Hepatic Encephalopathy: Natural History, Epidemiology, and Treatment Modalities

Abstract
Hepatic encephalopathy (HE) is a neuropsychiatric complication of either acute or chronic hepatic insufficiency. HE can be overt, with characteristic neurological manifestations ranging from asterixis and confusion to coma, or minimal, with subtle mental changes that can be detected only with psychometric testing. Most patients with cirrhosis will develop some degree of HE during the course of their disease, with up to 45% developing overt HE and up to 80% developing minimal HE.

HE results from impaired first-pass removal of ammonia by a compromised liver, thus increasing the concentration of arterial ammonia. Ammonia accumulates in the brain and ultimately results in astrocyte swelling and increased intracranial pressure. Current therapies act by decreasing the production of ammonia in the colon and include nonabsorbable disaccharides such as lactulose, minimally absorbed antibiotics such as rifaximin, and probiotics. This review summarizes recent advances in the diagnosis and treatment of HE, with an emphasis on minimal HE.

Educational Objectives
Upon completion of this activity, participants should be better able to:
- Review the epidemiology and natural history of hepatic encephalopathy (HE)
- Outline how increases in arterial ammonia ultimately result in the neuropsychiatric abnormalities seen in HE
- Differentiate between factors considered in the diagnosis of overt HE and those considered in the diagnosis of minimal HE
- Describe treatment modalities used in the treatment of HE

Target Audience
This activity has been designed to meet the educational needs of hepatologists, gastroenterologists, physician assistants, and nurse practitioners involved in the management of chronic liver disease (CLD).

Goal Statement
To provide important clinical data about the management of hepatic encephalopathy (HE)
Hepatic encephalopathy (HE) is a disturbance in central nervous system function that can occur in patients with either acute or chronic hepatic insufficiency. HE includes a spectrum of neuropsychiatric abnormalities ranging from mild changes in personality or behavior to stupor and coma. The subtype referred to as minimal HE (MHE), the most common form of HE, is associated with cognitive and motor abnormalities that can be diagnosed only with psychometric or neurophysiologic tests. Overt HE (OHE) can be diagnosed by clinical signs and symptoms, the existence of acute or chronic liver disease, and the exclusion of other causes of an abnormal mental state.¹

Treatment goals for OHE include provision of supportive care, identification and removal of precipitating factors, reduction of nitrogenous load from the gut, and an assessment of the need for long-term therapy.¹ It is now recognized that MHE associated with cirrhosis can have a profound effect on a patient’s quality of life, impairs driving skill and work performance, and portends a high probability of progression to OHE.²⁵ While standard-of-care for therapy has not been established for MHE, several treatment options exist. This newsletter will review HE in general, with a special emphasis on recent advances in the diagnosis and treatment of MHE.
Epidemiology and Natural History of HE

HE occurs as a complication of advanced liver disease, either chronic or acute. It is difficult to accurately assess the disease burden of chronic liver disease (CLD) since liver disease frequently has an insidious onset and a long latency period. Most patients, therefore, do not seek medical attention until late in the clinical course of the disease when complications develop. The prevalence of CLD in the United States is approximately at between 7 and 11 million cases. Approximately 150,000 individuals are newly diagnosed with CLD each year by gastroenterologists, and, of these, approximately 30,000 (20%) present with cirrhosis. Chronic hepatitis C, either alone or in combination with alcohol-related disease, accounts for nearly two-thirds of newly diagnosed CLD (Figure 1). While the prevalence of hepatitis C is decreasing, complications including cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and death in the large cohort of patients infected in the 1980s and early 1990s are expected to increase significantly through 2030 as the disease progresses.

