.

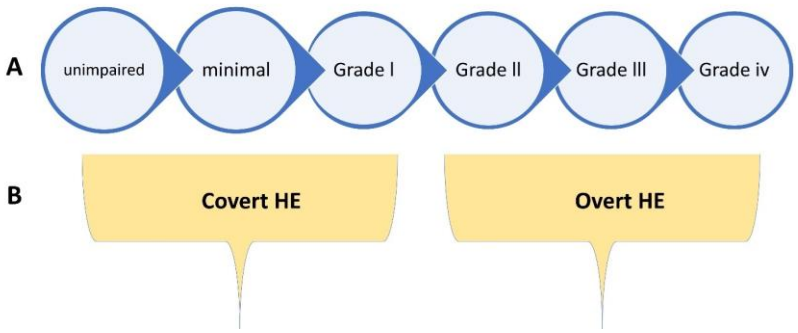

Fig. 1. Classification of HE: (A) WHC grade, (B) ISHEN grade

2.3. Disease's development over time

The progression of HE is categorized into three distinct periods: episodic, recurring, and permanent. During an episodic interval, patients encounter episodes of hepatic HE that are separated by more than 6 months. Patients experiencing recurrent HE endure episodes that occur within a timeframe of 6 months or fewer. In case of permanent, patients commonly experience continuous behavioral changes that are accompanied by recurring episodes of overt HE **[7, 8, 9]**.

2.4. The presence of triggering events

Precipitating factors are crucial for diagnosing, verifying, and establishing the appropriate treatment for both acute and recurrent HE. Based on the presence of precipitating variables, HE is categorized as spontaneous or precipitated. Understanding and addressing the causes, like infections and electrolyte imbalance, that trigger a certain incident could help in preventing its recurrence **[7]**.

3. Epidemiology

According to one population-based study, more than 40% of people diagnosed with cirrhosis may experience the onset of HE within a span of 5 years **[11]**. According to a long-term cohort-based study using data from the US Commercial Medical Claims Database, approximately 202,000 people experienced HE in 2018 **[12]**. Another study discovered that out of more than 9000 patients recently diagnosed with cirrhosis, approximately one-third had decompensated cirrhosis, and within this group, 51% had HE **[13]**. The prevalence of overt HE at the moment of diagnosis of cirrhosis is estimated to be between 10% and 14% in general cases **[14]**, 16% and 21% in cases of decompensated cirrhosis **[15]**, and 10% and 50% in patients who have undergone a transjugular intrahepatic portosystemic shunt (TIPS) procedure **[16]**. The prevalence of MHE in patients with cirrhosis varies between 20% and 80% **[17, 18, 19]**. The probability of experiencing the initial occurrence of overt HE is around 25% during a span of 5 years following the diagnosis of cirrhosis. This likelihood is contingent upon the existence of risk factors such as MHE, grade 1 HE, diabetes, hyponatremia, and hepatitis C **(20, 21, 22)**. Patients who have experienced a previous episode of overt HE have a 42% chance of experiencing a recurrence within one year. Similarly, patients who have recurrent overt HE have a 46% chance of experiencing another episode within 6 months, even with normal therapy **[23, 24]**. Patients who have cirrhosis and experience mild cognitive dysfunction or minor electroencephalogram slowing have a one-year probability of approximately 33% to get an episode of overt HE **[23, 25]**.

Egypt is recognized as having one of the highest rates of hepatitis C virus (HCV) infections worldwide, which significantly contributes to the development of liver cirrhosis and hepatocellular carcinoma. The progression to end-stage liver disease is characterized by synthetic dysfunction and portal hypertension, resulting in various complications, including HE. Studies indicate that HE affects approximately 30% to 45% of patients with cirrhosis, with an incidence rate of 14.3% specifically among those with cirrhosis related to HCV **[26]**.

