Optimizing Outcomes of Patients Hospitalized for Hepatic Encephalopathy: Focus on Early Intervention and Transitional Care
Faculty

Arun B. Jesudian, MD, FACG
Assistant Professor of Medicine
Joan and Sanford I. Weill Department of Medicine
Director
Inpatient Liver Services
Weill Cornell Medical College
New York, New York
Faculty Disclosures

- Consultant: Valeant Pharmaceuticals North America LLC
- Speakers’ Bureaus: Valeant Pharmaceuticals North America LLC
Learning Objectives

- Describe an approach to the early diagnosis of patients with hepatic encephalopathy (HE) that is consistent with current guideline recommendations
- Summarize clinical trial data on the efficacy and safety of options for acute treatment and prophylaxis of HE
- Implement a transitional care plan to prevent future hospitalizations among patients with HE
HE in the Hospital Setting
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

HRQOL, health-related quality of life; PSS, portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt.
# HE Burden in the Hospital Setting

<table>
<thead>
<tr>
<th>HE Inpatient Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual inpatient incidence</strong></td>
</tr>
<tr>
<td><strong>Length of hospital stay</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Inpatient mortality</strong></td>
</tr>
</tbody>
</table>

Readmission Rates Among Patients Hospitalized with HE

Adults discharged with a primary diagnosis of HE (N=8,766)

- 30 days post-discharge: 27.4% (All-cause) vs. 17.6% (HE-related)
- 1 year post-discharge: 56.4% (All-cause) vs. 39.5% (HE-related)

Factors Associated with a High Likelihood of HE Readmission

- Poor social support
- Failure to fill a prescription
- Lack of follow-up with a healthcare provider

Pathogenesis of HE
Factors Contributing to HE Pathogenesis

Diagnosis of HE
Approach to the Diagnosis of HE

- Overt HE diagnosis is based primarily on clinical examination
  - Disorientation and asterixis are reliable overt HE markers
  - Mild hypokinesia, psychomotor slowing, and lack of attention are easily overlooked in clinical examination
- Specific quantitative tests are only needed in study settings
- The West Haven Criteria (WHC) is the gold standard for staging disease severity

Precipitating Factors for Overt HE

- Lactulose nonadherence
- Dehydration
- Acute renal failure
- Constipation
- Infections
- Opioids and benzodiazepines
- Hypokalemia
- TIPS
- Gastrointestinal bleeding
- Large-volume paracentesis
- Hyponatremia sodium
- High-protein diet
- Unknown precipitants

Retrospective study (N=149)
Prospective study (N=45)

### Site of Infection in Patients with Overt HE

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Retrospective study (N=149)</th>
<th>Prospective study (N=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infections</td>
<td>8.0</td>
<td>13.0</td>
</tr>
<tr>
<td>SBP</td>
<td>2.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Other abdominal infections</td>
<td>3.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Respiratory infections</td>
<td>3.4</td>
<td>13.0</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>2.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>20.1</td>
<td>42.0</td>
</tr>
</tbody>
</table>

SBP, spontaneous bacterial peritonitis.

Patients with Overt HE and Multiple Precipitating Factors

Retrospective study (N=149) vs. Prospective study (N=45)

Diagnostic Tests

- CBC, CMP
- Blood cultures
- Urine analysis and culture
- Chest x-ray
- Paracentesis
- Alcohol level/drug screen if suspicion arises based on history

CBC, complete blood count; CMP, comprehensive metabolic panel.
## West Haven Criteria Minimal and Grade I HE

<table>
<thead>
<tr>
<th>WHC</th>
<th>Description</th>
<th>Operative Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unimpaired</strong></td>
<td>• No encephalopathy, 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 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 month or week, month, season, or year)  
• ± Other symptoms |
| Grade III | • Somnolence to semistupor  
• 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.

ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE, minimal HE (covert HE).

## HE Types Based Upon Underlying Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Underlying Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Acute liver failure</td>
</tr>
<tr>
<td>B</td>
<td>PSS or bypass</td>
</tr>
<tr>
<td>C</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

Differential Diagnosis of HE

<table>
<thead>
<tr>
<th>Overt HE or Acute Confusional State</th>
<th>Other Presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diabetes</td>
<td>• Dementia</td>
</tr>
<tr>
<td>• Alcohol</td>
<td>• Brain lesions</td>
</tr>
<tr>
<td>• Drugs</td>
<td>• Obstructive sleep apnea</td>
</tr>
<tr>
<td>• Neuroinfections</td>
<td></td>
</tr>
<tr>
<td>• Electrolyte disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nonconvulsive epilepsy</td>
</tr>
<tr>
<td></td>
<td>• Psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>• Intracranial bleeding and stroke</td>
</tr>
<tr>
<td></td>
<td>• Severe medical stress</td>
</tr>
</tbody>
</table>

Treatment of Acute Overt HE
A Four-Pronged Approach to the Management of Overt HE

- Provide supportive care for unconscious patients
- Find and treat alternative causes
- Identify and address precipitating factors
- Initiate empirical HE treatment

Available Therapies for the Treatment of Acute Overt HE

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonabsorbable disaccharides</td>
<td>Promotes conversion of NH3 to NH4+ in the colon, shifting colonic flora from urease- to non-urease-producing bacteria; has a cathartic effect</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria; indicated for reducing risk of overt HE recurrence in adults</td>
</tr>
<tr>
<td>Zinc</td>
<td>Enhances urea formation from ammonia and amino acids</td>
</tr>
<tr>
<td>BCAAs</td>
<td>Source of glutamate, which helps to metabolize ammonia in skeletal muscle</td>
</tr>
<tr>
<td>MARS</td>
<td>Removes non–protein-bound ammonia that accumulates in liver failure; primarily used in research</td>
</tr>
<tr>
<td>Percutaneous embolization of PSSs</td>
<td>Rescue treatment for patients with persistent or recurrent HE despite optimal medical management</td>
</tr>
</tbody>
</table>

Emerging Ammonia-Lowering Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action/Byproduct</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</td>
<td>• Purgative; causes water to be retained in the colon and produces a watery stool</td>
</tr>
<tr>
<td>solution</td>
<td></td>
</tr>
<tr>
<td>Ornithine phenylacetate</td>
<td>• Nitrogen removal in the form of urinary PAGN</td>
</tr>
</tbody>
</table>

PAGN, Phenylacetylglutamine.
Pathways Targeted by Specific Ammonia-Lowering Medications

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)

*P<.01; †P=.002; ‡P=.01

PEG, polyethylene glycol 3350-electrolyte solution; HESA, hepatic encephalopathy scoring algorithm.
Microbiota Changes Associated with RIX Therapy

A significant decrease in *Veillonellaceae* and increase in *Eubacteriaceae* abundance were observed after RIX therapy.*

*No significant change in the principle component of microbiota was observed.*

Fatty Acids and Intermediates of Carbohydrate Metabolism Are Increased Following RIX Therapy

Univariate Serum Metabolomic Analysis

Change After Rifaximin (%)

Carbohydrate Metabolism
- Sucanin acid: 10%
- Fructose: 70%
- Citramalic acid: 50%

Lipid Metabolism
- Palmitoleic acid: 50%
- Palmitic acid: 30%
- Oleic acid: 50%
- Myristic acid: 30%
- Methyhexadecanoic acid: 20%
- Linolenic acid: 30%
- Linoleic acid: 50%
- Isolinoleic acid: 40%
- Icosenoic acid: 30%
- Citramalic acid: 50%
- Caprylic acid: 20%
- Arachidonic acid isomer: 20%
- Arachidonic acid: 20%

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.
Common AEs Observed with Rifaximin Treatment*

The incidence of AEs did not differ significantly between groups.

*AEs occurring at an incidence rate of 10% or higher in the rifaximin group.
RIX Added on to Lactulose in the Treatment of Acute Overt HE

### Causes of Persistent Overt HE

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSS</strong></td>
<td>- 71% of patients with persistent overt HE show patent, large PSSs vs 14% of those without</td>
</tr>
<tr>
<td></td>
<td>- Interventional radiologic embolization or coiling may improve symptoms</td>
</tr>
<tr>
<td><strong>TIPS</strong></td>
<td>- A minority of patients develop persistent overt HE after TIPS</td>
</tr>
<tr>
<td></td>
<td>- Radiological interventions (eg, ballooning) may be required to occlude the TIPS shunt</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
<td>Undiscovered source of sepsis (eg, abscesses)</td>
</tr>
<tr>
<td></td>
<td>- Inability to tolerate medications prescribed for overt HE</td>
</tr>
</tbody>
</table>

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

LT, liver transplant.
Prophylaxis of Recurrent Overt HE
Lactulose Prevents Recurrence of HE in Patients with Cirrhosis


Probability of HE

<table>
<thead>
<tr>
<th>Follow-up (Months)</th>
<th>Placebo (n=64)</th>
<th>Lactulose (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>46.8%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

P = .001
Effect of RIX Treatment on Breakthrough HE Episodes and HE-related Hospitalizations

Over a 6-month period, treatment with RIX resulted in a greater proportion of patients maintaining remission vs placebo.

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

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 PBO.
PYE, person-years of exposure; bid, twice a day; PBO, placebo.
Comparison of Lactulose and Probiotics vs PBO for the Prevention of HE Recurrence

Additional Considerations for Treatment Selection
# RIX vs Lactulose: Impact on Hospitalization Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Lactulose-treated patients*</th>
<th>RIX-treated patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of hospitalizations</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean days per hospitalization</td>
<td>7.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Total time hospitalized</td>
<td>1.8 weeks</td>
<td>0.4 weeks</td>
</tr>
<tr>
<td>Estimated hospitalization charges per patient (per 6-month period)**</td>
<td>$56,635</td>
<td>$14,222</td>
</tr>
</tbody>
</table>

*Greater than 6 months of treatment

**Hospitalization charges were estimated based on average cost per hospital day in 2005 US dollars

**Impact of RIX Treatment of HE on Liver-related Healthcare Utilization**

Liver-related resource use in the 6 and 12 months pre-rifaximin-α and post-rifaximin-α initiation—intention-to-treat population.

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.3 ± 0.5</td>
<td>1.7 ± 0.8</td>
</tr>
<tr>
<td>Hospitalisations</td>
<td><strong>N=125 P&lt;.001</strong></td>
<td><strong>N=125 P&lt;.001</strong></td>
</tr>
<tr>
<td>Bed Days</td>
<td>18.6 ± 1.3</td>
<td>21.6 ± 1.5</td>
</tr>
<tr>
<td><strong>N=145 P&lt;.001</strong></td>
<td><strong>N=145 P&lt;.001</strong></td>
<td></td>
</tr>
<tr>
<td>Critical Care Bed Days</td>
<td>6.1 ± 0.3</td>
<td>8.4 ± 0.3</td>
</tr>
<tr>
<td><strong>N=145 P=.035</strong></td>
<td><strong>N=145 P=.068</strong></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of Costs Associated with RIX vs Lactulose Treatment of Patients with Overt HE

Mean drug cost per patient/month

Mean total treatment cost/patient/year

Total treatment cost/year

Long-term Management of HE
### ISHEN/AASLD 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><strong>Energy</strong></td>
<td>35 kcal-40 kcal</td>
</tr>
<tr>
<td><strong>Protein</strong></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

- **Prebiotics**
  - 25 g to 45 g of fiber daily

- **Micronutrients**
  - 2-week multivitamin course in patients with decompensated cirrhosis or those at risk for malnutrition
  - Specific treatment of clinically apparent vitamin deficiencies
  - Slow correction of hyponatremia
  - Avoidance of long-term treatment with manganese-containing nutritional formulations

Patients’ ability was evaluated by a professional driving instructor on being fit to drive.

Minimal HE and HE were associated with significantly reduced rates of driving fitness.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Fit to Drive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>48</td>
<td>87%</td>
</tr>
<tr>
<td>No HE</td>
<td>10</td>
<td>75%</td>
</tr>
<tr>
<td>Minimal HE</td>
<td>27</td>
<td>48%</td>
</tr>
<tr>
<td>Grade I HE</td>
<td>14</td>
<td>3%</td>
</tr>
</tbody>
</table>

Challenges in Evaluating Driving Ability in Patients with MHE

MHE, minimal HE (covert HE).

Planning for Patient Discharge

Neurological Status
- Confirm status
- Assess other contributing causes
- Inform caregivers of potential changes after acute illness resolution and need for monitoring

Precipitating Factors
- Identify and discuss with patient and caregivers
- Plan for future clinical management

Postdischarge Follow-up
- Ensure patients follow-up with PCPs who can:
  - Adjust prophylactic treatment
  - Advise on avoiding precipitating factors
  - Act as liaison between patient’s family, caregivers, and other HCPs

HCP, healthcare provider; PCP, primary care provider.
Case Evaluations
A 61-year-old man presents with noticeable confusion, disorientation, and asterixis. He appears to know where he is, but is confused about how long he has been at the hospital. His wife reports that “he has not been himself lately” and has recently shown signs of increased fatigue, somnolence, and diminished ability to communicate. His medical history includes HCV-related cirrhosis, asthma, and allergic rhinitis. During the previous year, he was treated for an episode of overt HE, but was discharged without maintenance therapy.
Based on his history and current symptoms, you determine that the patient is experiencing an episode of HE. How would you classify this patient?

A. West Haven Criteria Grade I
B. **West Haven Criteria Grade II**
C. West Haven Criteria Grade III
Case Evaluation #1: Discussion Question 2

What type of additional testing, if any, would be most appropriate for the patient?

A. Ammonia levels
B. Serum electrolytes
C. Computed tomography or magnetic resonance imaging
Case Evaluation #1: Discussion Question 3

What recommendation would you make for this patient after resolution of the current overt HE episode and prior to discharge?

A. Limit exposure to precipitating factors
B. Involve family and caregivers in HE management
C. Pharmacologic prophylaxis
A 72-year-old woman presents with symptoms consistent with an acute overt HE episode. Her daughter reports that she is currently on lactulose maintenance therapy, but is only sporadically adherent. She explains that her mother’s medication makes her feel nauseous and bloated, and that she tends to stop taking it when she has not had an acute episode for several weeks.
Case Evaluation #2: Discussion Question

What type of intervention would you recommend to improve the patient’s adherence?

A. Provide education on the importance of medication adherence
B. Adjust the patient’s dose of lactulose
C. Prescribe rifaximin as an alternative maintenance treatment
Summary

- HE is a major complication of liver disease that represents a substantial healthcare burden in the hospital setting.
- Management goals include active treatment of acute episodes, prevention of recurrence, and evaluation for surgical intervention.
- Several agents have shown good efficacy when administered as acute treatment or secondary prophylaxis.
- Following an acute episode of HE, prophylaxis and patient education are crucial for preventing unnecessary recurrence and hospitalization, as well as improve(ing?) health outcomes.
Clinical Pearls

- For patients with decompensated liver disease, obtain a thorough history of mental status changes, administer tests to rule out other causes of neurological disturbances, and evaluate the need for HE treatment.

- Treatment of acute overt HE should incorporate complementary strategies for ammonia reduction, supportive care, and nutritional support.

- Consider secondary prophylaxis with lactulose and/or rifaximin in patients with previous overt HE episodes and at high risk for rehospitalization.

- Assess the nutrition of all patients with cirrhosis and HE, and encourage an individualized plan for maintaining adequate intake of calories, fiber, and micronutrients.
Questions and Answers
Thank You!