Diagnosis and Management of Hepatic Encephalopathy

This is a PDF version of the following document:
Section 3: Management of Cirrhosis-Related Complications
Topic 4: Diagnosis and Management of Hepatic Encephalopathy

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Background

Hepatic encephalopathy describes a broad range of neuropsychiatric abnormalities caused by advance hepatic insufficiency or portosystemic shunting.[1,2,3] The likelihood of developing hepatic encephalopathy correlates with the severity of the liver disease. Hepatic encephalopathy is broadly classified as either overt hepatic encephalopathy (neurologic and neuropsychiatric abnormalities detected with bedside examination and bedside tests) or minimal hepatic encephalopathy (normal mental status and normal neurologic examination in conjunction with abnormalities on psychometric testing).[4] Overt hepatic encephalopathy will occur in approximately 30 to 40% of individuals with cirrhosis at some point during their illness.[2] Patients with cirrhosis who undergo transjugular intrahepatic portosystemic shunts also frequently develop overt hepatic encephalopathy, with an estimated incidence of 30 to 50%.[3,5] Minimal hepatic encephalopathy is estimated to develop in more than 60% of patients with cirrhosis. The onset of hepatic encephalopathy in a patient with cirrhosis signals a very poor prognosis and reduced survival, especially if liver transplantation is not performed.[6,7]

Pathogenesis

Although some of the precise details of the pathogenesis of hepatic encephalopathy remain incompletely understood, there is a general consensus that elevated levels of ammonia play a central role in this disorder, primarily by acting as a neurotoxin that generates astrocyte swelling.[1] As part of the normal physiologic process, colonic bacteria and gut mucosal enzymes break down dietary proteins, which results in the release of ammonia from the gut into the portal circulation.[3,4] Normally, the ammonia is converted to urea in the liver. In many persons with liver failure or portosystemic shunting, the ammonia released into the portal circulation does not get adequately eliminated by the liver and it accumulates at high levels in the systemic circulation.[1,4] The circulating ammonia results in substantial levels of ammonia crossing the blood-brain barrier where rapid conversion to glutamine occurs by astrocytes; in the brain, astrocytes are the only cells that convert ammonia to glutamine.[1,4] Within astrocytes, glutamine levels accumulate, acting as an osmolyte to draw water inside the cell, which causes astrocyte swelling. The end result of the high circulating levels of ammonia is cerebral edema and intracranial hypertension.[4] Other factors, such as oxidative stress, neurosteroids, systemic inflammation, increased bile acids, impaired lactate metabolism, and altered blood-brain barrier permeability likely contribute in the process of hepatic encephalopathy.[1,4,8]

Nomenclature

In 1998, a consensus group at the 11th World Congress of Gastroenterology in Vienna proposed a
standardized nomenclature for hepatic encephalopathy based on the type of hepatic abnormality, the severity of the manifestations, and the frequency (episodic or persistent) (Figure 1).[9] The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus identifies disorientation or asterixis as the beginning of overt hepatic encephalopathy (grade II through IV), which consists of neurological and psychiatric abnormalities that can be detected by bedside clinical tests, whereas covert hepatic encephalopathy (minimal and grade 1) can only be distinguished by specific psychometric tests, as these patients have normal mental and neurological status on clinical examination.[4,10]
Clinical Features and Clinical Scales

Clinical Manifestations

Patients with hepatic encephalopathy may present with a wide array on neurologic and psychiatric manifestations, including alterations in intellectual capacity, memory, emotional, behavioral, psychomotor speed, and fine motor skills.[3,4] These can lead to apathy, irritability, decreased energy level, impaired sleep-wake cycle, impaired cognition, diminished consciousness, asterixis, or loss of motor control.[2,3] Although patients with hepatic encephalopathy may develop focal neurologic findings, such as hemiplegia, an alternative cause for a new focal neurologic deficit (e.g. intracerebral hemorrhage) should be investigated further. Often asterixis can be detected in patients with early to middle stages of hepatic encephalopathy.[2,4] To test for asterixis, the patient should extend their arms, dorsiflex their wrist, and hold this position (Figure 2).[3] A positive test for asterixis is characterized by an involuntary flapping tremor at the wrist due to abnormal functioning of the motor centers that control the tone of muscles involved with maintaining posture; this tremor can also be seen in the tongue, eyelids, lower extremities.[2,3] If the patient is too somnolent to raise his or her hands, then oscillating grip strength is another means to test for asterixis.[5] Parkinsonian-like symptoms, such as rigidity and tremors, can also be present.[2] Patients with severe hepatic encephalopathy can develop somnolence that can progress to coma. When evaluating a patient with suspected hepatic encephalopathy, it is important to consider and evaluate other causes of altered mental status.[4]