HE, which is a result of significant liver dysfunction, is influenced by the seriousness of the underlying hepatic condition, its clinical progression, and the management of the condition. Patients with cirrhosis who experience overt HE have a relatively short median survival time of a few months. Additionally, they have a 2-fold higher risk of mortality within one year compared to cirrhotic patients who do not have HE **[14, 27]**.

The healthcare resource needs of patients with HE pose a problem from a public health

standpoint. During the period of 2010–2014, hospitalization increased by 30% due to HE **[3]**. Moreover, the burden of chronic liver disease (CLD) and cirrhosis is on the rise in the majority of countries, mostly attributed to an increase in cirrhosis caused by non-alcoholic steatohepatitis. As a result, a higher number of cases with HE is expected in the future.

4. The bidirectional relationship between the liver and the brain

The bidirectional relationship between the liver and the brain is a complex interplay that significantly influences both organ systems. This relationship is characterized by various communication pathways, including neural, hormonal, and immune-mediated interactions, which facilitate the exchange of information and metabolic signals between the two organs. One of the primary mechanisms of communication is through the autonomic nervous system, where the liver is innervated by both sympathetic and parasympathetic fibers. This anatomical arrangement allows for direct neural communication, enabling the liver to relay metabolic information to the brain and vice versa **[28]**. For instance, the liver's role in glucose homeostasis is crucial for brain function, as the brain relies on a steady supply of glucose for energy. Disruptions in liver function can lead to unstable glucose levels, which may result in cognitive impairments and neurological symptoms, such as those observed in HE **[29, 30]**. Moreover, the liver-brain axis is also influenced by inflammatory processes. Chronic liver diseases often lead to systemic inflammation, which can affect brain function and contribute to neuroinflammation. This inflammation is mediated by various cytokines and other inflammatory markers that can cross the blood-brain barrier, impacting neuronal health and function **[31, 32]**. Furthermore, the gut microbiome, which interacts with both the liver and the brain, plays a pivotal role in this axis by modulating inflammatory responses and metabolic processes **[33, 34]**. The implications of this bidirectional relationship are profound, particularly in the context of neurodegenerative diseases. Research has shown that liver dysfunction can exacerbate conditions such as Alzheimer's disease and other forms of dementia, suggesting that maintaining liver health is essential for cognitive function **[35]**. Conversely, neurological conditions can also impact liver metabolism, as seen in cases of traumatic brain injury, where brain damage can lead to alterations in hepatic lipid metabolism **[36]**.

5. Pathophysiology

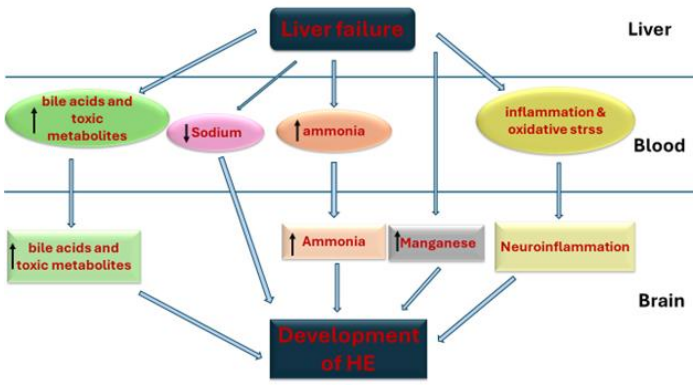

Fig. 2. Pathophysiology of hepatic encephalopathy, the development of essential HE is closely linked to hyperammonemia, oxidative stress, and inflammation. Additionally, abnormal signaling of bile acids has recently been identified as a contributing factor in the pathogenesis of hepatic encephalopathy through neuronal dysfunction and blood-brain barrier permeability. Furthermore, Manganese, a cofactor in glutamine synthetase, is involved in ammonia elimination. In advanced liver illness, it accumulates in the basal ganglia, leading to psychomotor impairment. Moreover, Hyponatremia is associated with a rise in the risk of developing HE

Neurological impairment and cognitive decline caused by liver failure are the outcome of blood-derived substances that affect permeability and compromise the integrity of the blood-brain barrier. In the condition of cirrhosis, substances that are typically blocked from crossing the BBB can enter the brain, such as inflammatory cytokines, ROS, and bile acids. Additionally, molecules like ammonia, which can ordinarily pass through the BBB, excessively accumulate in the brain. This leads to the activation of pathophysiological pathways and the occurrence of detrimental effects **(Fig. 2)**.