As with CLD in general, accurate data about the incidence and prevalence of HE is lacking. It is thought that most patients with cirrhosis will develop some degree of HE at some point during the course of the disease. Current estimates are that MHE occurs in up to 80% of cirrhotic patients, while OHE occurs in up to 45% of cirrhotic patients and up to 50% of patients with transjugular intrahepatic portosystemic shunts (TIPS). Patients with MHE have a higher likelihood of developing OHE than those with no symptoms. OHE is associated with a poor prognosis. Following the first episode of OHE, 1 study found that survival probability was 42% at 1 year and 23% at 3 years. OHE also occurs as a complication of acute liver failure.

Pathogenesis of HE

While several theories have been proposed to explain the pathogenesis of HE, the exact cause is still controversial. A multifactorial etiology is most likely involved in which arterial ammonia, cerebral edema, oxidative stress, and inflammatory mediators are implicated (Figure 2). HE is

Precipitating Factors for HE

<table>
<thead>
<tr>
<th>Precipitating Factor</th>
<th>Possible Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive protein intake</td>
<td>Increased ammonia production</td>
</tr>
<tr>
<td>Constipation</td>
<td>Increased ammonia absorption</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Astrocyte swelling</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>Increased ammonia production</td>
</tr>
<tr>
<td>Infection (eg, spontaneous bacterial peritonitis)</td>
<td>Synergistic effects of cytokines</td>
</tr>
<tr>
<td>Sedative drugs</td>
<td>Increased brain sensitivity</td>
</tr>
<tr>
<td>Azotemia</td>
<td>Increased ammonia generation</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Increased renal production of ammonia</td>
</tr>
<tr>
<td>Surgery</td>
<td>Protein catabolism</td>
</tr>
<tr>
<td>Alkalosis</td>
<td>Increased diffusion of ammonia through blood-brain barrier</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Mechanism uncertain</td>
</tr>
<tr>
<td>– Fluid restriction</td>
<td>– Diarrhea</td>
</tr>
<tr>
<td>– Diuretics</td>
<td>– Vomiting</td>
</tr>
<tr>
<td>– Excessive paracentesis</td>
<td></td>
</tr>
<tr>
<td>Arterial hypotension/hypovolemia</td>
<td></td>
</tr>
<tr>
<td>– Gastrointestinal bleeding</td>
<td>– Shock, operation</td>
</tr>
<tr>
<td>– Peripheral vasodilation</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
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<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Psychotropic medications (benzodiazepines, morphine)</td>
<td></td>
</tr>
<tr>
<td>Portosystemic shunts</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
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<tr>
<td></td>
<td>Protein catabolism</td>
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<tr>
<td></td>
<td>Central nervous system depression</td>
</tr>
<tr>
<td></td>
<td>Reduced metabolism of toxins</td>
</tr>
<tr>
<td></td>
<td>Hepatic dysfunction</td>
</tr>
</tbody>
</table>

Table 1
Adapted from Mullen KD. Aliment Pharmacol Ther. 2006;25(Suppl 1):11-16.
Nom enclature for Categorizing Hepatic Encephalopathy According to Cause, Duration, and Characteristics

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Category</th>
<th>Subcategory</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Acute liver failure)</td>
<td>Hepatic encephalopathy associated with acute liver failure</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>B (Bypass)</td>
<td>Hepatic encephalopathy associated with portosystemic bypass and no intrinsic hepatocellular disease</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| C (Cirrhosis)| Hepatic encephalopathy associated with cirrhosis and portal hypertension or portosystemic shunts | Episodic                    | • Precipitated  
              |                                                   | Persistent          | • Spontaneous  
              |                                                   |                    | • Recurrent       |
|              |                                                                 | Minimal                     | • Mild                           |
|              |                                                                 |                             | • Severe                         |
|              |                                                                 |                             | • Treatment-dependent            |

Table 2
Adapted from Mullen KD. *Aliment Pharmacol Ther.* 2006;25(suppl 1):11-16.

### Common Neurologic Manifestations of HE

- Confusion or coma
- Cognitive deficits detected by special testing
- Hyperreflexia
- Babinski sign
- Slow, monotonous speech
- Extrapyramidal-type movement disorders
- Loss of fine motor skill
- Asterixis
- Clonus
- Decerebrate posturing
- Decorticate posturing
- Hyperventilation
- Seizures

Table 3
Adapted from Mullen KD. *Semin Liver Dis.* 2007;27(suppl 2):3-9.

