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Faculty Disclosures

- Alpesh Amin, MD, has no real or apparent conflicts of interest to report.
Learning Objectives

- Describe the burden and need to prevent recurrence and rehospitalizations for overt hepatic encephalopathy (HE)

- Evaluate the efficacy and safety of available and emerging agents for secondary prophylaxis of HE

- Develop a multidimensional long-term management plan that includes pharmacologic and nonpharmacologic strategies to care for patients with HE
Overview of HE

- Brain dysfunction caused by liver insufficiency and/or PSS
- Occurs in 30% to 45% of patients with cirrhosis and 10% to 50% of patients with TIPS
- Symptoms include neurological or psychiatric abnormalities ranging from subclinical alterations to coma
- Without successful treatment of the underlying liver disease, HE is associated with high risk of recurrence, diminished HRQOL, and poor survival

PSS, portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt; HRQOL, health-related quality of life; AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of Liver Disease.

## Impact of HE on HRQOL

<table>
<thead>
<tr>
<th>Individual SF-36 Domain/Summary Component</th>
<th>No HE</th>
<th>Subclinical HE</th>
<th>Overt HE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>61.5</td>
<td>52</td>
<td>44.2</td>
<td>.01</td>
</tr>
<tr>
<td>Role limitations (due to physical health issues)</td>
<td>44.4</td>
<td>25</td>
<td>22.9</td>
<td>.02</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>52.3</td>
<td>51.4</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>41.4</td>
<td>37</td>
<td>31.7</td>
<td>.03</td>
</tr>
<tr>
<td>Vitality</td>
<td>40.4</td>
<td>37.6</td>
<td>30.3</td>
<td>NS</td>
</tr>
<tr>
<td>Social functioning</td>
<td>73.5</td>
<td>58.6</td>
<td>50</td>
<td>.002</td>
</tr>
<tr>
<td>Role limitations (due to emotional health issues)</td>
<td>70</td>
<td>52.3</td>
<td>53</td>
<td>.03</td>
</tr>
<tr>
<td>General mental health</td>
<td>75</td>
<td>63</td>
<td>64.1</td>
<td>.03</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>35.6</td>
<td>33.2</td>
<td>29.3</td>
<td>.02</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>50</td>
<td>42.4</td>
<td>44</td>
<td>.03</td>
</tr>
</tbody>
</table>

SF-36, Short Form-36 questionnaire; NS, not significant.

Effect of HE on Employment and Financial Status

Burden of HE on Caregivers

Perceived caregiver burden domains

- Zarit burden interview
- Total perceived caregiver burden
- Impact on finances
- Sense of abandonment
- Impact on schedule
- Impact on personal health
- Sense of entrapment

Caregivers of patients without previous HE
Caregivers of patients with previous HE

*P<.05; †P<.01

Readmission Rates Among Patients Hospitalized with HE

- Retrospective analysis of >500 US hospitals
- Adults discharged with a primary diagnosis of HE (N=8,766)

<table>
<thead>
<tr>
<th>Reason for Readmission</th>
<th>30-day</th>
<th>1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause</td>
<td>27.4%</td>
<td>56.4%</td>
</tr>
<tr>
<td>HE-related</td>
<td>17.6%</td>
<td>39.5%</td>
</tr>
</tbody>
</table>

Neff G. *Hepatology*. 2013;58(S1):390A–391A.
Majority of Patients with HE do not Receive Maintenance Therapy at or After Discharge


- **2009**: 60.3% Patients NOT receiving ongoing therapy, 39.7% Patients receiving ongoing therapy
- **2010**: 62.3% Patients NOT receiving ongoing therapy, 37.7% Patients receiving ongoing therapy
- **2011**: 63.9% Patients NOT receiving ongoing therapy, 36.1% Patients receiving ongoing therapy
Pathogenesis of HE
Role of Ammonia in HE

Neurotoxic Effects of Ammonia

Impairment of amino acid metabolism and energy utilization in the brain

Alteration in the transport of amino acids, water, and electrolytes across astrocytes and neurons

Inhibition of excitatory and inhibitory postsynaptic potentials
Recognition and Diagnosis of HE
Case Study #1: Background

- 66-year-old man is brought to the hospital noticeably confused and disoriented, accompanied by his wife and son

**Social history:**
- Former smoker with 30 pack-year history
- Retired general contractor
- Lives with his wife

**Medical history:**
- COPD (gets very winded when walking)
- Cirrhosis
- HE

COPD, chronic obstructive pulmonary disease.
Case Study #1: Background and Physical Exam

- Additional clinical history provided by family
  - Incoherent late-night phone calls
  - Family often unable to communicate with him
  - Sometimes forgets where he is
  - Suffers from panic attacks
  - Fell and hit his head a few days ago (severity of the injury is unclear because he was home alone)

- Physical exam
  - Ascites
  - Edema
Case Study #1: Discussion

- What type of testing would be appropriate for further evaluation of this patient?
  - Paracentesis
  - CT scan

CT, computed tomography.
Approach to the Diagnosis of HE

- Diagnosis is based primarily on clinical examination
  - Disorientation and asterixis are reliable markers
  - Mild hypokinesia, psychomotor slowing, and lack of attention are easily overlooked
- The West Haven Criteria is the gold standard for staging severity
- Specific quantitative tests are not routinely recommended for practice settings

*Recommendations about the place of quantitative testing for diagnosis continue to evolve.

Most Frequent Clinical Manifestations of HE

- Confusion: 78%
- Changes in mental status: 57%
- Lethargy: 48%
- Asterixis: 46%
- Disorientation (time): 45%
- Disorientation (place): 41%
- Somnolence: 33%
- Forgetfulness: 28%
- Changes in sleep pattern: 23%
- Difficulty in concentration: 22%
- Loss of concentration: 20%

### West Haven Criteria (Minimal and Grade I HE)

<table>
<thead>
<tr>
<th>WHC</th>
<th>DESCRIPTION</th>
<th>SUGGESTED OPERATIVE CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unimpaired</td>
<td>• No encephalopathy, no HE history</td>
<td>• Normal test results</td>
</tr>
</tbody>
</table>
| Minimal    | • Alterations in psychomotor speed/executive functions or on neurophysiological measures  
              • No clinical evidence of mental change                                             | • Abnormal results on established psychometric or neurophysiological tests  
              • No clinical manifestations                                                      |
| Grade I    | • Trivial lack of awareness  
              • Euphoria or anxiety  
              • Shortened attention span  
              • Impairment of addition or subtraction  
              • Altered sleep rhythm                                                           | • Orientation in time and space  
              • Cognitive/behavioral decay with respect to standard on clinical examination, or to caregivers |

All conditions are required to be related to liver insufficiency and/or PSS.  
West Haven Criteria (Grades II, III, and IV HE)

<table>
<thead>
<tr>
<th>WHC</th>
<th>DESCRIPTION</th>
<th>SUGGESTED OPERATIVE CRITERIA</th>
</tr>
</thead>
</table>
| Grade II |  • Lethargy or apathy  
  • Disorientation for time  
  • Obvious personality change  
  • Inappropriate behavior  
  • Dyspraxia  
  • Asterixis |  • Disoriented for time (≥3 of the following errors: day of the month, day of the week, month, season, or year)  
  • ± other symptoms |
| Grade III |  • Somnolence to semi-stupor  
  • Responsive to stimuli  
  • Confused  
  • Gross disorientation  
  • Bizarre behavior |  • Disoriented for space (≥3 of the following errors: country, state [or region], city, or place)  
  • ± other symptoms |
| Grade IV |  • Coma |  • Does not respond even to painful stimuli |

All conditions are required to be related to liver insufficiency and/or PSS.  
Covert vs Overt HE

ISHEN

Covert HE

Overt HE

MHE
Grade I

Grade II
Grade III
Grade IV

WHC

ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; WHC, West Haven criteria; MHE, minimal HE

Covert HE is Associated with Overt HE Development

Cumulative Incidence of OHE

Time from Initial Visit to First Overt HE Episode

CHE, covert hepatic encephalopathy; OHE, overt hepatic encephalopathy.

Covert HE Is Associated with Decreased Survival and Increased Risk for Hospitalization and Deaths


Txp, transplant.
Management of Overt HE
A Four-pronged Approach to the Management of Overt HE

1. Provide supportive care for unconscious patients
2. Find and treat alternative causes
3. Identify and address precipitating factors
4. Initiate empirical HE treatment

## Differential Diagnosis of HE

### Overt HE or Acute Confusional State

| • Alcohol    | • Nonconvulsive epilepsy          |
| • Drugs      | • Psychiatric disorders           |
| • Neuroinfections | • Intracranial bleeding and stroke |
| • Electrolyte disorders | • Severe medical stress |
| • Diabetes   |                                |

### Other Presentations

| • Dementia                         |
| • Brain lesions                  |
| • Obstructive sleep apnea        |
Precipitating Factors for Overt HE

*Recent unpublished case series confirm the dominant role of infections. GI, gastrointestinal; TIPS, transjugular intrahepatic portosystemic shunt

# Available Treatments for HE

## Pharmacologic

- Nonabsorbable disaccharides
- Rifaximin (RIX)*
- Zinc
- L-ornithine-L-aspartate†
- BCAAs

## Nonpharmacologic

- Percutaneous embolization of large PSSs
- MARS‡

*Indicated for prophylaxis; †Not available in the US; ‡Primarily for research purposes.

BCAAs, branched chain amino acids; PSS, portosystemic shunt; MARS, molecular adsorbent recirculating system

RIX Added on to Lactulose in the Treatment of Overt HE

Impact of RIX Treatment on Covert HE

MHE, minimal hepatic encephalopathy

Adverse Effects of Lactulose

- Aspiration
- Dehydration
- Hypernatremia
- Severe perianal skin irritation
- Precipitation of HE with overuse

Note: Data for precise frequency of AEs are not available.

AE, adverse effects.

Adverse Effects of RIX

- Peripheral edema
- Nausea
- Dizziness
- Fatigue
- Ascites
- Diarrhea
- Headache

Note: Although these AEs were reported in ≥5% patients, incidences did not differ significantly between the PBO and RIX groups ($P > .05$ for all comparisons).

PBO, placebo.

## Emerging Ammonia-lowering Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action/by product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerol phenylbutyrate</td>
<td>• Nitrogen removal in the form of urinary PAGN</td>
</tr>
<tr>
<td>Polyethylene glycol 3350-electrolyte solution</td>
<td>• Purgative; causes water to be retained in the colon and produces a watery stool</td>
</tr>
<tr>
<td>Ornithine phenylacetate</td>
<td>• Nitrogen removal in the form of urinary PAGN</td>
</tr>
<tr>
<td>AST-120</td>
<td>• Binding of neuroactive substances (including ammonia) in the GI tract</td>
</tr>
</tbody>
</table>

PAGN, Phenylacetylglutamine.

Effect of Glycerol Phenylbutyrate Treatment in Patients with HE

HALT-HE Study

- All Patients
  - GPB: Red line
  - Placebo: Dashed line
  - P value: .0354

- Non-Rifaximin Patients
  - GPB: Red line
  - Placebo: Dashed line
  - P value: .0002

- Patients on Rifaximin Patient at Study Entry or During the Study
  - GPB: Red line
  - Placebo: Dashed line
  - P value: .5955

GPB, glycerol phenylbutyrate.

PEG Treatment in Patients with Cirrhosis Hospitalized for HE

HELP Trial

PEG vs standard lactulose therapy:

- % of patients with a HESA score improvement ≥1*
- mean change in HESA score at 24h†
- rate of HE resolution‡ (graph)

![Graph showing time to HE resolution for Lactulose and PEG]

<table>
<thead>
<tr>
<th>Time to HE Resolution, d</th>
<th>No. at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lactulose</td>
</tr>
<tr>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*P<.01; †P = .002; ‡P=.01

PEG, polyethylene glycol 3350-electrolyte solution; HESA, hepatic encephalopathy scoring algorithm

Liver Transplantation

- **Indication:**
  - HE cannot be improved despite maximal medical therapy
  - HE severely compromises HRQOL
  - Only for HE associated with poor liver function

- **Considerations:**
  - Large PSSs may cause neurological disturbances and persistent HE, even after LT
  - Shunts should be identified and embolization should be considered before or during transplantation
Significance of MELD Scoring

- Scores ≥30 reflect high likelihood of transplant and death in the absence of timely transplant.
- Score does not correlate well with the HE severity or ascites.
- Lower scores are associated with a shorter hospital stay for patients with HE*.

*Except for MELD <10.
MELD, model for end-stage liver disease.

# Child-Pugh Scoring

<table>
<thead>
<tr>
<th>Measure</th>
<th>+1 Points</th>
<th>+2 Points</th>
<th>+3 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&lt;2 mg/dL</td>
<td>2–3 mg/dL</td>
<td>&gt;3 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5 g/dL</td>
<td>2.8–3.5 g/dL</td>
<td>&lt;2.85 g/dL</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7–2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Medically controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Medically controlled</td>
<td>Poorly controlled</td>
</tr>
</tbody>
</table>

INR, international normalized ratio

Secondary Prophylaxis of HE
45-year-old female presents with complaints of worsening HE symptoms over the past 2 weeks

- Increased fatigue
- Somnolence
- Diminished concentration and ability to communicate at work

Medical History:

- Chronic hepatitis C (genotype 1)
- Previously treated for 2 OHE episodes
- Prescribed lactulose prophylaxis on both occasions
- Only sporadically adherent reportedly due to poor tolerance
Case Study #2: Physical Examination and Laboratory Testing

- Physical examination:
  - Lethargic
  - Asterixis
  - Ascites (confirmed by ultrasound)
Case Study #2: Discussion

- What modification to the patient’s therapeutic regimen, if any, would you recommend?
- How long should this patient be maintained on prophylactic treatment? What factors should be taken into consideration?
1. Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)

2. Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)

3. Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
Lactulose Prevents HE Recurrence in Patients with Cirrhosis


Follow-up (Months)

Probability of HE

Placebo (n=64)
- 46.8%
- 19.6%

Lactulose (n=61)
- 19.6%

P = .001
RIX vs Placebo: Time to First Breakthrough HE Episode and HE-related Hospitalization

Note: >90% of patients received concomitant lactulose during the study period.

Time to First Breakthrough HE Event During Treatment with RIX or Placebo

![Graph showing Time to First Breakthrough HE Event](image)

**Proportion Maintaining Remission**

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>Placebo RCT</th>
<th>Rifaximin OLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo RCT</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>Rifaximin OLM</td>
<td>62</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

*Event rate was calculated for 168 days of the RCT and the first 168 days in the OLM study.

OLM, open-label maintenance; RCT, randomized placebo-controlled trial.

Treatment with RIX Decreases the Rate of HE Breakthrough Episodes

*P < .0001 vs placebo.

Long-term Maintenance of Remission From Overt HE with RIX

Treatment with RIX (550 mg bid) for ≥2 years reduced the rate of HE-related and all-cause hospitalization, without increasing the rate of adverse events.

*P < .001 vs placebo.
PYE, person-years of exposure; bid, twice a day.

RIX Treatment Improves HRQOL in Cirrhotic Patients with HE

<table>
<thead>
<tr>
<th>Domain</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>.0087</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>.0090</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>.0160</td>
</tr>
<tr>
<td>Activity</td>
<td>.0022</td>
</tr>
<tr>
<td>Emotional function</td>
<td>.0065</td>
</tr>
<tr>
<td>Worry</td>
<td>.0436</td>
</tr>
<tr>
<td>Overall</td>
<td>.0093</td>
</tr>
</tbody>
</table>

LS, least squares; CI, confidence interval.

Comparison of Lactulose and Probiotics Vs Placebo for the Prevention of HE Recurrence

Probability of Development of HE

Follow-up (Months)

Gp-N: No therapy
Gp-P: Probiotics
Gp-L: Lactulose

P = 0.001

Case Study #2: Management

- Medications prescribed:
  - Rifaximin 550 mg bid

- Patient education:
  - Critical importance of medication adherence
  - Recognition of symptom onset
  - Precipitating factors
  - Nutritional guidance
  - Family/caregiver involvement
Nutritional Considerations for HE Management
**ISHEN/AASLD/EASL Recommendations: Energy and Protein Requirements**

<table>
<thead>
<tr>
<th></th>
<th>Optimal Daily Intake Per Kg Ideal Body Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>35 kcal–40 kcal</td>
</tr>
<tr>
<td>Protein</td>
<td>1.2 g–1.5 g</td>
</tr>
</tbody>
</table>

- Small meals throughout the day and a late-night snack of complex carbohydrate (to minimize protein utilization)
- Diet rich in vegetable and dairy protein
- BCAA supplementation may allow attainment/maintenance of recommended nitrogen intake in patients intolerant of dietary protein

BCAA, branched-chain amino acid.

**ISHEN Recommendations: Fiber and Micronutrient Provision**

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prebiotics</strong></td>
</tr>
<tr>
<td>• 25 g to 45 g of fiber daily</td>
</tr>
<tr>
<td><strong>Micronutrients</strong></td>
</tr>
<tr>
<td>• 2-week multivitamin course for decompensated cirrhosis or risk for malnutrition</td>
</tr>
<tr>
<td>• Specific treatment of clinically apparent vitamin deficiencies</td>
</tr>
<tr>
<td>• Slow correction of hyponatremia</td>
</tr>
<tr>
<td>• Avoidance of long-term treatment with manganese-containing nutritional formulations</td>
</tr>
</tbody>
</table>
**Action Plan for Long-term HE Management**

**EDUCATE PATIENTS AND CAREGIVERS**
- Provide information on the nature of HE & options for prophylaxis
- Offer nutritional guidance

**PREVENT RECURRENCE**
- Advise on the avoidance of precipitating factors
- Prescribe/adjust prophylactic treatment

**MONITOR FOR NEUROLOGICAL SYMPTOMS**
- Evaluate gait & risk for falls
- Assess cognitive symptoms

**CONSIDER OTHER INTERVENTIONS**
- For recurrent HE despite optimal therapy:
  - Consider PSS embolization if liver function is good
  - Evaluate for LT if liver function is poor

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**Summary**

- HE is a major neurological complication of liver disease that imposes a significant health and economic burden on patients, families, and caregivers.
- Management goals include active treatment of acute episodes, prevention of recurrence, and evaluation for surgical intervention.
- Several available agents have shown good efficacy when administered as acute treatment or secondary prophylactic therapy.
- Appropriate therapy, patient education, and guidance can prevent unnecessary recurrence and hospitalization, and improve overall patient outcomes.
Thank You!