5.1. Ammonia

The development of HE involves multiple factors and is currently not fully comprehended. However, Ammonia is commonly recognized as a substantial contributor to disease progression **[1]**. The gastrointestinal tract is the principal source of ammonia, resulting from the breakdown of food protein through the process of amino acid deamination. Additionally, urease-producing bacteria within the gastrointestinal tract convert urea into ammonia, further contributing to its systemic levels **[37]**. Under normal physiological conditions, the liver effectively regulates ammonia levels in the bloodstream through the urea cycle. This metabolic pathway, which involves a series of liver-specific enzymes, converts ammonia into urea, a less toxic compound that can be safely excreted by the kidneys. Consequently, with CLD, the liver's capacity to eliminate ammonia is significantly impaired, leading to the development of hyperammonemia. Elevated blood ammonia levels can readily cross the BBB, leading to detrimental effects on brain function **[38]**. Extensive evidence supports the notion that elevated levels of ammonia in the brain are linked to disruptions in metabolic processes in astrocytes and neurons, activation of microglia, and the development of cerebral edema. These factors are all believed to have a role in the development of HE **[39]**.

5.2. Inflammation and oxidative stress

Systemic inflammation plays a pivotal role in the pathogenesis of HE, contributing to both the development and exacerbation of neurological dysfunction. In the context of liver disease, there is often a notable increase in pro-inflammatory cytokines, including interleukin-6 **(**IL-6) and tumor necrosis factor-alpha (TNF-α). Circulating inflammatory cytokines can activate the endothelial cells of the BBB to release inflammatory mediators. Once in the brain, these mediators can activate astrocytes and microglia to produce additional cytokines. This cascade of events contributes to cerebral inflammation and exacerbates neuroinflammatory processes **[40]**.

Furthermore, research indicates that peripheral cytokines may influence brain function through indirect pathways involving tissues innervated by the autonomic and peripheral nervous systems. In such scenarios, peripheral cytokines can transmit signals directly to the brain via the vagus nerve, thereby promoting inflammation. Moreover, pro-inflammatory cytokines can cross the BBB through active transport mechanisms or enter regions of the brain that lack a functional BBB, further contributing to cerebral inflammation **[41]**.

Oxidative stress, a widespread occurrence in cirrhosis, can impair the permeability of the BBB due to the increased reactivity of reactive oxygen species (ROS) with lipids, proteins, and DNA **[1]**. Furthermore, Increased levels of ROS can cause cellular damage in both astrocytes and neurons, while also activating microglia, which further intensifies the neuroinflammatory processes associated with HE **[42]**. Moreover, elevated ammonia levels have been shown to induce neutrophil dysfunction, which is characterized by impaired phagocytic activity and

the generation of ROS. The combination of oxidative stress and hyperammonemia creates a vicious cycle that intensifies the neurotoxic effects on the brain, leading to cognitive impairments and other neurological deficits **[43, 44]**.

5.3. Bile acids

Bile acids are metabolites derived from cholesterol and are synthesized in the liver by cytochrome P450 enzymes. During acute and chronic liver injury, there is an accumulation of bile acids within the liver due to impaired transport and metabolism. This buildup can contribute to further hepatic damage and then overflow into the systemic circulation **[45]**. Serum accumulation of bile acids can disrupt and penetrate the BBB via two established pathways. First, they can be transported across the BBB through bile acid transporters located in the choroid plexus. Second, bile acids can diffuse across the BBB, particularly when the barrier becomes increasingly permeable due to pathological conditions associated with liver disease **[46]**. Once bile acids accumulate in the brain can contribute to neuro-inflammation, exacerbating neurological symptoms associated with HE **[47, 48]**.

