Pathogenesis, Diagnosis, and Treatment of Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is a neuropsychiatric disorder seen in patients with advanced liver disease or porto-systemic shunts. Based on etiology and severity of HE, the World Congress of Gastroenterology has divided HE into categories and sub-categories. Many user-friendly computer-based neuropsychiatric tests are being validated for diagnosing covert HE. Currently, emphasis is being given to view HE deficits as a continuous spectrum rather than distinct stages. Ammonia is believed to play crucial role in pathogenesis of HE via astrocyte swelling and cerebral edema. However, evidence has been building up which supports the synergistic role of oxidative stress, inflammation and neurosteroids in pathogenesis of HE. At present, treatment of HE aims at decreasing the production and intestinal absorption of ammonia. But as the role of new pathogenetic mechanisms becomes clear, many potential new treatment strategies may become available for clinician. (J Clin Exp Hepatol 2011;1:77–86)

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome seen in liver dysfunction or in porto-systemic shunting without liver dysfunction.[1] This potentially reversible condition is associated with both acute and chronic liver disease. The neurological impairment in HE is a continuous spectrum which can be broadly divided into two categories: (1) overt hepatic encephalopathy and (2) covert hepatic encephalopathy.[2] Covert HE is a new term introduced at the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), 2011, to encompass minimal hepatic encephalopathy (MHE) and grade I overt HE.[3] User-friendly, computer-based diagnostic modalities are ready for clinical use in covert HE. Most of the theories explaining the pathogenesis of HE are centered around ammonia. However, in recent years, considerable progress has been made in elucidating new mechanisms of pathogenesis such as inflammation, oxidative stress, neurosteroids (NS), and endogenous benzodiazepines. Current treatment of HE is mainly aimed at reducing the production and intestinal absorption of ammonia. However, many other potential treatments targeting new pathophysiological mechanisms are under investigation. Over the past decade, there has been increasing evidence to suggest that covert HE affects the quality of life, driving abilities, and increases the risk of developing overt HE.[4,5]

CLASSIFICATION

A classification system for HE disorders was devised by the working Party at the 1998 World Congress of Gastroenterology (WCOG) in Vienna, Austria (Table 1). This classification has helped to standardize the nomenclature used in HE diagnosis and research.

PATHOGENESIS

Several mechanisms have been proposed to explain the pathogenesis of HE. As mentioned earlier, ammonia theory enjoys maximum attention. Some of the other relevant theories are detailed below.

The Ammonia Hypothesis

Ammonia is produced from the metabolism of proteins, amino acids, purines, and pyramidines. About half of the ammonia arising from the intestine is synthesized by bacteria, the remainder coming from dietary protein and glutamine. Most of the ammonia absorbed from the small intestine is drained into the liver by portal vein and detoxified there to form urea. Liver dysfunction, porto-caval

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Abbreviations: AAA: aromatic amino acid; BAUR: brain ammonia utilization rate; BCAA: branched-chain amino acids; CFF: critical flicker fusion; DBI: diazepam binding inhibitor; DST: digit symbol test; DWI: diffusion weighted imaging; ECAD: extra-corporeal albumin dialysis; EEG: electroencephalogram; FLAIR: fluid attenuation inversion recovery; HE: hepatic encephalopathy; HESA: hepatic encephalopathy scoring algorithm; ICT: inhibitory control test; IL: interleukin; LOLA: L-ornithine L-aspartate; LTT: line tracing test; MARS: molecular adsorbent reticulating system; MHE: minimal hepatic encephalopathy; MRI: magnetic resonance imaging; NAC: N-acetyl cysteine; NO: nitric oxide; NS: neurosteroids; NSAID: non-steroidal anti-inflammatory drugs; ODN: octadecaneuropeptide; OHE: overt hepatic encephalopathy; PTBR: peripheral-type benzodiazepine receptor; QOL: quality of life; SDT: serial dotting test; SEDACA: short epoch, dominant activity, and cluster analysis; SIBO: small intestinal bacterial overgrowth; SIRS: systemic inflammatory response syndrome; SOD: superoxide dismutase; SONIC: spectrum of neurological impairment; TLP: TransLocator Protein; TNF: tumor necrosis factor
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Table 1 Classification of hepatic encephalopathy by working party.