Associated with increased arterial levels of ammonia in both acute and chronic liver disease. Approximately 80% of ammonia in the portal vein, derived from both urease activity of colonic bacteria and the deamidation of glutamine in the small bowel, is normally removed with first-pass extraction in those with a healthy liver. Impaired first-pass removal of ammonia by a liver compromised by either advanced disease or a portal-systemic shunt results in increased levels of arterial ammonia in the systemic circulation. The increased arterial concentration of ammonia increases the permeability of the blood brain barrier to ammonia. As ammonia accumulates in the brain, it is taken up by astrocytes which synthesize glutamine by the amidation of glutamate. Accumulation of glutamine in the astrocytes results in osmotic swelling of the astrocytes leading to increased intracranial pressure. Inflammation is thought to have a synergistic effect on the cerebral effects of ammonia. A precipitating factor can frequently be identified in cases of OHE (Table 1).

### Diagnosis of HE

The nomenclature for characterizing the various forms of HE according to cause, duration, and characteristics has been standardized and has been generally accepted. (Table 2). Common neurologic manifestations of HE are listed in Table 3. For OHE, the characteristic neurologic features, the existence of acute or chronic liver disease, the exclusion of other etiologies of neuropsychiatric symptomatology, and the identification of a precipitating factor are essential for establishing a diagnosis.
hepatic encephalopathy (PHES). A patient is considered to have MHE if they fall more than 2 standard deviations from normal on at least 2 psychometric tests. Administration of psychometric tests can take from one-half to 1 hour depending on the tests utilized. Although psychometric tests can be administered in the office setting, it is probably best to have the tests performed in a psychology testing laboratory where the staff is experienced in administering and interpreting the tests.

A recent survey of American Association for the Study of Liver Diseases members found that, while 84% of those surveyed thought that MHE was a significant problem and 74% thought that it should be tested for, 34% tested less than 50% of their at-risk patients and 38% never tested for MHE. Among reasons given for not testing were that testing adds time to the clinic visit (cited by 85% of those who did not test) and that testing was difficult and expensive and required trained personnel (cited by 75% of those who did not test). Recently developed computer-based tests may improve testing rates. The Critical Flicker Frequency (CFF) test and the Inhibitory Control Test (ICT) are 2 such tests. To administer the CFF, a portable, battery-powered analyzer (Hepatonorm Analyzer) evokes pulses of light. The initial frequency of the pulse is 60 Hz which gives the impression of a steady light. The frequency is gradually reduced, and the patient identifies the frequency at which the steady light changes to a flicker by pressing a switch. In a recent clinical study, 35 patients with cirrhosis and MHE (diagnosed by PHES) had a lower mean CFF (35.6±4.1 Hz) compared with 79 patients with cirrhosis without MHE (40.5±3.7) or compared with 103 healthy controls (42.7±3.6) (P<0.001). The mean CFF correlated with PHES (r=0.54; P<0.001). The authors concluded that “CFF is a simple, reliable, and accurate method for the diagnosis of MHE.”