5.4.Metals

The enzyme glutamine synthetase (GS) functions to remove ammonia from the body, and manganese is an essential cofactor for its functioning. The biliary system is normally responsible for excreting manganese. But in people with extensive liver disease, this mechanism is impaired, and manganese builds up in the basal ganglia. This buildup is believed to cause the psychomotor impairment seen in HE **[49, 50]**. Moreover, copper is typically eliminated by the liver, and its levels in the bloodstream rise during liver failure. The accumulation of copper and manganese in liver failure poses significant risks to cerebral function. The mechanisms underlying their neurotoxic effects include oxidative and nitrosative stress, glutamate receptor-mediated excitotoxicity, and neuroinflammation. Furthermore, copper and manganese can also influence iron metabolism in the brain. The dysregulation of iron homeostasis can lead to iron deposition, which is known to contribute to oxidative stress and neurodegeneration. The interaction between these metals and iron can create a vicious cycle of toxicity, exacerbating the neurotoxic effects observed in HE **[51]**. Additionally, the antioxidant enzyme superoxide dismutase requires zinc as a cofactor. Researchers have discovered that patients with HE frequently exhibit a deficiency in zinc levels **[52]**.

6. Diagnosis

It is imperative to differentiate between the occurrence of asterixis and tremulousness, as these symptoms might occasionally be linked to alcohol withdrawal or misuse. Various tests are used to diagnose HE.

6.1. Ammonia level

Measurement of serum ammonia levels is a commonly employed biochemical test in patients at various stages of HE. It is crucial to note that there is no strong evidence that serum ammonia levels are significantly correlated with HE severity. Additionally, hyperammonemia could not be utilized as a diagnostic tool for HE on its own. The serum ammonia level, on the other hand, has the potential to be a predictor of mortality and hospitalization linked to HE **[53]**.

6.2. Liver function tests

Abnormalities in hepatic function test levels are frequently observed as a result of underlying liver disease. This can be observed as increased concentrations of bilirubin, Aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and

prothrombin time **(13)**.

6.3. 3-nitrotyrosine and interleukin-6 levels

A cohort study demonstrated that the measurement of 3-nitro-tyrosine level in serum is a convenient and efficient method for identifying individuals with MHE, and this method has a high level of sensitivity and specificity **[54]**. It was shown that cirrhotic patients with MHE had a serum IL-6 level that was more than double that of patients without MHE **[55]**.

6.4. PHES

PHES measures psychomotor speed as well as visuospatial ability. Five tests make up the PHES: two that measure number connections, one that measures serial dotting, one that measures digit symbol, and one that measures line tracing **[56]**. However, the availability of the test is limited due to the substantial time required for its administration, ordering, and interpretation by a psychologist **[55, 57]**.

6.5. Electroencephalogram (EEG)

An electroencephalogram (EEG) is a technique used to assess the electrical activity in the cortex. The EEG usually shows a decrease in the normal rhythmic activity with triphasic waves and anomalies that are more pronounced in the front part of the brain in cases with HE. These deviations can be seen in overt HE or MHE and are associated with the intensity of HE and the severity of cirrhosis **[58]**. EEG can be used to exclude the presence of epilepsy, which is particularly valuable in cases where patients exhibit aberrant movements or are in a state of coma. A proper diagnosis requires the expertise of trained neurophysiologists to conduct EEG readings **[59, 60]**. In addition, EEG abnormalities may be absent at times and are not exclusive to HE. These abnormalities can also be found in other metabolic encephalopathies such as sepsis, hypercapnia, or drug-induced encephalopathy **[60]**. Furthermore, the limited accessibility of EEG poses a significant barrier to its utilization in routine medical practice.

6.6. Inhibitory control test

Attention, working memory, and response inhibition are all assessed in the inhibitory control test **[61]**. While the procedure may not be acceptable and easily accessible for patients with lower cognitive abilities, it can be performed by any healthcare worker who has received proper training, rather than only by a psychologist **[62]**.

6.7. Brain imaging

Radiological examinations and neuroimaging procedures are noninvasive diagnostic tests conducted to exclude the presence of lesions and monitor metabolic alterations. Modern techniques such as magnetic resonance imaging, positron emission tomography, and computer X-ray tomography can be used. In order to ensure accurate diagnosis, it is imperative to conduct these tests in conjunction with additional procedures that measure sensitivity and specificity **[63]**.

7. Experimental models for HE

Different experimental models for the evaluation of HE are shown in **Table 1**.

8. Management

The majority of therapy for HE focuses on reducing the levels of ammonia in the body **(Table 2)**. The majority of therapy for HE focuses on reducing the levels of ammonia in the body. Most of the ammonia is synthesized in the gastrointestinal tract, and in cases of cirrhosis, the liver fails to efficiently convert ammonia into urea. Additionally, the muscle gradually assumes a more significant function in the process of ammonia metabolism **[71]**.

Table 1: Experimental models for HE

Model	Dose	Subjects	References
Chemotherapy (Epirubicin)-induced HE	(9 mg/kg, Intravenous) single dose	Mice	**(64)**
Thioacetamide-induced HE	(3. 5%, 350 mg/kg, intraperitoneal (IP), Once for 3 days	Rats	**(65)**
Carbon tetrachloride (CCL_4) induced HE	1 mL/kg 35% (diluted with olive oil), IP, twice a week for 12 weeks	Rats	**(66)**
Galactosamine induced HE	(250 mg/kg, ip) twice a week for 30 days	Rats	**(67)**
Azoxymethane induced HE	a single IP injection at 100 mg/kg.	Mice	**(68)**
Bile duct ligation (BDL) induced HE	4 weeks	Rats	**(69)**
Ammonium acetate	4.5 mmol/kg using two IP injections with a 15 min interval between them	Mice	**(70)**

Table 2. Treatments for hepatic encephalopathy

Treatment	Mode of action	References
Lactulose	Acidifies the colon to decrease ammonia generation, functions as a laxative, and assists in the restoration of the gut microbiota.	**(2, 72)**
Rifaximin	An antibiotic that is highly effective and nonabsorbable, and that inhibits the formation of ammonia.	**(75, 76)**
LOLA	It facilitates the conversion of ammonia by glutaminase and expedites its removal from the body.	**(78, 79)**
Probiotics	Food supplements that promote effective bowel movement and restore the balance of normal flora	**(80, 81)**
Laxatives	Facilitate defecation and alleviate constipation	**(100)**
BCAA	Enhances the ammonia removal process and facilitates its conversion into glutamine.	**(84)**

Albumin	anti-inflammatory and remove a multitude of toxic substances that build up during liver failure.	**(86)**
0.9% saline	increasing the excretion of ammonia	**(101)**
Diet	Sufficient supply of body weight, fuel, and amino acids	**(88, 89, 90).**
OP	Enhance the process of muscle ammonia detoxification by stimulating the enzyme GS.	**(102)**
Sodium phenylbutyrate	effectively decreases ammonia levels	**(102)**
FMT	to improve the imbalance of microbial populations in the gut	**(103, 104).**
LSPD	remove tiny ionizable compounds, such as ammonia	**(105).**
Activated carbon microspheres	absorb ammonia and other organic compounds in the digestive system	**(94)**
GS replacement	plays a crucial role in ammonia metabolism	**(106, 107, 108)**

8.1. Lactulose

Lactulose is the predominant medication employed for the purpose of decreasing ammonia levels. Lactulose is a non-absorbable disaccharide that functions as a laxative by stimulating the generation of significant quantities of ammonia in the stool **[2]**. Moreover, it acidifies the colon to decrease ammonia generation **[72]**. Lactulose, either on its own or in conjunction with rifaximin, is extensively utilized for the management of HE and improvement of the overall quality of life **[73]**. Additionally, it hinders the excessive growth of bacteria in the intestines, prevents the spread of bacteria to other parts of the body, and reduces the resistance of the intestines to bacterial infections. This intervention reduces systemic inflammatory responses and hyperammonemia in rats with HE. **[2]**.

8.2. Antimicrobial agents: Rifaximin

Rifaximin is a poorly absorbed antibiotic in the gastrointestinal tract, resulting in greater concentration in the intestines. It is hypothesized that it reduces the generation of ammonia by specifically targeting and removing bacteria in the colon that produce ammonia. To do this, rifaximin blocks RNA synthesis in bacteria by attaching to DNA-dependent RNA polymerase. Patients who are intolerant to or do not react to lactulose may benefit from this option **[74, 75, 76]**.

The efficacy of lactulose was higher when combined with rifaximin than when taken alone **[77]**.

8.3. L-Ornithine and L-aspartate

L-ornithine L-aspartate (LOLA) is the salt of the natural amino acid aspartate. It aids glutaminase in converting ammonia and expediting its removal from the body. The effectiveness of LOLA, together with its minimal

adverse effects, renders it a feasible choice in portosystemic shunt HE. LOLA is mostly utilized as an adjuvant treatment in conjunction with other medications. Therefore, it is not recommended as a standalone choice **[78, 79]**.

8.4. Probiotics

Probiotic treatment is a novel supplementary therapy for HE. Probiotics have been demonstrated in clinical research to effectively prevent the initial and subsequent episodes of HE in individuals with cirrhosis **[80, 81]**. Probiotics consist of diverse microorganisms that directly enhance the composition of the intestinal microbiota. This leads to a reduction in the production of bacterial ammonia and the absorption of ammonia and other toxins in the intestines **[82]**. Furthermore, probiotics can enhance the synthesis of short-chain fatty acids by augmenting the prevalence of several bacteria, such as *Calibacterium Prausnitzii* **[83]**.

8.5. Branched-chain amino acids

Branched-chain amino acids (BCAA) consist of valine, leucine, and isoleucine. Patients suffering from liver failure experience a disparity in the levels of BCAA and aromatic amino acids. BCAA improves the process of removing ammonia and converting it into glutamine **[84]**.

8.6. Embolization of portosystemic shunts

It should be considered in patients with HE who are challenging to treat or experience repeated episodes. This is especially relevant when the liver function is not significantly impaired and there is a potential for a big portosystemic shunt. Based on the existing evidence, it appears that shunt embolization is an effective therapy option for patients with cirrhosis and HE. However, it is recommended to view it as a temporary solution till transplantation in the majority of instances **[85]**.

8.7. Albumin

Albumin is a versatile protein that is produced in the liver. However, patients with cirrhosis see a notable decrease in both the amount and quality of albumin. Previously, albumin was regarded as a substance that increases the volume of plasma. Albumin has been found to possess many supplementary functions, such as anti-inflammatory characteristics and the capacity to bind and eliminate numerous harmful chemicals that accumulate during liver failure **[86]**. The addition of albumin to lactulose proved to be more efficacious than lactulose alone in achieving complete reversal of HE **[87]**.

8.8. Diet

Limiting protein consumption should only be recommended after careful evaluation by experts, as it can potentially result in muscle loss. Muscle tissue has a crucial function in converting ammonia to glutamine, which leads to a decrease in blood ammonia levels. Therefore, it is essential to take appropriate measures to avoid malnutrition, as it significantly impacts the outlook. Recent studies on the efficacy of nutrition therapy have shown that the recommended daily energy intake should range from 35 to 40 kcal/kg and protein intake from 1.2 to 1.5 grams of protein per kilogram of body weight. Moreover, consuming calories is crucial to avoid excessive gluconeogenesis and maintain a steady production of glucose in the body. This is particularly crucial in individuals with HE as the process of converting amino acids into glucose leads to the depletion of tissue protein reserves and the creation of ammonia, so consuming frequent small meals throughout the day is important to avoid fasting **[88, 89, 90]**.

9. Novel treatment strategies

There are several groundbreaking and innovative treatments for HE that are presently in the pre-clinical development phase, in addition to

various options that are currently being assessed in clinical trial settings.

9.1. Pre-clinical stage

9.1.1. Liposome-supported peritoneal dialysis (LSPD)

A novel detoxification method has been developed that incorporates micrometer-sized liposomes with a transmembrane pH gradient into dialysis fluids. This approach aims to enhance the removal of small ionizable substances, particularly ammonia. In experimental studies using a rat model of cirrhosis, LSPD demonstrated effectiveness in sequestering ammonia, leading to reduced plasma ammonia concentrations and decreased brain edema when compared to traditional peritoneal dialysis techniques **[91]**.

9.1.2. Genetically engineered bacteria:

Genetically modified strains of E. coli* Nissle have been designed to metabolize ammonia. When administered, these engineered bacteria have been shown to decrease blood ammonia levels in animal models of liver injury induced by thioacetamide and bile duct ligation **[92, 93]**.

9.1.3. Activated carbon microspheres

AST-120, a formulation designed to adsorb ammonia and other organic substances in the gastrointestinal tract, has shown potential in lowering blood ammonia levels in animal studies of liver disease. Nevertheless, the compound did not fulfill its primary endpoint in a phase II clinical trial (ASTUTE trial). This outcome may be influenced by the design of the trial, indicating that activated carbon microspheres warrant further investigation **[94]**.

9.1.4. GABAA receptor-modulating steroid antagonists (GAMSA)

Patients experiencing HE often exhibit elevated GABAergic activity, exacerbated by neurosteroids that contribute to neuroinhibition. A newly developed drug, characterized by a 3-beta-hydroxysteroid structure, has been shown to effectively antagonize this pathway, thereby restoring brain function in rat models of experimental hyperammonaemia and HE. Additionally, it counteracts the effects of neurosteroids in healthy subjects. This drug is currently undergoing clinical trials and has been recognized as a promising therapeutic target for HE **[95]**.

9.1.5. Glutamine synthetase (GS) replacement therapy

GS is predominantly located in the liver and muscle tissues. In models of ALF and CLD, GS expression is upregulated in muscle tissue. Selective knockout of GS in either the liver or muscle has been associated with hyperammonaemia. Restoration of GS activity in animal models of hyperammonaemia effectively lowered ammonia levels. These findings support the development of strategies aimed at inducing or replacing GS enzyme activity. Preliminary results from a study indicated that AM-535, a recombinant form of GS, successfully reduced ammonia levels in animal models of cirrhosis and urea cycle enzyme deficiencies **[1, 96]**.

9.1.6. Brain clearance systems

The brain's clearance mechanisms, including the glymphatic system and the meningeal lymphatic system, are thought to be crucial in the context of HE. Research conducted on animals has shown that enhancing meningeal lymphangiogenesis can improve the symptoms of HE. Therefore, targeting and adjusting these brain clearance systems could represent an innovative approach to treating HE **[97]**.

9.2. Clinical stage:

9.2.1. Fecal material transplantation (FMT)

An increasing number of clinical studies have demonstrated that FMT may be a novel and promising treatment for overt HE. The initial open-label randomized trial assessing the impact of FMT from a single stool donor in cirrhotic individuals with recurrent HE demonstrated positive outcomes in this high-risk group. Additionally, a recent investigation indicated that microbiota transplantation might help mitigate splanchnic hyperdynamic circulation by enhancing vascular responsiveness and reducing mesenteric angiogenesis. Currently, a larger open-label randomized trial is underway, examining the effects of FMT from multiple stool donors in cirrhotic patients who continue to experience recurrent HE episodes despite ongoing treatment with lactulose or antibiotics (ClinicalTrials.gov: NCT03439982) **[97]**.

9.2.2. Ornithine phenylacetate (OP)

This compound, which combines ornithine and phenylacetate, is designed to enhance ammonia detoxification in muscles by stimulating the enzyme glutamine synthetase (GS). This process leads to the production of glutamine, which is converted into phenylacetylglutamine, thus preventing glutamine metabolism and ammonia regeneration. OP has been shown to significantly reduce blood ammonia levels in various animal models of liver disease. Preliminary results from a phase 2b study indicated that OP reduced ammonia levels in patients with overt HE in a dose-dependent manner, although it did not meet its primary endpoint regarding the time to improvement in HE. A phase III study is planned **[98]**.

9.2.3. Glycerol/sodium phenylbutyrate

Sodium phenylbutyrate is primarily used for patients with genetic urea cycle disorders. A recent small study suggested that it could improve neurological outcomes and lower blood ammonia levels in cirrhotic patients in intensive care. Despite the lack of a control group, the correlation between neurological improvement and reduced ammonia is significant. In a randomized controlled trial, glycerol phenylbutyrate was effective in lowering ammonia levels and reducing the incidence of HE events and related hospitalizations. Its future as a treatment for HE is still uncertain **[99]**.

10. Search strategy

In this review, a thorough literature search was performed utilizing a systematic approach to identify relevant published literature that illuminated the pathophysiology and management of hepatic encephalopathy. The search was conducted across multiple databases, including PubMed, Google Scholar, Scopus, Web of Science, and ScienceDirect. Specific search terms such as "hepatic encephalopathy," "classification," "epidemiology," "pathophysiology," "diagnosis," and "management" were employed as part of the selection criteria. The inclusion criteria focused on papers written in English that provided full-text access and primarily addressed the pathophysiology and management of hepatic encephalopathy. Conversely, papers that were not written in English or that contained only abstracts were excluded from consideration. Additionally, the reference lists of the selected papers were analyzed to identify other articles deemed important for the review.

11. Conclusion and future directions

In conclusion, this review highlighted the complex pathophysiology and management strategies associated with hepatic encephalopathy (HE), a significant complication of liver disease that poses considerable challenges in clinical practice. The literature indicates that HE manifests as a spectrum of neuropsychiatric abnormalities, ranging from mild cognitive

impairment to severe disorientation and coma, with ammonia accumulation being a central factor in its pathogenesis. Despite advancements in understanding the underlying mechanisms, there remains a substantial unmet need for effective therapies. Future research should focus on elucidating the molecular signatures associated with HE, as demonstrated in recent metabolomics studies, which may provide insights into novel therapeutic targets **[109].** Additionally, the exploration of extracorporeal liver support devices and their effects on HE management warrants further investigation, as preliminary studies suggest potential benefits in improving patient outcomes **[110]**. Furthermore, the integration of probiotic therapies and their efficacy in preventing overt HE presents an exciting avenue for future clinical trials **[111]**.

Abbreviations

ALF, acute liver failure; BCAA, branched-chain amino acids; CLD, Chronic liver disease; EEG, Electroencephalogram; FMT, Fecal material transplantation; GS, Glutamine synthetase; HCV, hepatitis C virus; HE, Hepatic encephalopathy; IP, intraperitoneal; ISHEN, International Society of Hepatic Encephalopathy and Nitrogen Metabolism; LOLA, L-Ornithine L-aspartate; LSPD, Liposome-supported peritoneal dialysis; MHE, Minimal hepatic encephalopathy; OP, Ornithine phenylacetate; PHES, Psychometric hepatic encephalopathy score; WHC, West Haven criterion.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

All data generated or analyzed are included in the main manuscript. All figures included in this manuscript were designed by the authors. These figures are uploaded again separately for high resolution.

Competing interests

The authors declare that no competing interests exist.

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Author's Contribution

All authors contributed to the study conception, design, material preparation, data collection, and analysis. The first draft of the manuscript was written by Manar M. Esmail, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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