Clinical Scales for Grading Hepatic Encephalopathy

The following is a summary of the major scales used to grade the severity of hepatic encephalopathy.[5]

- **West Haven Criteria**: The West Haven criteria grades the severity of the hepatic encephalopathy based on a clinical assessment, with a score ranging from grade 0 (no abnormalities) to grade 4 (coma).[9,11]
- **International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN)**: The ISHEN consensus sets criteria for overt hepatic encephalopathy as onset of disorientation or asterixis.[10,12]
- **Full Outline of Unresponsiveness (FOUR)**: The FOUR score is a coma scale that assesses brain-stem and respiratory function through the scoring of four components: eye response, motor response, brain-stem reflex, and respirations.[13] This scale is a highly discriminating scoring system for assessment of patients with hepatic encephalopathy who become unresponsive.[14,15]
- **Glasgow Coma Scale**: For patients with grade 3 and 4 hepatic encephalopathy, the Glasgow Coma Scale is often used.[16]
- **Hepatic Encephalopathy Scoring Algorithm (HESA)**: This scoring system has been used to grade hepatic encephalopathy in clinical trials but use is not widespread in clinical practice.[17,18]
- **Clinical Hepatic Encephalopathy Staging Scale (CHESS)**: The CHESS system grades the severity of the hepatic encephalopathy on a linear scale that ranges from 1 to 9; the CHESS encephalopathy scale has primarily been used in clinical trials and is not widely used in clinical practice.[19]
- **Spectrum of Neurocognitive Impairment in Cirrhosis (SONIC)**: The SONIC approach provides a continuous spectrum for assessing hepatic encephalopathy rather than a categorical approach.[12]
Diagnosis and Testing

Diagnosis

Overt hepatic encephalopathy is diagnosed based on clinical findings and by excluding other causes of altered mental status.[2] The most common disorders to consider in the differential diagnosis of overt hepatic encephalopathy are medication-related adverse effects, severe electrolyte disorders (hyponatremia and hypercalcemia), uremia, systemic infection, central nervous system infection, psychiatric disorders, alcohol-related (intoxication, withdrawal, or Wernicke-Korsakoff syndrome), hypoglycemia, hypercapnia, nonconvulsive epilepsy, and intracranial bleeding or stroke.[2,4] As part of the diagnostic process, the clinician should categorize the type and severity of the overt hepatic encephalopathy.[2] For most patients, the West Haven criteria is considered the gold standard for categorizing the severity of overt hepatic encephalopathy; it grades the severity of the hepatic encephalopathy based on a clinical assessment, with a score ranging from grade 0 (no abnormalities) to grade 4 (coma) (Figure 3).[9,10] The Glasgow Coma Scale, however, may be more useful in patients with severe encephalopathy and a marked alteration in mental status (Figure 4).[2] The diagnosis of minimal hepatic encephalopathy requires specific psychometric testing.[20,21,22]

Laboratory Testing

In patients with known cirrhosis and suspected hepatic encephalopathy, laboratory testing serves an important role in identifying precipitating factors and in excluding alternative causes of altered mentation. Common laboratory testing includes assessment of liver and renal function, electrolytes, glucose, cultures, and drug screening. Although arterial and venous ammonia levels may correlate with the severity of hepatic encephalopathy, the blood sample has be to collected without the use of a tourniquet and must be transported on ice to the laboratory to be analyzed within 20 minutes to ensure accuracy of the results.[4] In addition, there are many non-hepatic causes of hyperammonemia, such as gastrointestinal bleeding, renal failure, hypovolemia, extensive muscle use, urea cycle disorder, parenteral nutrition, urosepsis, and use of certain medications (e.g. valproic acid). Although patients with hepatic encephalopathy have elevated serum ammonia levels, the severity of hepatic encephalopathy does not correlate with serum ammonia levels beyond a certain point.[23,24] For all of these reasons, obtaining serum ammonia levels to diagnose hepatic encephalopathy is not recommended, but if the test was ordered and the result was normal, the diagnosis of hepatic encephalopathy should prompt a reevaluation.[2] If a patient has known hepatic encephalopathy and is receiving medication treatment to specifically lower ammonia levels, serial monitoring of blood ammonia levels may be used to assess efficacy of treatment.[2]

Imaging

Brain computed tomographic (CT) imaging has low sensitivity for detecting early cerebral edema but may help to exclude other causes of altered mentation, such as an intracerebral hemorrhage. Brain magnetic resonance imaging (MRI) can be used to diagnose cerebral edema and other brain abnormalities associated with hepatic encephalopathy. Bilateral and symmetric hyperintensity of the globus pallidus in the basal ganglia on T1-weighted MRI imaging can be seen in patients with cirrhosis and hepatic encephalopathy, but these findings do not correlate with hepatic encephalopathy grade.[25] This finding is thought to result from excess circulating manganese levels. It is unclear if these MRI changes are associated with hepatic encephalopathy specifically, or instead may be caused by cirrhosis or portosystemic shunting. Thus, MRI is not used to diagnose or grade hepatic encephalopathy. Other types of imaging can also be used to assess for hepatic encephalopathy precipitating factors, such as chest radiograph to evaluate for infection or bowel abdominal imaging to evaluate for obstruction or ileus.

Psychometric Tests
In the absence of obvious physical examination findings of hepatic encephalopathy, neuropsychometric tests can be used to identify disturbances in attention, visuospatial abilities, fine motor skills, and memory. These neuropsychometric tests are necessary to make the diagnosis of minimal hepatic encephalopathy.[26] Unfortunately, most of these tests require special expertise, can be very time consuming to administer, and may not be widely available for use in the United States, as normative data for the local population is needed. They are also nonspecific as any cause of brain dysfunction can lead to abnormal results. From a practical standpoint, the diagnosis of minimal hepatic encephalopathy is important since it is often associated with impaired driving skills.[27, 28] The following summarizes some of the most highly recognized and widely used psychometric tests to diagnose minimal hepatic encephalopathy.[2, 21, 22, 29]

- **Critical Flicker-Frequency Test (CFF):** The CFF test utilizes the Schuhfried Test System to assess visual discrimination and functional efficiency of the cerebral cortex (general arousal).[30, 31] The CFF is performed by using a luminous diode to generate intrafoveal stimulation and thereby assess the patient’s ability to detect light flickering; the test is a sensitive and reproducible means to quantify the severity of minimal hepatic encephalopathy.[30, 31] From a practical standpoint, this test requires specialized equipment and it is not valid in persons with red-green color blindness.[2]

- **Stroop Test:** The Stroop Test evaluates selective attention and processing speed by the interference between visual color and a written color name. EncephalApp Stroop is a smartphone application that utilizes a smartphone or tablet as a screening tool for minimal hepatic encephalopathy by assessing selective attention and inhibitory responses.[32, 33] The test utilizes an "off state" that has neutral stimuli and an "on state" that has incongruent stimuli.

- **Inhibitory Control Test (ICT):** The ICT is a computerized test that evaluates sustained attention and working memory impairment.[34, 35] During the ICT, which takes about 15 minutes, subjects see a continuous stream of letters on a computer screen and they are instructed to hit a button if they see an X followed by a Y; the test utilizes lures (XX or YY) to evaluate the ability of the subject to inhibit the response to the lures.[34, 35] The test is scored based on the number of correct responses to targets and the lure rate.[21, 36]

- **Number Connection Test Part A and Part B:** The Number Connection Tests can be quickly and easily administered in the office or at the bedside, but these tests have limited specificity. (Figure 5).[37, 38] The number tests can be administered as a stand-alone test or as part of the Portosystemic Encephalopathy (PSE) Syndrome Test or Psychometric Hepatic Encephalopathy Score (PHES).

- **Portosystemic Encephalopathy (PSE) Syndrome Test:** The PSE is a paper-and-pencil battery of approximately 30 different psychometric tests to assess various cognitive domains; the PSE was endorsed by the Working Party at the 1998 World Congress of Gastroenterology in Vienna as the gold standard for the diagnosis of minimal hepatic encephalopathy, but clinically this test has been replaced by more practical tests.[9, 38].

- **Psychometric Hepatic Encephalopathy Score (PHES):** The PHES utilizes a subset of five tests taken from the Portosystemic Encephalopathy (PSE) syndrome test.[38] The five tests consist of: (1) Number Connection Test A, (2) Number Connection Test B, (3) Digit Symbol Test, (4) Serial Dotting Test and the (5) Line Tracing Test.[21, 38] This test primarily evaluates attention, visuospatial perception, visuospatial construction, psychomotor speed, and motor accuracy.[21, 22]

- **Repeatable Battery for the Assessment of Neurological Status (RBANS):** The RBANS are computerized psychometric tests (e.g. inhibitory control test) and neurophysiologic tests used to diagnose hepatic encephalopathy in clinical trials.[26, 39]

- **Continuous Reaction Time (CRT) Test:** The CRT index test measures the stability of motor reaction times (pressing of a button as a response to auditory stimuli) and requires simple software and hardware to administer.[40, 41]

- **SCAN Test:** The SCAN Test measures speed and accuracy on a digit recognition memory exam in a computerized format.[42]
Electroencephalography

Electroencephalography (EEG) can assess for mild hepatic encephalopathy and is more objective than psychometric tests, but it is also nonspecific as it can be affected by other metabolic disturbances. It requires special instruments and thus is not commonly used in clinical practice.[5]
Approach to the Management of Hepatic Encephalopathy

Basic Principles of Management

The 2014 Practice Guideline on Hepatic Encephalopathy from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver provides excellent recommendations regarding the management of patients with hepatic encephalopathy.[2] This 2014 Practice Guideline on Hepatic Encephalopathy recommends that, in most cases, treatment of hepatic encephalopathy is indicated only for patients with overt hepatic encephalopathy.[2] The initial approach to management of acute hepatic encephalopathy should focus on providing supportive care, identifying and treating any precipitating causes, reducing nitrogenous load in the gut, and assessing the need for long term therapy and liver transplant evaluation.[43] Infections play a particularly important role in precipitating overt hepatic encephalopathy.[44, 45] The AASLD 2014 Practice Guideline on Hepatic Encephalopathy has the following key recommendations for the general principles regarding prevention and management of episodic overt hepatic encephalopathy resulting from cirrhosis (type C):[2]

- Patients with an episode of overt hepatic encephalopathy should be actively treated, regardless of whether it occurred spontaneously or it was precipitated.
- Primary prophylaxis to prevent an episode of overt hepatic encephalopathy is not required (even after transjugular intrahepatic portosystemic shunt [TIPS] placement), unless the patient has known high risk for developing hepatic encephalopathy.
- Initiate secondary prophylaxis against hepatic encephalopathy after an episode of overt hepatic encephalopathy.
- Patients with liver failure and intractable overt hepatic encephalopathy should be considered for referral for liver transplantation.

Correction of Precipitating Factors

Among the precipitating factors for hepatic encephalopathy, common categories include: (1) increased nitrogen load (e.g. gastrointestinal bleed, infection, excess dietary protein), (2) decreased toxin clearance (e.g. hypovolemia, renal failure, constipation, portosystemic shunt, medication noncompliance, acute or chronic liver failure), and (3) altered neurotransmission (e.g. sedating medication, alcohol, hypoxia, hypoglycemia).[43] At least 80% of patients with overt hepatic encephalopathy improve after correction of these precipitating factors.[46] Patients with grade 3 or higher hepatic encephalopathy may need to be managed in an intensive care or step down unit, with consideration of intubation for airway protection if needed.[2]

Prevention of Recurrent Hepatic Encephalopathy

Once patients demonstrate clinical improvement, management then transitions to the prevention of recurrent hepatic encephalopathy, including reinforcement of compliance with treatment. Therapy for hepatic encephalopathy may be discontinued if a precipitant is identified and appropriately managed in patients who do not have a prior history of overt hepatic encephalopathy. Large dominant spontaneous portosystemic shunts can be embolized in select patients with reasonable liver function leading to improvement or resolution of overt hepatic encephalopathy.[47]

Liver Transplantation Referral

In one retrospective study, it was found that after the first episode of acute hepatic encephalopathy, survival probability drops to less than 50% at 1 year and less than 25% at 3 years.[48] The 2014 Practice Guideline on Hepatic Encephalopathy states that overt hepatic encephalopathy by itself is not an indication for liver transplantation, but patients who have severe overt hepatic encephalopathy that is refractory to maximal therapy, may be considered for liver transplant referral.
In contrast, these guidelines recommend that liver transplantation is indicated for patients with liver failure who have overt hepatic encephalopathy that is recurrent and intractable poor liver function. In addition, in certain patients who do not have liver failure, transplantation should be considered if the hepatic encephalopathy has not improved with optimal medical therapy and it has severely compromised the patient's quality of life.\[2\]
Medical Therapy for Overt Hepatic Encephalopathy

Rapid response to first-line medical therapy supports the diagnosis of hepatic encephalopathy. Most patients will respond within 24 to 48 hours of initiation of treatment. Prolongation of symptoms beyond 72 hours despite attempts at treatment should prompt further investigation for other causes of altered mentation. In most situations, the preferred approach is to initiate empiric therapy for hepatic encephalopathy and concomitantly assess for alternative causes of altered mental status and identify precipitating causes. Treatment of acute overt hepatic encephalopathy should be followed by prevention of secondary hepatic encephalopathy. Medical therapy for overt hepatic encephalopathy includes management of episodic hepatic encephalopathy (Figure 6) and persistent hepatic encephalopathy (Figure 7).

Nonabsorbable Disaccharides

Nonabsorbable disaccharides, such as lactulose or lactitol (not available in the United States), decrease the absorption of ammonia and are considered a first-line treatment for overt hepatic encephalopathy. Lactulose is metabolized by bacteria in the colon to acetic and lactic acid, which reduces colonic pH, decreases survival of urease producing bacteria in the gut, and facilitates conversion of ammonia (NH₃) to ammonium (NH₄⁺), which is less readily absorbed by the gut. The cathartic effect of these agents also increases fecal nitrogen waste. Although conflicting data exists on the effectiveness of nonabsorbable disaccharides in the management of hepatic encephalopathy, extensive clinical experience supports use of this therapy. Lactulose-related adverse effects include abdominal cramping, flatulence, and diarrhea; excessive doses of lactulose should be avoided as it can cause severe diarrhea that can lead to hypovolemia and electrolyte imbalances.

- **Initial Dosing:** For acute overt hepatic encephalopathy, the usual starting dose of lactulose is 25 mL (16.7 g) oral syrup every 1 to 2 hours until the patient has at least two soft bowel movements.
- **Maintenance Dosing:** Once the initial effect of lactulose has been achieved the dose should be adjusted with the goal for the patient to have 2 to 3 soft bowel movements per day. This dose typically falls in the range of to 10 to 30 g (15 to 45 mL) 2 to 4 times daily. Lactulose may be continued indefinitely for those with recurrent or persistent hepatic encephalopathy.
- **Comatose Patients:** For comatose patients, the medication can be administered through a nasogastric tube or rectally as an enema (300 mL in 1 L of water every 6 to 8 hours) until the patient is awake enough to start oral therapy.

Antimicrobial Therapy

The goal of antimicrobial therapy is to alter the gut microbiota to create a more favorable microbiome that results in lower endogenous bacterial production of ammonia. Rifaximin is now the preferred antimicrobial agent for the treatment of overt hepatic encephalopathy.

- **Rifaximin:** The oral antimicrobial rifaximin is minimally absorbed (less than 0.4%) and has broad-spectrum activity against gram-positive, gram-negative aerobic, and anaerobic bacteria. Rifaximin (550 mg twice daily) has been shown to be effective in treating hepatic encephalopathy. In a large, multicenter trial, rifaximin with lactulose maintained remission from hepatic encephalopathy better than lactulose alone and also reduced the number of hospitalizations involving hepatic encephalopathy. Although rifaximin is usually well tolerated, lactulose should be used as the initial first-line treatment with rifaximin used as add-on therapy if needed.
- **Neomycin:** The oral antimicrobial neomycin reduces bacterial production of ammonia by inhibiting the enzyme activity of glutaminase, an enzyme that converts glutamine to glutamate and ammonia. Oral neomycin (1 to 4 g daily in divided doses) has been
shown to have some efficacy for the treatment of hepatic encephalopathy, but this agent is not routinely used because of major potential adverse effects, including ototoxicity and nephrotoxicity.[11,55,57] Neomycin should be considered only as an alternative agent for treating overt hepatic encephalopathy.[2]

- **Metronidazole**: Treatment of overt hepatic encephalopathy with metronidazole targets the treatment of gram-negative anaerobic gut bacteria. These anaerobic bacteria produce urease that hydrolyzes urea to ammonia; decreasing the quantity of anaerobic organisms is postulated to result in decreased ammonia production in the gut.[55] In one study, oral metronidazole 200 mg 4 times daily had similar efficacy as neomycin.[58] Long-term use of metronidazole is associated with potential neurotoxicity. Metronidazole should be considered only as an alternative agent for treating overt hepatic encephalopathy.[2]

### Nutrition

Around 75% of patients with hepatic encephalopathy have moderate-to-severe protein-calorie malnutrition. Overall, patients with overt hepatic encephalopathy should have a total daily energy intake of 35 to 40 kcal/kg (based on ideal body weight). In addition, patients should ideally have multiple evenly distributed small meals (or liquid nutritional supplements) throughout the day, along with a nighttime snack.[2]

- **Protein Intake**: Dietary protein restriction is not advised for the management of hepatic encephalopathy since loss of skeletal muscle, which metabolizes ammonia, can lead to worsening hepatic encephalopathy.[59,60] For patients with hepatic encephalopathy, the recommended protein intake should be in the range of 1.2 to 1.5 g/kg/day.[2] Some experts have recommended a relative higher intake of vegetable and dairy sources of protein than animal-based protein sources.[2,60,61] In addition, the intake of increased fiber can have benefit as non-absorbable vegetable fiber can help promote nitrogen clearance via the stool.[55]

- **Branched-Chain Amino Acids**: Patients with cirrhosis can have an alteration in the balance of amino acids with a relative increase in aromatic amino acids relative to branched-chain amino acids, which is believed to contribute to hepatic encephalopathy.[62,63] The impact of oral branched-chain amino acids on patients with episodic hepatic encephalopathy was recently summarized in a metaanalysis of 16 randomized clinical trials; this analysis concluded that use of branched-chain amino acids had a beneficial effect on hepatic encephalopathy but did not impact nutritional parameters, quality of life, or mortality.[64] Intravenous branched-chain amino acids have no benefit for patients with hepatic encephalopathy.[65] The use of oral branched-chain amino acids is considered as an alternative (or additional) agent in treatment of patients with hepatic encephalopathy who have not responded to combination therapy with lactulose and rifaximin.[2] The oral formulations of branched-chain amino acids are not used in first-line treatment as they are unpalatable and costly.

- **L-Ornithine-L-Aspartate**: Studies in animals suggest that L-ornithine-L-aspartate can lower blood concentration of ammonia and potentially improve hepatic encephalopathy. One randomized study showed use of intravenous L-ornithine-L-aspartate (20 g/day infused over 4 hours) for 7 days was associated with improved psychometric testing and lower post-prandial levels of ammonia.[66] The use of intravenous L-ornithine-L-aspartate should be considered as an alternative (or additional) agent in treatment of patients with hepatic encephalopathy who have not responded to combination therapy with lactulose and rifaximin.[2] Oral therapy with L-ornithine-L-aspartate is not effective and is not recommended for treatment of hepatic encephalopathy.[2]

- **Zinc**: The element zinc is a cofactor for urea cycle enzymes and it is an important cofactor in ammonia detoxification; for multiple reasons, it is commonly deficient in cirrhotic patients.[55] A randomized, open-label trial suggested possible benefit with zinc supplementation in patients with hepatic encephalopathy,[67] but other studies have shown no benefit.[68] Thus, zinc supplementation cannot be routinely recommended in patients.
with hepatic encephalopathy.
Summary Points

- Overt hepatic encephalopathy consists of neurological and psychiatric abnormalities that can be detected by bedside clinical tests, whereas minimal hepatic encephalopathy can only be distinguished by specific psychometric tests.
- There are many grading scales available for hepatic encephalopathy, including the long standing West Haven Criteria, which is the most commonly used system.
- Diagnosis of overt hepatic encephalopathy requires the exclusion of alternate causes of altered mental status. Serum ammonia levels should not be used as a diagnostic tool or as a means of monitoring response to treatment.
- Treatment of acute overt hepatic encephalopathy should include: (1) supportive care, (2) identifying and treating any precipitating factors, (3) reduction of nitrogenous load in the gut, and (4) assessment of need for long-term therapy and liver transplant evaluation.
- Lactulose can be used as initial drug therapy for the treatment of acute hepatic encephalopathy. Rifaximin should be added for those patients who do not have an adequate response to lactulose. Subsequently, the addition of oral branched-chain amino acids or intravenous L-ornithine-L-aspartate can be considered in patients who do not respond to the combination of lactulose and rifaximin.
- Prevention of recurrent hepatic encephalopathy or treatment of persistent hepatic encephalopathy includes drug therapy as well as prevention or avoidance of precipitating factors.
- Protein restriction should be avoided as a general rule, as it can actually lead to worsening of hepatic encephalopathy. Cirrhotic patients are advised to consume 1.25 to 1.5 g/kg protein daily.
- Liver transplant evaluation should be considered in appropriate candidates once a diagnosis of overt hepatic encephalopathy is made. Liver transplantation is indicated in patients who have liver failure and recurrent intractable overt hepatic encephalopathy.
Citations


References


**Figures**

**Figure 1 Proposed Nomenclature of Hepatic Encephalopathy**


<table>
<thead>
<tr>
<th>Type</th>
<th>Encephalopathy Associated With</th>
<th>Subcategory</th>
<th>Subdivisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Acute liver failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Portal-systemic bypass and no intrinsic hepatocellular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Cirrhosis and portal hypertension and/or portal-systemic shunts</td>
<td>Episodic</td>
<td>Precipitated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spontaneous*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent**</td>
<td>Mild (grade 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe (grades 2 to 4)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment-dependent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimal</td>
<td></td>
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</tbody>
</table>

*Without recognized precipitating factors
*Recurrent = two episodes within one year
**Persistent = cognitive deficits that impact negatively on social and occupational functioning
Figure 2 Testing for Asterixis (Flap Test)

To test for asterixis, the arms are extended and the wrists dorsiflexed. The presence of asterixis is defined as a tremor of the hand with arm extended and wrist held back (dorsiflexed); tremor of hands and extended failure to hold hands in this position.

Source: photograph by David H. Spach, MD
**Figure 3 West Haven Criteria for Semiquantitative Grading of Mental Status**


<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trivial lack of awareness  &lt;br&gt; Euphoria or anxiety  &lt;br&gt; Shortened attention span  &lt;br&gt; Impaired performance of addition</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy or apathy  &lt;br&gt; Minimal disorientation of time or place  &lt;br&gt; Subtle personality changes  &lt;br&gt; Inappropriate behavior</td>
</tr>
<tr>
<td>3</td>
<td>Somnolence to semi-stupor but responsive to verbal stimuli  &lt;br&gt; Confusion  &lt;br&gt; Gross disorientation</td>
</tr>
<tr>
<td>4</td>
<td>Coma (unresponsive to verbal or noxious stimuli)</td>
</tr>
</tbody>
</table>
**Figure 4 Glasgow Coma Scale**


<table>
<thead>
<tr>
<th>Glasgow Coma Scale</th>
<th>Scale</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Opening Response</strong></td>
<td>Eyes open spontaneously</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Eyes open to verbal command, speech, or shout</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Eyes open to pain (not applied to face)</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No eye opening</td>
<td>1 Point</td>
</tr>
<tr>
<td><strong>Verbal Response</strong></td>
<td>Oriented</td>
<td>5 Points</td>
</tr>
<tr>
<td></td>
<td>Confused conversation, but able to answer questions</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Inappropriate responses, words discernible</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Incomprehensible sounds or speech</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No verbal response</td>
<td>1 Point</td>
</tr>
<tr>
<td><strong>Motor Response</strong></td>
<td>Obeys commands for movement</td>
<td>6 Points</td>
</tr>
<tr>
<td></td>
<td>Purposeful movement to painful stimulus</td>
<td>5 Points</td>
</tr>
<tr>
<td></td>
<td>Withdraws from pain</td>
<td>4 Points</td>
</tr>
<tr>
<td></td>
<td>Abnormal (spastic) flexion, decorticate posture</td>
<td>3 Points</td>
</tr>
<tr>
<td></td>
<td>Extensor (rigid) response, decerebrate posture</td>
<td>2 Points</td>
</tr>
<tr>
<td></td>
<td>No motor response</td>
<td>1 Point</td>
</tr>
</tbody>
</table>

**Minor Brain Injury** = 13-15 points; **Moderate Brain Injury** = 9-12 points; **Severe Brain Injury** = 3-8 points
In the number connection test Part A, the patient is instructed to join up the numbers in sequence as fast as possible.

In the number connection test Part B, the patient is instructed to join the numbers and the letters alternatively in sequence as fast as possible. For example, connect 1 to A to 2 to B to 3, etc.

Figure 6 Therapies for Overt Episodic Hepatic Encephalopathy


<table>
<thead>
<tr>
<th>Therapies for Overt Episodic Hepatic Encephalopathy (HE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Supportive care, airway protection</td>
</tr>
<tr>
<td>2. Identification and treatment of precipitating causes</td>
</tr>
<tr>
<td>3. Lactulose: 10 to 30 g (15-45 mL) orally (per nasogastric tube) every 1 to 2 hours until bowel movement, then 10 to 30 g orally 2 to 4 times daily, titrated to 2 to 3 soft stools daily; or lactulose enema (300 mL in 1 L water) every 6 to 8 hours until able to take oral form of medication</td>
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<tr>
<td>4. Rifaximin: 550 mg PO twice daily</td>
</tr>
<tr>
<td>5. Do not limit protein intake</td>
</tr>
<tr>
<td>6. Consider need for long term management of HE and liver transplant evaluation</td>
</tr>
</tbody>
</table>
**Figure 7 Therapies for Overt Persistent Hepatic Encephalopathy**


<table>
<thead>
<tr>
<th>Therapies for Overt Persistent Hepatic Encephalopathy (HE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Avoidance and prevention of precipitating factors</td>
</tr>
<tr>
<td>2. Lactulose: 10 to 30 g PO 2 to 4 times daily, titrated to 2 to 3 soft stools daily</td>
</tr>
<tr>
<td>3. Rifaximin 550 mg PO twice daily</td>
</tr>
<tr>
<td>4. Maintain protein intake of 1.0 to 1.5 g/kg daily, over 4 to 6 meals daily with nighttime snack. Vegetable-based protein is preferred for patients with severe persistent HE. Oral branched-chain amino acid supplementation may be considered in those who are intolerant of protein.</td>
</tr>
<tr>
<td>5. For severe persistent HE, some patients may be considered for closure or reduction of transhepatic intrahepatic portosystemic shunt (TIPS) diameter or occlusion/embolization of larger portosystemic collaterals (not commonly done in the US)</td>
</tr>
<tr>
<td>6. Liver transplant referral for appropriate candidates</td>
</tr>
</tbody>
</table>