The ICT is a computer based test that has been utilized to characterize other central nervous system disorders such as schizophrenia and traumatic brain injury. The test consists of a presentation of letters at 500 ms intervals.
interspersed with the letters X and Y. The patient is instructed to respond only when X and Y are alternating (called targets) and to refrain from responding when X and Y are not alternating (called lures). The test consists of a training run and 6 test runs of approximately 2 minutes each. The 6 test runs contain 40 lures, 212 targets, and 1728 random letters. The lure and target response rates and the lure and target reaction times are automatically calculated. Lower lure response rates, higher target response rates, and shorter lure and target response times are indicative of good psychometric performance.19,21 A recent trial compared ICT lure and target response rates and lure and target reaction times in cirrhotic patients diagnosed as MHE+ (n=87) or MHE– (n=48) by NCT A, BDT, and DST. Using a cut off of >5 lures per person to diagnose MHE, of the 87 patients identified as MHE+ by psychometric testing, 76 had >5 lures. Of the 48 patients identified as MHE– by psychometric testing, 37 had ≤5 lures. ICT testing was performed on a subpopulation of patients (n=10) tested prior to (2±6±5 days) and after (3±5±8 days) transvenous intrahepatic portosystemic shunting (TIPS) placement. Mean ICT lure response increased significantly from 5.2±3.8 to 9.4±4.6 (P=0.02). Conversely, a subgroup of patients (n=17) placed on a 60-day probiotic yogurt supplemental diet had a significant decrease in lure response from 10±5 prior to the diet to 5±3 after 60 days of yogurt supplementation (P=0.002). The ICT appears to be a sensitive, reliable, and valid test for both the diagnosis of MHE and for monitoring changes in clinical status.19

### Treatment of HE

Treatment objectives depend on the type and grade of HE and include the reversal of acute episodes, the prevention of acute episodes, improvement in persistent HE, and improvement in MHE.22 For OHE, treatment goals include provision of supportive care (eg, nursing support for disoriented patients, prophylactic tracheal intubations for deeper stages, adequate nutrition during altered mental state), identification and removal of precipitating factors (see Table 1), reduction of nitrogenous load from the gut (eg, the use of nonabsorbable disaccharides and/or antibiotics), and assessment of the need for long-term therapy (control of potential precipitating factors, higher likelihood of recurrent encephalopathy, assessment of the need for liver transplantation).1 Treatment of MHE is targeted toward reduction in ammonia created by bacterial degradation of protein in the colon and includes nonabsorbable disaccharides, antibiotics, and probiotics.

### Nonabsorbable Dissacharides

The nonabsorbable disaccharides lactulose and lactitol are considered the standard treatment...
for HE. A recent systemic review of randomized trials concluded, however, that there is insufficient evidence to support or refute the use of nonabsorbable disaccharides for HE. Only lactulose is available in the United States and it has been approved since 1988 for the treatment of portal-systemic encephalopathy including the stages of hepatic pre-coma and coma. It is available under the trade names Cholac, Enulose, and Generlac as well as several generic versions as a solution containing 10 gm/15 mL that can be used for oral or rectal administration. Lactulose is metabolized by colonic bacteria to lactic acid and acetic acid, creating an unfavorable acidic environment for bacteria involved in the production of ammonia and a modification of the bacterial flora. Absorbable ammonia is converted to nonabsorbable ammonium ion in the acidic pH. Ammonia is thus trapped in the colon which effectively lowers plasma ammonia concentrations.

Table 6 presents data from clinical trials that have studied the effect of lactulose on the performance of psychometric tests in patients with MHE. Doses utilized ranged between 18 and 40 gm/day; treatment durations ranged between 2 and 3 months. Each trial found a statistically significant improvement in psychometric tests at trial end compared with baseline in the lactulose study arms, while no change was observed in test results in the no-treatment study arms. Adverse events associated with the use of lactulose include abdominal cramping, diarrhea, and flatulence. If diarrhea develops, dosage should be reduced. Protracted diarrhea may cause hypertonic dehydration and hyper-natremia which may aggravate the patient's mental state. The adherence rate for lactulose is low.