Type of HE	Etiological nomenclature		
A	Encephalopathy associated with acute liver failure		
B	Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease		
C	Encephalopathy associated with cirrhosis and portal hypertension/or portal-systemic shunts	**Subcategory**	**Subdivisions**
		Episodic HE	Precipitated Spontaneous (without identifiable precipitating factor) Recurrent
		Persistent HE	Mild Severe Treatment dependent
		Minimal HE	

HE: hepatic encephalopathy.

shunting or defects in urea cycle increase blood ammonia levels which can cause HE. In liver dysfunction, skeletal muscle and astrocytes in brain play a significant role in detoxification of ammonia by converting it to glutamine.

Ammonia is thought to play a fundamental role in causation of HE. Ammonia levels are raised in majority of the patients with HE.[6] HE symptoms were originally induced in dogs after creating a porto-caval shunt by Nencki et al in 1890s.[7,8] It was proposed that as the blood bypassed the liver urea cycle, arterial ammonia concentration rose and the dogs exhibited a syndrome resembling HE. Experiments in rats by Ehrlich et al produced similar results when ammonium acetate was injected after porto-caval anastomosis.[9] Lockwood et al[10] used a radionuclide ^{13}N labeled ammonia to investigate the metabolism of ammonia in liver disease patients. They found that brain uptake of ammonia and brain ammonia utilization rate (BAUR) was higher in subjects with HE compared with normal subjects.[10] Permeability of ammonia across the blood–brain barrier is also noted to be increased in patients with MHE.[11]

The following mechanisms were proposed to explain how hyperammonemia causes HE.

(a) Effects on Astrocyte

Astrocytes are a type of glial cells found in central nervous system. Astrocytes are involved in providing nutrients to neuron and also form an important part of the blood–brain barrier. They have the enzyme, glutamine synthase, which converts ammonia and glutamate to form glutamine. Hyperammonemia can lead to increased production and accumulation of glutamine in astrocytes. This leads to increased osmotic pressure and edema of astrocytes. This could result in cerebral edema and increased intracranial hypertension seen especially in patients with fulminant hepatic failure. In patients with chronic liver disease, there is definite but lesser degree of brain edema as compensatory mechanisms come into action in the astrocytes. Over time, these astrocytes undergo morphologic changes resulting in what is called Alzheimer type 2 astrocytosis.

(b) Effects on Neurotransmission

Ammonium ions, in high concentrations, are shown to interfere with glutamatergic excitatory transmission. Chronic hyperammonemia increases serotonin turnover and this may be responsible for altered sleep patterns seen in HE.[12] Ammonia is also shown to impair brain energy metabolism and autoregulation of blood flow.[13,14]

Evidence has been building for other causative factors that act synergistically with hyperammonemia in initiating and worsening HE. These factors include inflammation, infection, and associated oxidative stress.

Role of Infection and Inflammation

Patients with advanced liver disease are prone to infection as they have an impairment of host defense mechanisms. Infection and/or associated systemic inflammatory response syndrome (SIRS) appear to worsen HE in patients with acute liver failure.[15] In a study by Shawcross et al, induced hyperammonemia caused significant deterioration in neuropsychological test scores when evidence existed for inflammatory state, but not after its resolution.[16] This study suggests that inflammation and its mediators may be important in modulating the cerebral effect of ammonia in liver disease. This synergistic effect of inflammation and ammonia on worsening of HE symptoms was seen across the spectrum of patients with varying degrees of HE.[17,18] Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1beta (IL-1β), and IL-6 are produced by peripheral immune system during infection. Although they cannot cross the blood–brain barrier, they can still signal the brain to elicit an inflammatory response. Brain signaling may occur through the direct transport of the cytokine across the blood–brain barrier via active transport, the interaction of the cytokine with circumventricular organs, and the activation of afferent neurons of the vagus nerve.[19] Endothelial cells have receptors for IL-β and TNF-α that can transduce signals that results in intracerebral synthesis of NO and prostanoids.[20] Cauli et al have shown that learning difficulties/cognitive impairment of the rats with porto-caval shunting is

reversible with the administration of ibuprofen.[21] Chronic treatment with ibuprofen normalized cyclooxygenase and inducible NO synthase activities in these rats. This supports the role of inflammation in the induction of HE. It remains to be seen what clinical role non-steroidal anti-inflammatory drugs (NSAIDs) play in the future.

An important recent study by Shawcross et al shows that grade 3/4 encephalopathy correlates with the presence of SIRS and not with ammonia.[22] This demonstrates the major importance of the inflammation in HE.

Several in vitro and ex vivo studies have shown that ammonia contributes to neutrophil swelling and phagocytosis dysfunction. This in turn may play an important role in the predisposition to infection and inflammation in cirrhosis.[20]

Role of Oxidative Stress

Oxidative stress is a condition in which the production of free radicals exceeds their clearance. Several animal models of liver failure have shown evidence of oxidative/nitrosative stress in the brain. These findings include increases in endothelial nitric oxide synthase (eNOS) mRNA expression, nitrite/nitrate levels, brain nitric oxide production, lipid peroxidation, superoxide dismutase (SOD) activity, and hydrogen peroxide production.[23] They have also showed decreases in activities of glutathione peroxidase and SOD enzymes. Several experimental treatments to reduce the oxidative stress have been shown to be beneficial in animal models such as indomethacin, N-acetyl cysteine, (NAC) ascorbate, alpha-tocopherol, deferoxamine, melatonia, and L-carnitine.[23] Hypothermia and sodium benzoate have been shown to be beneficial in humans with liver failure.[23] But, it is not clear whether the beneficial effect is directly related to the reduction of oxidative stress.

Neurosteroids

They are steroid hormones synthesized by glial cells and neurons in the brain via activation of "peripheral-type" benzodiazepine receptor (PTBR). The PTBR is now called TransLocator Protein 18 kDa (TLP). Some NS such as 3alpha–5alpha-tetrahydroprogesterone (allopregnanolone) and 3alpha–5alpha-tetra-dehydrodeoxy-corticosterone (THDOC) are among the most potent endogenous positive modulators of gamma-aminobutryic acid (GABA)-A receptor function.

In human and experimental models with HE, NS biosynthesis was noted to be altered. The following changes were noted in both acute and chronic liver failure.

(1) Components of PTBR are up-regulated in human and experimental HE.
(2) Known mediators of PTBR activation such as ammonia and manganese accumulate in brain following liver failure.
(3) Endogenous PTBR agonists such as the diazepam binding inhibitor (DBI) and the octadecaneuropeptide (ODN) are increased in human and experimental HE.
(4) NS such as allopregnanolone and THDOC accumulate in brain in HE.[24]

Neurosteroids such as allopregnanolone also modulate serotonin (5-HT) receptors. This action along with the increased GABA-ergic tone is thought to play an important role in the pathophysiology of HE. NS system presents multiple potential targets for development of drugs which may target the synthesis of NS or the receptors.

Manganese

Manganese is found to accumulate in the basal ganglia in patients with HE. This accumulation is shown to be reversible on magnetic resonance imaging (MRI) of the brain after liver transplantation.[25] This deposition in the basal ganglia was thought to be contributing to extra-pyramidal symptoms in some patients with HE.

Diagnosis of Hepatic Encephalopathy

As mentioned in Table 1, the WCOG classification of HE describes three main types of HE: Type A, Type B, and Type C.[1] Type C HE is most commonly encountered by clinicians. It is important to establish the diagnosis of chronic liver disease or cirrhosis in a patient with suspected type C HE who presents without any prior history of liver disease. Laboratory testing involves the confirmation of chronic liver disease with tests such as liver function tests, serum albumin, prothrombin time, and complete blood count. The etiology for liver disease can be assessed with a whole battery of blood tests which are beyond the scope of this review article. However, we would like to mention about measuring serum ammonia which always debated in the context of HE. Studies have shown that both venous and arterial ammonia correlate well with the severity of HE but there is some overlap in the stages of HE.[26] It is not routinely recommended for the diagnosis of HE, as a normal ammonia level in the setting of HE would not preclude treatment. The rule of the thumb is if a patient with chronic liver disease presents with altered mental status, it should be treated as HE until proven otherwise.[27] Serum ammonia does have a role in the setting of urea cycle disorders. The test should be carried out meticulously. Tables 2 and 3 mention the recommended

Table 2 Recommended methods for measuring serum ammonia.

The blood should be collected from stasis free vein.
Avoid clenching of fist or application of tourniquet as it can falsely elevate ammonia due to release of ammonia from skeletal muscle.
Green top glass vacutainer which contains lithium or sodium heparin should be used to collect blood. It must then be stored in ice bath and immediately transported for assay within 20 minutes of collection.

Table 3 Common causes for falsely elevated serum ammonia.

Improper collection techniques such as fist clenching or using tourniquet.
Hemolysis during venipuncture.
Delay in transportation.

method for measuring serum ammonia and the common causes for falsely elevated ammonia levels, respectively.

Diagnosis of Overt Hepatic Encephalopathy

The clinical presentation of patients with HE is a part of the continuous spectrum of neurological impairment in cirrhosis.[2] Conventionally, HE was staged according to clinical scales, West Haven criteria being the most popular. Due to some of its limitations, there are newer scales which are being developed. Section below discusses some of the clinical scales which are utilized in the diagnosis of HE.

West Haven Classification

This scale was validated by Professor Harold Conn in 1978 for the clinical diagnosis of overt HE.[28] This semi-quantitative scale is based on patients' behavioral symptoms and clinical signs of mental obtundation (neurological deterioration). All clinical studies to date have utilized this scale to define the various stages of HE. It extends from Stage I which is characterized by trivial lack of awareness by a patient, shortened attention span, and impaired addition to Stage III/IV which involves somnolence, stupor, and coma. While characterizing Stage III and Stage IV is relatively straightforward, identifying patients with lower stages of HE (Stage I/II) is subject to a lot of inter-observer variability.[29,30] In an effort to overcome some of the shortcomings, some other scales are being validated.

Hepatic Encephalopathy Scoring Algorithm

This scale was devised to improve the objectivity in the assessment of HE. It was validated on patients undergoing a study of the effects of extra-corporeal albumin dialysis (ECAD) by using the molecular adsorbent reticulating system (MARS).[31,32] It is a blended scale which combines the assessment of both clinical and neuro-psychometric tests to characterize patients into various stages of HE. This is particularly advantageous in lower grades of HE where these psychometric tests are very likely to be abnormal. Assessment of HE using the Hepatic Encephalopathy Scoring Algorithm (HESA) scale starts from Stage IV (comatose) and proceeds to lower stages going down the algorithm. Stage IV assessments are done mainly by clinical assessments but Stage I and Stage II have a combination of clinical assessment and neuropsychological tests. The components on the West Haven scale, which were prone to subjective bias, are replaced by more objective tests. Amnesia has been replaced by Wechsler's memory scale and the Hopkins verbal learning test, shortened attention span by the digit span test, impairment of simple calculations by arithmetic subtest of the wide range achievement test, and anxiety/depression by a one-item seven-point Likert scale. HESA completely eliminated asterixis, as this parameter can be bi-directional, i.e. absent in the lighter and deeper stages of HE. Further validation of this testing system is needed in larger trials.

Clinical Hepatic Encephalopathy Scoring System (CHESS)

To simplify the staging of HE, Cordoba et al[33] validated this scale which obviated the need for expert assessment for staging patients according to the West Haven classification. It provides a continuum score (0–9) without requiring the patient to be classified into specific stages as per the West Haven scale. The scale has assessments which include asking the patients questions about orientation to time, assessment of attention span by counting backwards, comprehension capability, and clinical assessment of arousal and ability to follow commands. Each item has a "Yes/No" answer and 1 point is awarded for the right answer. Scale 0 depicts minimal or no HE, and therefore will need further neuro-psychometric testing at this stage to diagnose MHE. This scale has a ceiling effect in comatose patients, where Glasgow coma scale has to be used instead. It needs further validation in larger trials.

Abolition of Stage I West Haven Criteria—the Concept of "Covert HE"

As described above, there have been several efforts to make the clinical assessment of HE more objective. MHE is seen in cirrhotics with completely normal neurological examination with abnormal performance in specific psychometric tests. Ideally, patients with prior episodes of overt HE cannot be classified into MHE. But the predicament lies in the fact that once overt HE is treated, patients may not completely recover but have MHE or Grade I HE. Studies have shown an increased inter-observer variability in diagnosing Grade I/Grade II HE. These issues impede in the process of research in the field of HE. Therefore, it has been proposed that the clinical presentation of HE extends as a continuous spectrum of neurological impairment (SONIC) rather than categorically into different stages. In addition, it was proposed to combine minimal HE and Stage I overt HE (West Haven Criteria) to be called "Covert HE" (Figure 1).[3]

Psychometric Tests

Diagnosis of MHE is based mainly on neuro-psychometric or neuro-physiological testing as these patients are asymptomatic and have nearly normal clinical examination. There are various cognitive domains in which abnormalities are identified in these patients. Some of these are attention, problem solving, executive functioning, psychomotor speed, and visuo-spatial co-ordination. Deficits in

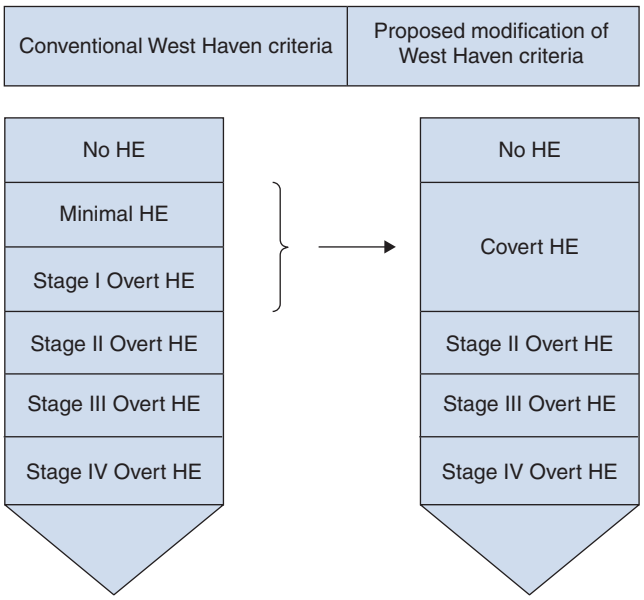

Figure 1 Proposed modification of the West Haven classification. HE: hepatic encephalopathy.

all these domains may not be seen in every patient; hence, a battery of psychometric tests is more sensitive for the diagnosis of MHE. Most psychometric tests are influenced by age, education status and demonstrate some learning effect.

Psychometric Hepatic Encephalopathy Score (PHES)

This psychometric test battery is the result of some early work by the neuropsychologist Wolfgang Hamster and Hans Schomerus. In the late 1990s, Weissenborn et al[34,35] validated this test for the diagnosis of MHE in non-alcoholic cirrhosis population in Germany. It is a paper-and-pencil psychometric test battery which is composed of the following five tests: number connection test A (NCT A), number connection test B (NCT B), digit symbol test (DST), serial dotting test (SDT), and line tracing test (LTT). It is imperative to have normative values (normal values from healthy controls) to interpret this performance by patients. Abnormality of >2 standard deviations from the mean in two or more tests is diagnostic of MHE. This test was proposed as the "Gold Standard" for the diagnosis of MHE by the Hepatic Encephalopathy Consensus group in Vienna, 1998.[1] This standardization of definition has led to an explosion in the field of research in MHE over the past decade. However, the main limitations of this test are the availability of the test itself due to copyright issues and the availability of normative population data for comparison, which is why this test failed to gain popularity in the United States.[36] In addition, this test battery faces criticism for excessive reliance of fine motor skills and failure to test memory or reaction time.

Inhibitory Control Test

In an effort to introduce a user-friendly computerized psychometric test in the United States, Bajaj et al[37,38] validated the inhibitory control test (ICT) for the diagnosis of MHE. This is a test of sustained attention, vigilance, working memory, and response inhibition. It is based on the principle of "Target" and "Lures". Subjects are exposed to continuous flashing of random alphabets on the screen with "X" and "Y" interspersed in between them. They are supposed to respond to a "Target" which is "X" followed by a "Y" or vice versa and avoid responding to a "Lure" which is "X" followed by "X" or "Y" followed by "Y". Abnormality of >5 lures has been shown to diagnose MHE with a sensitivity of 87% and a specificity of 77%. This test is available for use without fee on the internet.

Cognitive Drug Research (CDR) Test

This computerized psychometric test was developed by the Cognitive Drug Research Laboratory Ltd.[39] It mainly tests five cognitive domains: attention, continuity of attention, speed of memory, quality of episodic, and working memories. This battery was validated by Mardini et al in cirrhotic patients awaiting liver transplantation. It was shown to worsen with nitrogen challenge and improve with liver transplantation. It is available for use for a fee about USD 50.

Critical Flicker Fusion (CFF) Test

This is a neuro-physiological test which is based on the ability of a human brain to perceive flickering light as discrete light pulsations. It is influenced by cortical activity and to some extent by hepatic retinopathy (abnormal glial cells in the retina). In this test, patients are shown light pulsations starting at a very high frequency of 60 Hz (where the subject perceives it as a single stream of light) and slowly reduced. The critical frequency is the frequency at which the subject perceives them as discrete light pulsations. A threshold of 39 Hz or less is diagnostic of MHE with a sensitivity of 55% and a specificity close to 100%.[40] This test is very useful in the research setting as it is only minimally influenced by age, but not by educational status and does not have any learning effect on the subject.[41] It, however, does require patient to have binocular vision.

Electroencephalogram

This is an electrophysiologic technique most frequently used to assess the neuro-psychiatric status in a cirrhotic patient in a research setting. It provides a functional assessment of the nervous system and is complementary to neuroimaging. In overt HE, there is generalized slowing of background activity along with characteristic triphasic waves.[42] In MHE, there is slowing of the mean dominant frequency. There are recent developments which enhance the applicability of electroencephalogram (EEG). Some of these include ANNESS (artificial neural network expert

system software) and SEDACA (short epoch, dominant activity, and cluster analysis).[43,44]

Utility of Brain Imaging in Hepatic Encephalopathy

Computerized tomography of the head is essential to rule out other causes for neurological deterioration in a patient who presents acutely with an episode of HE. MRI using conventional techniques demonstrated cortical atrophy and hyperintense basal ganglia on T1 weighted imaging. Proton MR spectroscopy (H^1-MRS) has shown an increase in intracellular glutamate/glutamine signal and a decrease in myoinositol, taurine, and choline signals.[45] Newer techniques in brain imaging such as FLAIR (fluid attenuation inversion recovery) and DWI (diffusion weighted imaging) have demonstrated a diffuse increase in white matter signal intensities in cirrhotic patients with HE.[46] This indicates fluid or brain edema predominantly in the white matter.

Treatment

Prior to initiating treatment for HE, other non-hepatic causes for neurological alteration have to be excluded. Treatment of HE varies based on the acuity and severity of the HE.

Acute Episode of Overt Hepatic Encephalopathy

Treatment of acute overt HE is broadly divided into two areas:

(1) Identification and treatment of precipitating factor.
(2) Interventions primarily aiming at decreasing the production and absorption of nitrogenous compounds from the gut.

Identification and Treatment of Common Precipitating Factors

- *Infection:* Chest X-ray, urine analysis, culture of urine, and blood. If the patient has ascites, ascitic fluid should be analyzed for infection. If infection is found, it should be treated with appropriate antibiotics.
- *Sedative medications:* Usage of benzodiazepines and narcotics should be restricted.
- *Constipation:* Should be treated to produce two to three soft bowel movements per day.
- *Gastrointestinal hemorrhage:* Upper and lower gastrointestinal bleeds should be treated promptly.
- *Dehydration:* Hypovolemia and electrolyte abnormalities should be treated. Diuretics should be avoided.

Interventions Aiming at Decreasing Ammonia

Non-absorbable Disaccharides

Lactulose is a non-absorbable disaccharide used widely in the treatment of overt HE. Lactulose is not absorbed in the small intestine and gets broken down into fatty acids and hydrogen. The breakdown by the bacteria acidifies the colonic contents. Lactulose is thought to reduce the blood ammonia concentration by the following mechanisms:[47]

(1) *Laxative effect* decreases the colonic transit time to reduce the time available for ammonia absorption into circulation.
(2) *Leaching of ammonia* from circulation into colon by colonic bacteria. Intra-luminal pH changes cause the colonic bacteria to use the ammonia as a nitrogen source for protein synthesis.
(3) *Reduction of ammonia* synthesis by the small intestine by decreasing the glutamine uptake by the small intestine.[48]

The dosage of lactulose should titrate to produce two to three soft bowel movements per day. Typical dosage ranges from 15–30 mL twice a day. Lactulose may be administered via nasogastric tube in comatose patients. Lactitol is another alternative oral agent for patients who are intolerant of lactulose. It is shown to be equally effective as lactulose and is better tolerated.[49] Lactulose and lactitol are shown to be effective in enema form also.[50] The efficacy of non-absorbable disaccharides came under scrutiny in a systematic review of randomized trials by Als-Nielsen in 2004.[51] Although there is not enough evidence from placebo-controlled trials of the efficacy of lactulose, current guidelines favor its use because of the logical rationale behind it, a vast amount of clinical experience, affordability, and good tolerability.[52] A recent non-blinded study by Prasad et al[53] has showed that lactulose improves cognitive function and quality of life (QOL) in patients with MHE.

Antibiotics

A recent study by Gupta et al[81] showed high prevalence of small intestinal bacterial overgrowth (SIBO) in patients with cirrhosis with MHE. This study gives the rationale of treatment directed against SIBO and gut dysmotility, which may include non-absorbable antibiotics such as rifaximin, probiotics, and prokinetics. Antibiotics used in HE are directed toward reducing the ammonia producing intestinal bacteria. As a result, the ideal antibiotic will act locally without significant systemic absorption or side effects. Neomycin was considered a standard treatment in the past. But its use fell into disfavor as it was shown to have a systemic absorption with significant side effects such as ototoxicity and nephrotoxicity. A placebo-controlled study by Strauss et al[54] showed that neomycin is not efficacious in treatment of patients with HE.

Rifaximin, a synthetic derivative of rifamycin, is widely used in the treatment of HE. It has very low systemic absorption and is well tolerated. Rifaximin was shown to be as effective as lactitol in patients with grade 1–3 HE in a randomized, double-blind, double-dummy, controlled clinical trial.[55] In a double-blind, randomized trial, rifaximin was found to be as effective as neomycin with much better safety profile.[56] A recent multicentric double-blind placebo-controlled study demonstrated reduction in episodes of

recurrent overt HE and hospital admissions with overt HE.[57] Typical dosage is 550 mg PO twice daily.[58] Cost and possible emergence of multi-drug resistant organisms are the apprehensions associated with its use.

Metronidazole

In a small study involving 18 patients, Morgan et al[59] concluded that metronidazole may be as effective as neomycin in the treatment of mild to moderate HE. Its long-term use may cause neurotoxicity and gastrointestinal disturbance.

Nitazoxanide

A small pilot study by Basu et al[60] showed improvement in HE. Further studies are underway.

Branched-Chain Amino Acids (BCAA)

In HE patients, BCAA levels are decreased and aromatic amino acid (AAA) levels are observed to be increased. This imbalance was thought to contribute to HE as the AAA may act as false neurotransmitters.

BCAA supplementation has been used in the treatment of HE for some time. Supplementation can be done via oral or intravenous routes. The BCAA may improve HE by promoting ammonia detoxification, correction of the plasma amino acid imbalance, and by reduced brain influx of AAAs.[61] Several recent randomized trials demonstrated that BCAA supplementation improves MHE and nutritional status.[62,63] Parenteral supplementations are shown to decrease the severity of encephalopathy in acute HE.[64] Cochrane review by Als-Nielsen et al[65] concluded that oral and intravenous BCAA treatment significantly improved HE patients compared with control regimens such as carbohydrates, neomycin/lactulose, and isonitrogenous control.

L-Ornithine L-Aspartate

L-ornithine L-aspartate (LOLA) is a stable salt of two amino acids L-ornithine and L-aspartate. LOLA decreases ammonia levels by stimulating hepatic urea cycle activity and promoting glutamine synthesis.[66] Both oral and intravenous forms of LOLA are shown to decrease ammonia levels and improve HE.[67,68] Intravenous form is felt to be more effective than oral form as the intravenous route avoids the transamination in the intestinal mucosa. The maximal recommended infusion dose is 5 g LOLA/h.

Zinc

Zinc is an essential component of many enzymes including the ones involved in the urea cycle. Serum zinc concentration is reduced in patients with HE and inversely correlates with blood ammonia concentration. Zinc supplementation in such patients decreased serum ammonia concentration and improved HE in some human studies.[69] It may be appropriate to give zinc supplementation to patients who have zinc deficiency. Safety of long-term supplementation remains a concern.

Levodopa and Bromocriptine

Decreased dopaminergic neurotransmission is proposed as a possible mechanism of HE. Consequently, Levodopa and dopamine agonist bromocriptine were studied for their effects on patients with HE. In a small study done by Morgan et al,[70] bromocriptine improved HE clinically and EEG was normalized in a few patients. The usual dose is 2.5 mg/day and can be increased up to 5 mg twice daily. This treatment should be reserved for patients with well-compensated liver disease and patients should have audiograms every 6 months to monitor for ototoxicity.

Sodium Benzoate

Sodium benzoate lowers serum ammonia concentration by the activation of a non-urea cycle pathway of ammonia removal and urinary excretion. In a randomized controlled trial by Sushma et al,[71] sodium benzoate was shown to be as effective as lactulose in improving HE. The daily recommended dose is 5 g twice daily. Patients rarely tolerate higher doses due to gastrointestinal side effects.

Flumazenil

Flumazenil is a benzodiazepine receptor antagonist which has been studied for its use in HE. Als-Nielsen et al, in Cochrane database systemic review, looked at 13 trials involving 805 HE patients which compared the effect of flumazenil against placebo. They concluded that flumazenil improved HE particularly at the end of the treatment. But it did not have any effect on mortality. It is not used as a first line as it has side effects which include decreasing seizure threshold and worsening agitation.[72]

Probiotics

Urease-producing bacteria was noted to be high in the colon of patients with cirrhosis. They produce ammonia from their urease activity. Probiotic treatment aims at replacing the urease-producing bacteria with non-urease-producing bacteria such as *Enterococcus feacium* or *Lactobacillus acidophilus*. In a study done by Loguercio et al,[73] oral administration of *E. feacium* is shown to be as effective as lactulose in improving the mental status and ammonia concentration in patients with HE grades 1 and 2.

Liver Transplantation

Liver transplantation is the definitive cure for the HE and HE appears to be reversible after the liver transplantation in most cases. The cognitive deficits observed after the liver transplantation are felt to be secondary to possible persistence of porto-systemic shunts, preexisting damage to brain, or that happened during the transplantation surgery.[25]

Diet

Previously, low-protein diet was recommended for patients with HE as it was thought to decrease the production of intestinal ammonia and thus the severity of HE. In a randomized trial by Cordoba et al,[74] patients admitted with HE were randomized to receive either low-protein diet or normal protein diet alongside the standard treatment regimen. They concluded that the outcome of HE was not significantly different between both groups. Patients in the low-protein diet group showed higher protein breakdown. As skeletal muscle plays a significant role in ammonia metabolism in patients with HE, poor nutritional status may increase the levels of ammonia and may thus worsen the HE. Other studies suggest that vegetable protein diet may improve grading of HE compared with animal protein.[75] In addition, high fiber diet may be helpful in decreasing the colonic transit time and absorption of ammonia.

Covert Hepatic Encephalopathy

Covert HE is associated with impairment of driving ability, decrease in the QOL, and increased mortality.[76] So, increasing importance is being given to its treatment. Currently, the following treatments are shown to improve performance in the psychometric tests:

(1) Lactulose
(2) BCAA
(3) LOLA[77]
(4) Probiotics[78]
(5) Rifaximin[79]

FUTURE POTENTIAL THERAPIES

As the role of inflammation and oxidative stress is being unraveled, it provides us with multiple potential targets for intervention. These potential future treatments are detailed in Table 4. Future therapies may aim at reducing inflammation and oxidative stress such as antiinflammatories (COX inhibitors and minocycline), leukodepletion, antioxidants (N-acetyl cysteine and albumin), hypothermia, and antagonists for pro-inflammatory cytokines. Neurosteroid system also offers multiple potential targets. Another potential treatment strategy aims at down-regulating the activation and spontaneous oxidative bursts of the neutrophils via modulating toll-like receptor (TLR-4).[80]

Table 4 Proposed pathogenesis and potential treatment targets.

Proposed pathogenetic mechanism	Potential treatments
Inflammation	TLR antagonists Hypothermia NSAIDs Plasmapheresis
Oxidative stress	Hypothermia NMDA (N-methyl D-aspartate) antagonists N-acetylcysteine Minocycline Anticholine esterases
Neutrophil dysfunction	Leukodepletion Antagonism of proinflammatory cytokines and their receptors Granulocyte colony-stimulating factor
NS system	Inhibitors of NS synthesis Modulators of NS receptors

TLR: toll-like receptor; NS: neurosteroids.

CONFLICTS OF INTEREST

All authors have none to declare.

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