Minimally Absorbed Oral Antibiotics

Minimally absorbed antibiotics that have been used in the treatment of HE include neomycin (generics), metronidazole (Flagyl; generics), vancomycin (Vancocin), paromomycin (generics), and rifaximin (Xifaxan). Antibiotics can reduce or eliminate colonic bacteria and thus prevent the production of ammonia at its source. While the above antibiotics are largely unabsorbed, the potential for systemic adverse effects limits prolonged use of neomycin (ototoxicity, nephrotoxicity), metronidazole (peripheral neurotoxicity), vancomycin (increased risk for bacterial resistance), and paromomycin (ototoxicity, nephrotoxicity), making them unsuitable for use in MHE. Rifaximin, in contrast, has a more favorable safety and tolerability profile.
Data from studies supporting the safety and efficacy of rifaximin in the treatment of HE have been the subject of an extensive recent review by Lawrence and Klee. In reviewing more than 20 clinical trials, the authors concluded that rifaximin is equivalent to, and in some studies superior to, nonabsorbable disaccharides or other antibiotics in the treatment of HE, with response rates of 80% to 90%. Rifaximin was better tolerated than other pharmacologic treatments; adverse events were mostly minor gastrointestinal complaints. Preliminary results from a phase 3 study of rifaximin in maintaining remission in patients with a history of HE were presented at the 2009 Annual Meeting of the European Association for the Study of the Liver. Patients with cirrhosis who had ≥2 episodes of HE (Conn score ≥2) within 6 months prior to screening and who were currently in remission were enrolled. Rifaximin 550 mg twice daily was administered to 140 patients for 6 months; 159 patients received placebo. Continued therapy with lactulose was permitted in both study arms. The primary end point was the time to the first breakthrough HE episode. Rifaximin significantly (P<0.0001) reduced the risk of an HE breakthrough by 58% compared with placebo. At 6 months, 22% of the rifaximin patients had experienced a breakthrough compared with 46% in the placebo group (Figure 3). The safety profile of rifaximin was similar to placebo during the 6-month treatment period. A recent consensus conference recommended rifaximin as a viable alternative to lactulose in patients with HE.

Probiotic Yogurt
Probiotics can alter the intestinal flora mix by reducing urease-producing bacteria and promoting the growth of nonurease-producing species. While several studies have reported improvement in psychometric tests when probiotics are administered to patients with HE, a recent study using probiotic yogurt is of interest. Yogurt is a probiotic made from milk that is produced by fermentation of lactic acid using cultures of Lactobacillus bulgaricus and Streptococcus thermophilus. Following a diagnosis of MHE by psychometric testing, 17 patients received dietary supplementation with 12 ounces per day of probiotic yogurt (CC Jersey Crème, Spring Valley, WI) for 60 days, while 8 patients received no supplementation. Treatment end points were reversal of MHE, the development of OHE, and adherence. Figure 4 depicts the effect of probiotic yogurt on MHE reversal and the development of HE compared...
with no treatment. MHE was reversed in 71% of treated patients and in none of the non-treated patients; OHE developed in none of the treated patients, and in 25% of the non-treated patients. Two of 17 patients (12%) left the study early because they found the yogurt unpalatable. The remaining patients were 90% adherent to therapy according to container cap return. Probiotic yogurt dietary supplementation may offer a viable alternative to drug therapy in the treatment of MHE.\textsuperscript{5,31}

### Summary

Hepatic encephalopathy is a complication of acute or chronic hepatic insufficiency that presents as neuropsychiatric abnormalities ranging from mild changes in personality or behavior to stupor and coma. OHE can be diagnosed by the characteristic signs and symptoms in those with known liver disease. MHE can be detected only by the use of psychometric or neurophysiologic tests. MHE can have a profound effect on a patient’s quality of life, impairs driving skill and work performance, and is associated with a high probability of progression to OHE. In a recent survey of American Association for the Study of Liver Diseases members, 84% thought that at-risk patients should be tested for HE, yet 38% never tested and 34% tested less than 50% of the time. Computer based tests can be easily administered in the office setting. One is available online at HEcme.TV.

Increased levels of ammonia are implicated in the pathogenesis of HE and nonabsorbable dissacharides and minimally absorbed antibiotics have been effective in reducing the activity of colonic bacteria involved in the production of ammonia. These agents can be used in the acute situation and also prophylactically in those at risk for the development of HE.

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Access other HE resources and CME materials @ HEcme.TV
References


You must complete the Request for Credit, Posttest, and Evaluation forms to assure delivery of participation acknowledgement. Please provide current and complete information on the Request for Credit form. Do not use abbreviations.

Fax all 3 pages to: 973–939–8516.
1. A population-based study during 1999 to 2001 found that the underlying etiology responsible for the greatest percentage of newly diagnosed chronic liver disease was:
   a. Hepatitis B  
   b. Hepatitis C  
   c. Alcohol abuse  
   d. Nonalcoholic fatty liver disease

2. Based on current estimates, what percentage of patients with liver cirrhosis has minimal HE?
   a. Up to 20%  
   b. Up to 45%  
   c. Up to 80%  
   d. 100%

3. True or false. Impaired first-pass removal of ammonia by a liver compromised by either advanced disease or a portal-systemic shunt results in increased levels of arterial ammonia in the systemic circulation.
   a. True  
   b. False

4. The inhibitory control test that can be used to diagnose minimal HE is:
   a. A “pencil-and-paper” psychometric test  
   b. A computer-based psychometric test  
   c. A psychometric test in which the patient identifies the frequency at which a steady light changes to a flicker as the frequency of pulses of light are gradually reduced  
   d. None of the above

5. Which of the following statements best describe the results of the recent survey of the American Association for the Study of Liver Diseases members concerning minimal HE?
   a. Most think it is a relatively insignificant problem, but they still test nearly all of their at-risk patients for it  
   b. Most think it is a significant problem and most test for it  
   c. Most think it is a relatively insignificant problem and therefore do not test for it  
   d. Most think it is a significant problem, but 34% of respondents test less than 50% of at-risk patients and 38% never test

6. Which of the following agents used in the treatment of HE act by reducing or modifying colonic bacterial flora involved in the production of ammonia?
   a. Lactulose  
   b. Rifaximin  
   c. Probiotic yogurt  
   d. All of the above
Evaluation Form

Hepatic Encephalopathy:
Natural History, Epidemiology, and Treatment Modalities

You must complete this evaluation form to receive acknowledgement of participation for this activity.

Please answer the following questions by circling the appropriate rating:
5 = Outstanding  4 = Good  3 = Satisfactory  2 = Fair  1 = Poor

Extent to Which Program Activities Met the Identified Objectives
- Review the epidemiology and natural history of hepatic encephalopathy (HE) .................................................. 5 4 3 2 1
- Outline how increases in arterial ammonia ultimately result in the neuropsychiatric abnormalities seen in HE .................................................. 5 4 3 2 1
- Differentiate between factors considered in the diagnosis of overt HE and those considered in the diagnosis of minimal HE .................................................. 5 4 3 2 1
- Describe treatment modalities used in the treatment of HE .................................................. 5 4 3 2 1

Overall Effectiveness of the Activity
- Was timely and will influence how I practice .................................................. 5 4 3 2 1
- Will assist me in improving patient care .................................................. 5 4 3 2 1
- Fulfilled my educational needs .................................................. 5 4 3 2 1
- Avoided commercial bias or influence .................................................. 5 4 3 2 1

Impact of the Activity
- The information presented: (check all that apply)
  ❑ Reinforced my current practice/treatment habits
  ❑ Provided new ideas or information I expect to use
  ❑ Will improve my practice/patient outcomes
  ❑ Enhanced my current knowledge base

- Will the information presented cause you to make any changes in your practice? ❑ Yes ❑ No
  If yes, please describe any change(s) you plan to make in your practice as a result of this conference:

- How committed are you to making these changes?
  (Very committed) 5 4 3 2 1 (Not at all committed)

Future Activities
- Do you feel future activities on this subject matter are necessary and/or important to your practice? ❑ Yes ❑ No
- Please list any other topics that would be of interest to you for future educational activities:

Follow-up
As part of our continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

❑ Yes, I would be interested in participating in a follow-up survey ❑ No, I’m not interested in participating in a follow-up survey

Additional comments about this activity: