Management of Hepatic Encephalopathy
A focus on rifaximin

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Definition of Hepatic Encephalopathy (HE)

- Hepatic encephalopathy is brain dysfunction caused by liver insufficiency and/or porto-systemic shunting.
- It manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma.
Pathophysiology of HE

- Cirrhotic liver
  - Sensitization to bacterial products
  - Altered bile acid profile
- Inflammation
- Hyper-ammonemia
- Impaired urea cycle
- Urea cycle
- Ammonia
- Net ammonia producer and reduced excretion
- Astrocyte swelling
  - Microglia activation
  - Neuronal dysfunction
- Ammonia
- Indoles
  - Endotoxin
  - Inflammatory cytokines
- Shunting
- Gut
  - Slower intestinal motility
  - Altered bile acid profile
  - Impaired intestinal barrier
  - Dysbiosis
  - Bacterial translocation
- Ammonia
  - Glutamine
- Glutamate
  - Ammonia
  - Glutamine
  - a-ketoglutarate
- Skeletal muscle
  - Sarcopenia with impaired ammonia clearance
  - Glutamine
  - Glutamate

Bajaj JS Hepatology 2015
Role of Gut-Derived Toxins

- Impaired removal of gut-derived toxins (e.g., ammonia, endotoxins) plays a central role in the pathogenesis of HE\textsuperscript{1,2}
  - In patients with HE, portal blood containing gut-derived ammonia is inadequately detoxified because of\textsuperscript{1}
    - Liver damage (cirrhosis)
    - Portosystemic shunting
    - SIBO and delayed GITT

- High blood levels of gut-derived toxins (e.g., ammonia, endotoxins) can cause toxic effects in the brain, thereby leading to clinical HE symptoms

Multiple Factors Can Lead to HE Breakthrough

- Benzodiazepines
- Activation of central GABA-benzodiazepine receptors
- GI hemorrhage
- Hypokalemia
- Azotemia
- Constipation
- Excess dietary protein
- Infection
- Systemic alkalosis
- Inflammation
- Progressive parenchymal damage
- Dehydration
- Anemia
- Arterial hypotension
- Arterial hypoxemia
- Hepatoma
- Shunts
- ↑ Diffusion of ammonia across BBB
- ↑ Ammonia production
- ↓ Toxin metabolism
- Hyponatremia
- CNS depression
- Psychoactive drugs

BBB = blood brain barrier;
CNS = central nervous system;
GABA = γ-aminobutyric acid;
GI = gastrointestinal;
HE = hepatic encephalopathy.

Pathogenesis

• Accumulation of neurotoxins in brain
• Impaired Astrocytes function \[^{[1]}\]
• Synergistic neurotoxins
• Excitatory inhibitory neurotransmitters and plasma amino acid imbalance hypothesis
• Inflammation

Neurotoxins: Ammonia hypothesis

Production
• Ammonia is released from several tissues (kidney, muscle), but its highest levels can be found in the portal vein.
• Portal ammonia is derived from both the urease activity of colonic bacteria and the deamination of glutamine in the small bowel.

Degradation:
- Liver: (synthesis of urea, glutamine)
- Skeletal muscle: alternative target for NH₃ detoxification

Glutamine $\leftrightarrow$ glutamate + Ammonia
Ammonia Hypothesis ...continue

• In acute and chronic liver disease, increased arterial levels of ammonia are commonly seen.
• In FHF, elevated arterial levels (>200 mg/dl) have been associated with an increased risk of cerebral herniation.¹
• The blood-brain barrier permeability to ammonia is increased in patients with HE.²

Ammonia Hypothesis ...continue

• Furthermore, the alterations in neurotransmission induced by ammonia also occur after the metabolism of this toxin into astrocytes.\(^1\), resulting in a series of neurochemical events caused by the functioning alteration of this cell.\(^2\)

• Additional support for the ammonia hypothesis comes from the clinical observation that treatments that decrease blood ammonia levels can improve hepatic encephalopathy symptoms.\(^3\)

Glutamine

- Glutamine is neuronally inactive, it modifies astrocyte signaling and action of glutamate.
- In hepatic encephalopathy:
  1- cerebral glutamine are increased
  2- cerebral glutamate decreased
- Increased glutamine in astrocytes $\rightarrow$ osmotic stress $\rightarrow$ cellular swelling and cellular change, termed *Alzheimer type 2 astrocytosis*
Sources and potential role of ammonia with inflammation

Intestinal protein / bacteria
Reduced hepatic removal
Reduced muscle mass

$\text{NH}_3$ ↑

Inflammation

Alter BBB
Astrocyte damage
↑ glutamine
↓ Direct effects Excitatory pathways
ACLF is Associated with Systemic Inflammation

**White-cell count**

![Bar chart showing white-cell count for NO ACLF, ACLF-1, ACLF-2, and ACLF-3.](chart-white-cell)

**C-reactive Protein**

![Bar chart showing C-reactive protein for NO ACLF, ACLF-1, ACLF-2, and ACLF-3.](chart-c-reactive-protein)
Ex Vivo LPS-induced Inflammatory Genes in PBMCs From Healthy Controls and Cirrhotics

Additive mechanisms

- Benzodiazepinelike substances [1] have been postulated to arise from a specific bacterial population in the colon. [2]
- Other products of colonic bacterial metabolism [3], such as neurotoxic short- and medium-chain fatty acids, phenols, and mercaptans, are also produced.
- Manganese may deposit in basal ganglia and induce extrapyramidal symptomatology. [4]

Amino Acid Imbalance Hypothesis

- Abnormal balance between Branched chain Amino Acids (BCAA) and Aromatic Amino Acids (AAA).
- In Cirrhosis: ↓ BCAA and ↑ AAA

Two consequences:
1. ↑ protein catabolism = lean mass
2. ↑ Synthesis of false NT and ↓ Synthesis of normal NT

BCAA = Isoleucine, Leucine, Valine => metabolised in muscle & brain
AAA = Phenylalanine, Tyrosine, Tryptophan => metabolised in liver

Normally Leucine (BCAA) promote protein synthesis & inhibit protein catabolism
# Hyponatremia

997 consecutive patients from 28 centers in Europe, North and South America, and Asia for 28 days

- Inpatients and outpatients with cirrhosis and ascites

<table>
<thead>
<tr>
<th>Serum Sodium (mEq/L)</th>
<th>&lt;130</th>
<th>131-135</th>
<th>&gt;135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heptorenal Syndrome</td>
<td>3.45</td>
<td>1.75</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>3.40</td>
<td>1.69</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>1.48</td>
<td>0.93</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Bacterial Peritonitis</td>
<td>2.36</td>
<td>1.44</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver

Hendrik Vilstrup, Piero Amodio, Jasmohan Bajaj, Juan Cordoba, Peter Ferenci, Kevin D. Mullen, Karin Weissenborn, and Philip Wong

Clinical Practice Guidelines

EASL European Association for the Study of the Liver

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases

American Association for the Study of Liver Diseases*

European Association for the Study of the Liver*†
What is new in HE Diagnosis and Management?

- New nomenclature and definition
- Streamlining the diagnosis for overt HE
- Potential diagnostic strategies for covert or minimal HE
- Focus on nutritional therapy for HE
- Differentiating treatment strategies regarding primary and secondary prophylaxis
- Treatments for persistent HE
What has remained constant?

• Treatment strategies for an acute episode focused on specific and general management
• Need to identify precipitating factors and other causes of altered mental status
• Importance of HE stages that are not apparent clinically
• Evaluation of gut-based therapies for treatment and prevention of further HE episodes
### Overall Classification of HE: Four Axes

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade</th>
<th>Time Course</th>
<th>Presence of precipitating factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Acute Liver Failure)</td>
<td>Minimal 1</td>
<td>Covert Episodic (no further HE for ≥ 6 months)</td>
<td>Precipitated (specific factor found)</td>
</tr>
<tr>
<td>B (porto-systemic Bypass or shunt without cirrhosis)</td>
<td>2</td>
<td>Recurrent (further episode within 6 mths)</td>
<td></td>
</tr>
<tr>
<td>C (Cirrhosis)</td>
<td>3</td>
<td>Persistent (never resolved)</td>
<td>Spontaneous (no precipitating factor found)</td>
</tr>
</tbody>
</table>
# Classification of HE: Grades

<table>
<thead>
<tr>
<th></th>
<th>Unimpaired</th>
<th>Covert HE</th>
<th>Overt HE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental status</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Ranging from disorientation through coma</td>
</tr>
<tr>
<td>Performance on</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Not needed but will be abnormal if tested</td>
</tr>
<tr>
<td>specialized tests</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asterixis</strong></td>
<td>Absent</td>
<td>Absent</td>
<td>Present unless patient is in coma</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy

Bajaj JS et al ISHEN Consensus Statement
Aliment Pharmacol Ther 2011.
Key nomenclature changes

- **Covert HE** is a combination of minimal and **grade 1 HE** since grade 1 is difficult to diagnose.

- **Recurrent HE** or >1 episode within 6 months should prompt the search for a recurrent precipitant, whose correction may prevent costly readmissions.
Case- 1

• A 60 year old female on the transplant wait list is admitted for the 3\textsuperscript{rd} time in a month with acute mental confusion.

• She is already on lactulose and rifaximin and her caregivers maintain patient’s compliance.

• Patient is disoriented to time and place, but has no focal neurological deficits.

• Lab work up was notable for gross pyuria.

• She was treated with a course of antibiotics and got better and was discharged home
Case 1 is classified as

- Type C,
- overt
- Grade III,
- recurrent,
- precipitated by urinary tract infection
Case- 2

• A 65 year old male with HCV cirrhosis for a scheduled follow up. Has refractory ascites requiring serial LVPs and encephalopathy.

• Rifaximin was recently added to his regimen as he continued to remain confused and forgetful despite lactulose.

• Today, he reports being doing fine but appears slow and has asterixis. His wife reports he is taking all his medications as prescribed.

• There has been no recent fever, chills. His labs including comprehensive metabolic panel, urinalysis, and toxicology screen are all within normal.
Case 2 is classified as

- Type C,
- Overt,
- grade II,
- persistent HE,
- non-precipitated.
Case- 3

- A 47 year old man with alcoholic cirrhosis abstinent > 3 years was brought to clinic by his mother who claims that he is a “little bit slower than usual”.
- On examination, he does not have ascites, asterixis and is oriented to time, place and person.
- Since you have been seeing this patient for more than 3 years, you also agree with the mother that “something is not right”.
- On investigation, no signs of infection, changes in underlying liver function or addition of new medications are found. The cognitive tests performed show significant impairment in all fields tested.
Case 3 is classified as

- This would qualify as grade I in the West Haven criteria but this is only apparent because the patient is well-known to everyone concerned who can identify issues with them readily but would potentially be missed or misclassified in multi-center studies.
  - Type C,
  - Covert,
Covert / Minimal HE

- Present in around 40-60% of patients

- Cannot be diagnosed by simple physical exam but needs specialized testing

- Absence of asterixis or disorientation

- Is associated with
  - A higher progression to overt HE, hospitalization
  - Adds to the potential risk of transplantability
  - Poor quality of life
  - Worse socio-economic status
  - More falls
  - Poor driving skills and higher accidents

Minimal Hepatic Encephalopathy
Treatment

- Risk for developing overt HE
- Individualized decision based on:
  a) Psychometric testing
  b) MHE has an impact on quality of life

“Treatment with lactulose improves both cognitive function and HRQOL in patients with cirrhosis who have MHE”

Hepatology. 2014;60(2):715
Hepatology. 2007;45(3):549
Am J Gastroenterol 2011;106:307–316
Minimal Hepatic Encephalopathy

Rifaximin Improves Psychometric Performance and Health-Related Quality of Life in Patients With Minimal Hepatic Encephalopathy (The RIME Trial)

• 94 patients
• No lactulose
• HRQOL/SIP

Am J Gastroenterol 2011;106:307–316
“Rifaximin improves driving simulator performance in minimal hepatic encephalopathy: A double-blind, placebo-controlled, prospective randomized trial”

42 pts., baseline and 8 weeks follow up

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speeding tickets</td>
<td>4.1 → 2</td>
<td>2.7 → 2.8</td>
</tr>
<tr>
<td>Illegal turns</td>
<td>2.6 → 0.9</td>
<td>1.9 → 1.5</td>
</tr>
<tr>
<td>Collisions</td>
<td>3.2 → 2.6</td>
<td>2.7 → 3</td>
</tr>
<tr>
<td>Cognitive Battery</td>
<td>↑↑</td>
<td>-----</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Unchanged</td>
<td></td>
</tr>
</tbody>
</table>

Gastroenterology 2011;140:478
Covert HE can be an Independent Predictor of Survival

Dhiman et al DDS 2010, Amodio et al Hepatol 1999
Covert HE is independently associated with death, OHE and hospitalizations.
Covert HE is important to our patients

<table>
<thead>
<tr>
<th>Outcomes in cirrhotic patients</th>
<th>Affected?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to overt HE</td>
<td>✓</td>
</tr>
<tr>
<td>Health-related Quality of life</td>
<td>✓</td>
</tr>
<tr>
<td>Driving impairment and accidents</td>
<td>✓</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>✓</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>✓</td>
</tr>
<tr>
<td>Can be tested for</td>
<td>✓</td>
</tr>
</tbody>
</table>
Cirrhosis without overt HE

1. Current Drivers
2. Currently Employed
3. With Cognitive Complaints
4. Poor Quality of Life

Testing strategies (two needed)
- a. Paper-pencil
- b. Computerized
- C. Neuro-physiological

Impaired on at least 2 strategies compared to healthy local controls
- Patient has covert HE
- Consider retesting in 6 months

Unimpaired patients

Could use a high-sensitivity test at this stage:
- Sickness Impact Profile
- EncephalApp
- Stroop
EncephalApp Stroop App can test for Covert HE rapidly

- Tested in 4 US Centers
- Evaluates the time to respond to colors presented; if >190 seconds, it is suggestive of covert HE
- Can be given by nurses, medical assistants or other clinicians within 3-5 minutes
- Good test/retest reliability
- Can predict overt HE development
- Available for free download on iTunes and Android

EncephalApp based on direct population norms predicts time to OHE development

All cirrhotic patients

<table>
<thead>
<tr>
<th>Time</th>
<th>MHE</th>
<th>No MHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>15</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>20</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>25</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Those without prior OHE

<table>
<thead>
<tr>
<th>Time</th>
<th>MHE</th>
<th>No MHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>15</td>
<td>0.03</td>
<td>0.03</td>
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<tr>
<td>20</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>25</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

[Allampati et al Am J Gastro 2016]
Plug in the numbers at www.encephalapp.com

You will need
1. Age
2. Gender
3. Education level and
4. OffTime+OnTime
Covert HE diagnosis take-home points

1. Consider collaboration with a health psychologist who can perform testing and interpretation

2. Administer *Sickness Impact Profile* and if four selected questions are checked, it is 80% likely that the subject has CHE.

3. Administer the *EncephalApp Stroop* and if the OffTime+OnTime is >190 seconds, then the subject likely has CHE.
# Covert HE Treatment is Effective for Psychosocial Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Lactulose</th>
<th>Rifaximin</th>
<th>Probiotics (including synbiotics and yogurt)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of trials</strong></td>
<td>5 (2 against probiotics)</td>
<td>3</td>
<td>7 (2 against lactulose, 1 yogurt, 1 synbiotic)</td>
</tr>
<tr>
<td><strong>Double-blind, placebo-controlled?</strong></td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Improved cognition</strong></td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td><strong>Improved HRQOL</strong></td>
<td>3</td>
<td>2 (only psycho-social improvement in one trial)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Reduced overt HE</strong></td>
<td>1 (not all had covert HE)</td>
<td>0</td>
<td>2 (1 open-label and 1 trend)</td>
</tr>
<tr>
<td><strong>Improved driving</strong></td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Improved liver function</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CHE treatment take-home points

1. Agents used are primarily those that modify the gut microbial milieu such as lactulose, rifaximin and probiotics.

2. Treatment is not standard of care but can be prescribed on a case-by-case basis for those patients who have issues with daily functioning.
Overt Hepatic Encephalopathy
Treatment goals in overt HE

• **Acute HE episode**
  – Treatment of precipitating factors
  – Improvement in mental status
  – Evaluation for liver transplant

• **Episodic HE outpatient**
  – Improve daily functioning
  – Prevention of recurrent episodes of HE
  – Evaluation for liver transplant
Overt HE: Important Questions During the Acute Episode

- Is it really overt HE?
- Is the patient’s airway safe?
- What precipitated it?
- Should we check for ammonia levels?
- Should we restrict protein intake?
- Has the patient become alert after treatment? And if not, why not?
Differential Diagnosis of Overt HE

- **Diabetic** (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
- **Alcohol** (intoxication, withdrawal, Wernicke)
- **Drugs** (benzodiazepines, neuroleptics, opioids)
- **Electrolyte disorders** (hyponatremia and hypercalcemia)
- **Intracranial bleeding and stroke**
- **Neurological infections**
- **Nonconvulsive epilepsy**
- **Psychiatric disorders**
- **Severe medical stressful events** (organ failure and inflammation)
## Precipitating Factors for HE

<table>
<thead>
<tr>
<th>Episodic</th>
<th>Recurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Infections</td>
<td>– Electrolyte disorder</td>
</tr>
<tr>
<td>– GI bleeding</td>
<td>– Infections</td>
</tr>
<tr>
<td>– Diuretic overdose</td>
<td>– Unidentified</td>
</tr>
<tr>
<td>– Electrolyte disorder</td>
<td>– Constipation</td>
</tr>
<tr>
<td>– Constipation</td>
<td>– Diuretic overdose</td>
</tr>
<tr>
<td>– Unidentified</td>
<td>– GI bleeding</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy
Blood Ammonia Levels Not Useful for Individual Patient

- Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with cirrhosis.

- In a person with coma, however, a normal value calls for diagnostic reevaluation.

- Therefore routine blood ammonia measurements in a patient with cirrhosis and altered mental status are not usually useful.
AMMONIA LEVELS
Fig. 1. An overview of the latest European Association for the Study of the Liver/American Association for the Study of Liver Diseases (EASL/AASLD) treatment guidelines for overt hepatic encephalopathy 1, and the role of different medical specialists in the implementation of these guidelines according to our consensus recommendations (grey boxes indicate ‘optional’ involvement, if there is sufficient experience and confidence). BCAAs, branched chain amino acids; GE, gastroenterologist; GP, general practitioner; HE, hepatic encephalopathy; LOLA, L-ornithine L-aspartate.

How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist

EFFECTS of LACTULOSE vs NO TREATMENT in CIRRHOTICS WITHOUT ANY EPISODE OF OVERT HE

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Overt HE</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 with Lactulose</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>50 w/o Lactulose</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>

- 66% of the covert hepatic encephalopathy in the Lactulose group showed improvement.
- Followed monthly for 12 months

Lactulose Started After Index Episode

137 patients with cirrhosis (age 55±6 years, MELD 17±7)

• 103 (75%) developed recurrent PSE after 9±1 months
  – 39 (38%) were not adherent on lactulose
  – 56 (54%) were adherent
  – 8 (8%) had lactulose-associated dehydration → recurrent PSE
• Precipitating factors for recurrent PSE
  – Sepsis (19%), GI bleeding (15%), hyponatremia (4%), TIPS (7%).
• All patients without recurrence were adherent on lactulose
• Adherence rate for those who recurred was only 64% (P = 0.00001)
• Factors that predicted recurrent PSE (multivariate regression)
  – Lactulose non-adherence (OR 3.26)
  – MELD score (OR 1.14)
SECONDARY PROPHYLACTIC THERAPY FOR PREVENTION OF OHE IN CIRRHOTIC PATIENTS WHO HAVE EXPERIENCED AN OHE EPISODE

Figure 1: Probability of developing recurrent OHE in patients receiving prophylactic therapy with lactulose following an episode of OHE compared with patients receiving placebo.\textsuperscript{7}
PEG = Lactulose in an acute HE episode
In this study, patients with cirrhosis who were initiated on lactulose following an initial episode of HE in a liver transplant center were retrospectively followed. Recurrence of HE, precipitating factors, and adherence to lactulose were investigated using chart review and electronic pharmacy records, and predictors of HE recurrence were analyzed.

*Noncompliance inferred with evidence (as documented in patient charts) of discontinuation of lactulose as prescribed (determined by questioning patient or family members); lack of lactulose refill according to pharmacy records; and <2 bowel movements/day, for at least 1 month.

†Lactulose-induced dehydration defined as >4 bowel movements/day with dehydration and azotemia (new rise in serum creatinine >1.5 mg/dL).

<table>
<thead>
<tr>
<th>Precipitating Factor</th>
<th>Frequency per 200 Admissions</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose nonadherence</td>
<td>78</td>
<td>39</td>
</tr>
<tr>
<td>Constipation</td>
<td>44</td>
<td>22</td>
</tr>
<tr>
<td>Opioids and benzodiazepines</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>Dehydration</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Infections</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>17</td>
<td>8.5</td>
</tr>
<tr>
<td>Hypokalemia (potassium &lt;3.5)</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Large volume paracentesis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>TIPS</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Hyponatremia (sodium &lt;130)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>High protein diet</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Unknown precipitants</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 2: Factors identified as precipitants of OHE in 109 cirrhotic patients who had 200 hospital admissions with a primary diagnosis of OHE. TIPS, transjugular intrahepatic portosystemic shunt.
Overt HE diagnosis take-home points

1. *Any alteration in mental status* in subjects with cirrhosis can be considered overt HE unless proven otherwise.

2. Most of the time, it is the *caregiver* who reports these changes and it is essential to keep the caregivers and the family unit educated and engaged.

3. Most subjects with *overt HE require hospitalization* for work-up of precipitating factors, exclusion of other causes of altered mental status and potential liver transplant work-up.

4. *Blood ammonia levels are not usually useful* in monitoring therapy in patients with overt HE
Algorithm for Inpatient HE Management

Patient with possible overt HE

Confirm that it is HE: Yes

Search for precipitating factor

Precipitating factor(s) found

Treatment directed to the precipitating factor

Precipitating factor(s) not found

• Admit to ICU for grade ≥3 HE
• Specific HE therapy with lactulose or rifaximin
• Can consider second line therapies

No HE: Other causes of altered mental status

HE = hepatic encephalopathy

Bajaj JS. Aliment Pharmacol Ther 2010.
Treatment Options for Overt HE

- Reduction in the nitrogenous load arising from the gut that can reduce HE (lactulose, rifaximin, probiotics, laxatives)
  - Lactulose and rifaximin are the most widely used drugs in the US

- Drugs that modulate ammonia without affecting the gut (L-ornithine L-aspartate (LOLA), sodium benzoate, glycercyl phenylbutyrate)
  - These drugs are not used widely, or are experimental at this time

Adapted from Blei AT et al. Am J Gastroenterol. 2001
AASLD/EASL HE guidelines 2014.
Rifaximin

- Rifaximin is a semisynthetic, rifamycin-based non-systemic antibiotic.
- Rifaximin acts by inhibiting RNA synthesis in susceptible bacteria by binding to the beta-subunit of bacterial deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase enzyme.
- It is also used to treat diarrhea caused by E. coli and in irritable bowel syndrome.
- Half life: Approximately 6 hours
- Affected microorganisms: Enteric bacteria
- In March 2010, rifaximin was approved by the FDA to reduce recurrence of hepatic encephalopathy.
Rifaximin Vs lactitol vs rifaximin+lactitol

- Forty out-patients (29 males, 11 females, mean age: 59 years, range 40-70), with viral liver cirrhosis and chronic HE (1st-2nd degree) were studied. HE was assessed by considering: mental state, asterixis, number connection test (NCT), arterial blood ammonia levels. Patients were randomly assigned to the following treatments: rifaximin (gp R); lactitol (gp L); rifaximin plus lactitol (gp RL). All treatments were continued for 15 days for 3 cycles, intervalled by 15 days.

RESULTS:
- The 3 treatments reduced HE, but with different efficacy: patients of group R and RL significantly (p<0.05) documented a faster improvement in HE degree, a higher percentage of patients which normalized mental state and NCT, a faster improvement of asterixis and a longer persistence of normal ammonia levels than patients of group L.

CONCLUSIONS:
- Rifaximin in combination with lactitol represents an effective and safe treatment of chronic HE.

Rifaximin versus nonabsorbable disaccharides in the management of hepatic encephalopathy: a meta-analysis

• Methods: a meta-analysis of comparative randomized trials of rifaximin and nonabsorbable disaccharides.

• Results: 5 randomized controlled trials were included. There was no significant difference between rifaximin and nonabsorbable disaccharides on improvement in patients with hepatic encephalopathy [relative risk (RR) 1.08; 95% confidence interval (CI), 0.85-1.38; $P=0.53$]. RR was 0.98 (95% CI: 0.85-1.13; $P=0.74$) for acute hepatic encephalopathy in 157 patients and 0.87 (95% CI: 0.40-1.88; $P=0.72$) for chronic hepatic encephalopathy in 96 patients, respectively. There was no significant difference between rifaximin and nonabsorbable disaccharides on diarrhea (RR=0.90; 95% CI: 0.17-4.70; $P=0.90$). However, a significant difference in favor of rifaximin on abdominal pain (RR=0.28; 95% CI: 0.08-0.95; $P=0.04$) was identified.

• Conclusion: Rifaximin is not superior to nonabsorbable disaccharides for acute or chronic hepatic encephalopathy in the long-term or short-term treatment except that it may be better tolerated.

Study Objective And Key Eligibility Criteria

• Objective
  – Compare the maintenance of remission from previously demonstrated recurrent hepatic encephalopathy (HE) during 6 months of treatment with rifaximin at 550 mg twice daily (BID) or placebo

• Inclusion criteria
  – ≥2 episodes of HE (Conn score ≥2) associated with cirrhosis within 6 months of screening
  – Currently in HE remission (ie, Conn score = 0 or 1 and MELD score ≤25)

• Exclusion criteria
  – Active SBP or intercurrent infection
  – GI hemorrhage or TIPS placement within 3 months of screening
  – Chronic renal or respiratory insufficiency, anemia, or electrolyte abnormality

GI = gastrointestinal; HE = hepatic encephalopathy; MELD = model for end-stage liver disease; SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt.

Study Design\textsuperscript{1,2}

Concomitant lactulose (approximately 90% in both arms) use was permitted throughout the RCT and OLM trials.


\textbf{b.i.d.} = twice daily; OLM = open-label maintenance; RCT = randomized controlled trial.
RCT (Double-blind)  
N=299

Randomization 1:1

Rifaximin 550 mg BID (RFX)  
n=140

Placebo (PBO)  
n=159

New patients  
(OLM)  
n=170

Continuing Rifaximin  
RCT (RFX) → OLM (RFX)  
n=70

Placebo crossover  
RCT (PBO) → OLM (RFX)  
n=82

All OLM= 322

“All Rifaximin” population= 392 (140+170+82)
Daily Lactulose Use Remained Stable Throughout Pivotal Phase III Trial

Mean lactulose use, cups/d*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Xifaxan 550 mg b.i.d.</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily lactulose use, mean ± SD, cups/d*</td>
<td>3.14 ± 2.10</td>
<td>3.51 ± 2.59</td>
</tr>
<tr>
<td>Rate of change in lactulose use, mean ± SD</td>
<td>0.0030 ± 0.0377</td>
<td>0.0076 ± 0.1060</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; HE = hepatic encephalopathy; SD = standard deviation.
*1 cup = 15 mL/cup at 10 g/15 mL.

Figure and table adapted from Bass et al. *N Engl J Med.* 2010;362(12):1071-1081.
With permission. Copyright © 2010 Massachusetts Medical Society. All rights reserved.
Xifaxan 550 mg Reduced the Risk of Breakthrough HE Episode by 58% vs. Placebo\textsuperscript{1,2}

\begin{itemize}
  \item \textbf{Xifaxan 550 mg b.i.d. (n=140)}
  \item \textbf{Placebo (n=159)}
\end{itemize}

- 91% of all patients on lactulose in both groups

\[ \text{HR} = 0.42 \ (95\% \ CI, \ 0.28-0.64) \]

\[ P < 0.0001 \]

Xifaxan 550 mg Reduced The Risk of HE-Related Hospitalization by 50% vs. Placebo\textsuperscript{1,2}

Patients with no HE-related hospitalization, %

<table>
<thead>
<tr>
<th>Days post-randomization</th>
<th>Placebo (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>77%</td>
</tr>
</tbody>
</table>

91% of all patients on lactulose in both groups

HR = 0.42 (95% CI, 0.28-0.64)

\( P < 0.0001 \)

Xifaxan 550 mg Number Needed to Treat in Relation to Other Therapeutic Classes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>To Prevent</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HE¹</td>
<td>Xifaxan 550 mg + lactulose</td>
<td>Breakthrough HE First HE-related hospitalization</td>
<td>4 9</td>
</tr>
<tr>
<td>Hypertension²</td>
<td>Beta-blockers</td>
<td>CV event in 5 years</td>
<td>140</td>
</tr>
<tr>
<td>Diabetes³</td>
<td>Sulfonylurea-insulin</td>
<td>Diabetes-related death</td>
<td>29</td>
</tr>
<tr>
<td>Kidney transplant⁴</td>
<td>Sirolimus or everolimus</td>
<td>CMV disease Acute rejection</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18-41</td>
</tr>
<tr>
<td>CV disease⁵</td>
<td>Statins</td>
<td>CV event in 10 years</td>
<td>12-26</td>
</tr>
</tbody>
</table>

The above data is not a comparison of NNT among different treatments but is intended to provide an overview of published data on NNT.

**Xifaxan 550 mg in HE:**

**Rate of Adverse Events**

<table>
<thead>
<tr>
<th>Adverse event, *% (rate†)</th>
<th>RCT</th>
<th>All Xifaxan 550 mg b.i.d. patients‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xifaxan 550 mg b.i.d. (n=140)</td>
<td>Placebo (n=159)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (0.4)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15 (0.4)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6 (0.2)</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Ascites</td>
<td>11 (0.3)</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (0.2)</td>
<td>4 (0.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9 (0.2)</td>
<td>8 (0.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (0.3)</td>
<td>11 (0.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (0.2)</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (0.3)</td>
<td>13 (0.5)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>9 (0.3)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13 (0.4)</td>
<td>7 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (0.2)</td>
<td>4 (0.2)</td>
</tr>
</tbody>
</table>

b.i.d. = twice daily; HE = hepatic encephalopathy; RCT = randomized controlled trial. *Adverse events other than HE reported in >12% of patients in either RCT treatment group or “all Xifaxan” patients.

†Event rate was calculated as the number of events that occurred divided by patient exposure year).

‡Consists of patients who took ≥1 dose of rifaximin and for whom a safety assessment was conducted. Includes 140 patients from the RCT and 252 new rifaximin patients in the open-label extension trial.

Bass: NEJM special comments

• The current study differs from previous randomized studies in that it involved a larger group of patients and a longer study period. In previous randomized studies, rifaximin was administered for 21 days or less\textsuperscript{1,2,3} or intermittently, for 14 or 15 days per month for 3 or 6 months.

Nonabsorbale Antibiotics: including rifaximin

- The safety profile of rifaximin appears to be superior to that of systemic antibiotics, particularly for patients with liver disease.
- The occurrence of nephrotoxicity and ototoxicity with the use of aminoglycosides (e.g., neomycin and paromomycin) and of nausea and peripheral neuropathy with prolonged use of metronidazole restricts their use in patients with hepatic encephalopathy. 1,2,3

Meta-analysis

• Multiple clinical trials have demonstrated that rifaximin at a dose of 400 mg taken orally 3 times a day was as effective as lactulose or lactitol at improving hepatic encephalopathy symptoms.\textsuperscript{1,2,3}

Lactulose + Rifaximin is better than lactulose alone in an acute HE episode
Nutrition in HE
Sarcopenia in cirrhosis

Log Rank, $P=0.005$

- No Sarcopenia
- Sarcopenia
Diet

• Most patients with HE tolerate =60-80 g of protein /d.
• Furthermore, one study administered protein-rich diet (>1.2 g/kg/d) to patients with advanced disease awaiting liver transplantation, without inducing a flare of encephalopathy symptoms.[1]
• Another study randomized patients with severe episodic encephalopathy to low-protein diet Vs high-protein diet, administered via NG tube.[2] All patients received the same regimen of neomycin per NG tube. Mental function improved at the same rate in both treatment groups.

Protein content

- One skinless chicken breast (130g): 41g protein.
- One beef burger or pork sausage: 8g protein.
- Half a can of tuna: 19g protein.
- One portion of cheese (50g): 12g protein.
- One medium egg: 6g protein.
- 150ml glass of milk: 5g protein.
- One tablespoon of boiled red lentils (40g): 3g protein.
- One portion of tofu (125g): 15g protein.
- One slice medium wholemeal bread: 4g protein.
- One slice medium white bread: 3g protein.
Protein restriction does not help in overt HE

There were no statistical differences between the low-protein diet (white boxes) and the normal protein diet (gray boxes).

Cordoba et al 2004 J Hepatol
Nutritional Recommendations in HE as an Inpatient and for Long-term Outpatient Management

- Daily energy intakes should be 35–40 kcal/kg ideal body weight
- Daily protein intake should be 1.2–1.5 g/kg/day: DO NOT RESTRICT PROTEIN
- Small meals or liquid nutritional supplements evenly distributed throughout the day and a late-night snack should be offered

Overt HE treatment take-home points

• A **four pronged approach** is critical
  a. Evaluate for other causes of altered mental status
  b. Initiate care of the unconscious patient
  c. Search for precipitating factors
  d. Initiate empiric therapy for OHE

• Putting this **episode in context of the past history** in order to guide future management is essential

• **Do not restrict protein** in patients with OHE
Persistent HE
What if the Patient is Otherwise Compensated and has Recurrent Hepatic Encephalopathy? Look for Spontaneous Spleno-Renal Shunts

- Embolization of these shunts can improve the course of HE in selected patients with MELD <11 and one large shunt

Prevention of HE Recurrence
Overt HE: Important Questions at the Time of Discharge

- How can we prevent this from happening again?
- Are the caregivers able to handle the patient?
- Is the patient a transplant candidate?
Prevention of Overt HE recurrence: Lactulose

Sharma et al, Gastro 2009
Patients whose HE recurred (%)

Prevention of Overt HE recurrence: Rifaximin

*Patients who had ≥2 episodes of HE within 6 months prior to screening and who were in remission at trial start

Bass N et al. NEJM 2010
Xifaxan 550 mg Does Not Have an Adverse Effect on Mortality

<table>
<thead>
<tr>
<th>Analysis group</th>
<th>Death, n</th>
<th>Death rate*</th>
<th>Persons Years of Exposure</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo RCT (n=159)</td>
<td>11</td>
<td>0.2</td>
<td>46.0</td>
<td>—</td>
</tr>
<tr>
<td>All Xifaxan 550 mg b.i.d. (n=392)</td>
<td>76</td>
<td>0.1</td>
<td>510.5</td>
<td>0.1480</td>
</tr>
</tbody>
</table>

No significant difference in the occurrence or rate of mortality was observed with Xifaxan 550 mg versus placebo, indicating that Xifaxan 550 mg did not adversely affect long-term survival.

b.i.d. = twice daily; CI = confidence interval; OLM = open label maintenance; RCT = randomized controlled trial.

†Obtained from parameter estimates with effect for treatment and region.

*Includes patients in the placebo group of the RCT who switched to Xifaxan 550 mg during the OLM trial and patients newly recruited into the OLM trial.

Prevention of re-hospitalization with VSL#3

Persistent Encephalopathy

- Lactulose, Rifaximin, Na Benzoate, LoLa, BcAA
- Look for a splenorenal shunt on imaging studies
- Balloon-Occluded Retrograde Transverse Obliteration (BRTO)
- Coil-Assisted Retrograde Transvers Obliteration (CARTO)
- Vascular Plug-Assisted Retrograde Obliteration (PARTO)

J Gastroenterol Hepatol. 1996 Jan;11(1):51-8
Hepatol Res. 2012 Jun 6
Persistent Encephalopathy due to large varices and spontaneous PS Shunt
Persistent Encephalopathy improved: Shunt Embolized
Hepatic Encephalopathy

What is BRTO?

Balloon-occluded Retrograde Transvenous Obliteration

AJR Am J Roentgenol 2005; 184:1340-1346
Hepatic Encephalopathy
BRTO for HE

N = 7
Technical success = 100% (7/7)
Clinical success = 86% (6/7)
Complications
• Increased LFTs = 2
• ARF = 2

N = 7
Technical success = 100% (7/7)
Clinical success = 100% (7/7)
Follow up = 251 days
No major complications

Gwon DI et al Radiology 2013
Mukund A. et al JVIR 2012
Coil-Assisted Retrograde Transvenous Obliteration

Using embolization coils with gelfoam
- NO indwelling balloon
- NO Sclerosing agents

Safer with less complications
- No migration of sclerosing agents
- No Pulmonary embolism
- No fear of hematuria/renal failure

Overall, higher cost effectiveness
- No ICU beds, No second IR procedure
- Faster Procedure time
Hepatic Encephalopathy
CARTO for HE@UCLA

• CARTO was performed in 26 patients between 06/2012 – 03/2015.
  • Hepatic Encephalopathy (WH grade 3 or 4) in all 26 patients

• These cases were retrospectively reviewed for:
  1. Patient demographic information
  2. Clinical and technical outcomes
  3. Follow-ups
**Hepatic Encephalopathy**  
**CARTO for HE@UCLA**

<table>
<thead>
<tr>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Mean West Haven Score</strong></td>
</tr>
<tr>
<td><strong>Splenorenal : Gastrorenal: Other Shunts</strong></td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
</tr>
</tbody>
</table>
Hepatic Encephalopathy
CARTO for HE@UCLA

- CARTO in HE Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>%</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Success</td>
<td>26/26</td>
<td><strong>100%</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Success</td>
<td>21/26</td>
<td><strong>81%</strong></td>
<td>5 patients had no MS changes</td>
</tr>
<tr>
<td>West Haven Score</td>
<td>In 21 patients</td>
<td>3.45 ➔ 1.53</td>
<td></td>
</tr>
<tr>
<td>Ammonia Level</td>
<td>In 26 patients</td>
<td><strong>57% reduction</strong></td>
<td>142.8 ± 41.2 ➔ 60.9 ± 22.0</td>
</tr>
<tr>
<td>Bridge to Transplant</td>
<td>9/26</td>
<td><strong>35%</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Hepatic Encephalopathy

#### CARTO for HE@UCLA

**• CARTO in HE Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>%</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Complications</td>
<td>0/26</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Major Complications</td>
<td>0/26</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Minor Complications</td>
<td>11/26</td>
<td>42%</td>
<td>Onyx particle dislodge (n=1); Fever (n=3), Transient LFTs (n=9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abdominal discomfort (n=9), new Ascites/Hydrothorax (n=7)</td>
</tr>
<tr>
<td>CARTO-associated Mortality</td>
<td>0/26</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>21/26</td>
<td>81%</td>
<td>5 patients passed away due to other co-morbidities/liver failure</td>
</tr>
</tbody>
</table>
Hepatic Encephalopathy CARTO for HE@UCLA

67 / F
EtOH Cirrhosis; MELD 15
Multiple hospitalization due to Hepatic Encephalopathy
Refractory to medical tx
Transferred from OSH with severe HE and WH score of 3/4
A&Ox1 or none.
Ammonia level = 320
Requested for CARTO
1. Deployment of coils using the proximally placed microcatheter

2. Injection of gelfoam slurry via distally placed micro or macrocatheter

Selective venogram of a large gastrorenal shunt

Complete filling of gastrorenal shunt

Hepatic Encephalopathy
CARTO for HE@UCLA
Hepatic Encephalopathy  
CARTO for HE@UCLA

Post-CARTO Day 1
• Ammonia = 77
• Improvement of mental status (A&Ox3)

Post-CARTO Day 3
• Ammonia = 60
• CT = complete obliteration of a large gastrorenal shunt; e/o of new hydrothorax
• Mental status = A&Ox3 or 4
Hepatic Encephalopathy
CARTO for HE@UCLA

Pre-CARTO | 3d Post CARTO | 1m Post CARTO | 6m Post CARTO
Surgical shunt ligation + splenectomy
6 patients, F/U up to 36 months
Child-Pugh B and C
All alive and well without encephalopathy
One patient had shunt recurrence treated with BRTO
Hepatic Encephalopathy

TIPS & HE
Hepatic Encephalopathy
TIPS & HE

META-ANALYSIS AND SYSTEMATIC REVIEWS

Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: A systematic review

Ming Bai,* Xingshun Qi,* Zhiping Yang,‡ Zhanxin Yin,* Yongzhan Nie,† Shanshan Yuan,* Kaichun Wu,* Guohong Han* and Daiming Fan‡

*Department of Digestive Interventional Radiology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University and †State Key Laboratory of Cancer Biology, Xijing Hospital of Digestive Diseases, Fourth Military Medical University and ‡Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi’an, China

- Systemic reviews including 30 studies
- Most strong predictors = age, prior HE and high Child-Pugh

Bai M et al J Gastroenterolo Hepatol 2011
Hepatic Encephalopathy
TIPS Reduction

Portosystemic Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt in Patients With Cirrhosis: Clinical, Laboratory, Psychometric, and Electroencephalographic Investigations

Wilhelm Nolte,1 Jens Wiltfang,3 Christian Schindler,1 Hans Münke,1 Knut Unterberg,1 Uta Zumhasch,1 Hans R. Figulla,2 Gerald Werner,2 Heinz Hartmann,1 and Giuliano Ramadori1

- N = 55 Pts; Prospective Study
- HE Incidence in 3 months = 50.9%
- Prior HE and poor liver function – (+) associated with HE
- Arterial NH3 increased during first 3 months (p<0.001)
• N = 191 patients in 14 yrs (1999-2013)
• HE Incidence in 30 days = 42% (n=81)
• Only 3 pts required TIPS reduction
• MELD and Age – positive correlation with HE
• De novo HE – No correlation with 90-day mortality (p=0.40)
• Worsened HE – (+) correlation with 90d mortality (p<0.001)
Hepatic Encephalopathy
TIPS & HE

• N = 78 patients
• HE Incidence in 24 months F/U = 44.8% (n=35)
• 55% of HE patients = Grade III or IV
• 6 Patients required TIPS reduction
• Older Age, High Cr level, Low Sodium, Low Albumin level – independent factors associated with HE
Hepatic Encephalopathy
TIPS Reduction

N = 17 with refractory HE post-TIPS
76% clinical improvement of HE
Hepatic Encephalopathy
TIPS Reduction

Management of Refractory Hepatic Encephalopathy After Insertion of TIPS: Long-Term Results of Shunt Reduction With Hourglass-Shaped Balloon-Expandable Stent-Graft

OBJECTIVE. The purpose of this study was to review the use of an hourglass-shaped expanded polytetrafluoroethylene (ePTFE) stent-graft to reduce transjugular intrahepatic portosystemic shunts in patients with hepatic encephalopathy refractory to conventional medical therapy.

MATERIALS AND METHODS. From January 2000 through December 2008, 189 transjugular intrahepatic portosystemic shunt procedures were performed with self-expanding stent-grafts. After a mean period of 43.4 ± 57 weeks, hepatic encephalopathy developed in 12 patients and did not respond to conventional medical therapy with lactulose, nonabsorb-

• N = 12
• 100% clinical success with improvement of HE
  - in avg 22.3 hr, range 18-26 hrs
• 74 wks F/U with no recurrence of HE
### Hepatic Encephalopathy

#### TIPS Reduction

- **UCLA TIPS Reduction Results**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>%</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technical Success</strong></td>
<td>14/14</td>
<td><strong>100%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Success</strong></td>
<td>11/14</td>
<td><strong>79%</strong></td>
<td>3 patients had no changes of MS</td>
</tr>
<tr>
<td><strong>TIPS to Revision Time</strong></td>
<td>N=14</td>
<td><strong>207 ± 388 days</strong></td>
<td>Range (3-1449 days)</td>
</tr>
<tr>
<td><strong>Follow Up Period</strong></td>
<td>N=14</td>
<td><strong>229 ± 261 days</strong></td>
<td>Range (28-807 days)</td>
</tr>
</tbody>
</table>
Hepatic Encephalopathy
TIPS Reduction

53 yo Male
HCV Cirrhosis/Portal Hypertension
MELD 16
H/O Multiple esophageal variceal bleeding
TIPS placed in Nov 2014
Multiple hospitalization due to Hepatic Encephalopathy; Refractory to medical tx
Transferred from OSH with severe HE and WH score of 3
TIPS reduction requested.
Hepatic Encephalopathy

TIPS Reduction

Pre-reduction TIPS (10 mm) (PSG = 7 mmHg)

TIPS Reduction Double Stent Technique

TIPS Reduction Using 5 mm balloon

Post-reduction TIPS (5 mm) (PSG = 13 mmHg)

Lee EW et al 2015 (unpublished)
Post TIPS Hepatic Encephalopathy

- 45% of patients undergoing TIPS
- A precipitating factor should be ruled out first
- Tendency to be frequent over time
- Risk factors → Age >60, MELD >20
- Standard therapy for HE once HE post TIPS is manifest
- Refractory HE → 8%
- Good response to shunt reduction
Hepatic Encephalopathy
Conclusions

• Common cause of morbidity and mortality in cirrhotic patients

• Adversely impacts quality of life, earning capacity and driving ability

• Better tools for easy diagnosis of MHE

• Treat MHE if it is affecting quality of life

• A search for a precipitating factor and maintenance therapy are essential for prevention of recurrence of OHE
Caregivers: The forgotten frontier
<table>
<thead>
<tr>
<th>Variable</th>
<th>No HE (n=58)</th>
<th>HE (n=46)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zarit Burden Interview</td>
<td>11.5 ± 8.4</td>
<td>16 ± 9</td>
<td>0.016</td>
</tr>
<tr>
<td>Perceived care burden</td>
<td>65 ± 21.8</td>
<td>75.4 ± 19.2</td>
<td>0.015</td>
</tr>
<tr>
<td>- Financial</td>
<td>9.3 ± 3.3</td>
<td>10.6 ± 4.1</td>
<td>0.112</td>
</tr>
<tr>
<td>- Abandonment</td>
<td>14.6 ± 7.2</td>
<td>13.8 ± 3.3</td>
<td>0.45</td>
</tr>
<tr>
<td>- Schedule</td>
<td>11.9 ± 7.0</td>
<td>16.1 ± 6.2</td>
<td>0.005</td>
</tr>
<tr>
<td>- Health</td>
<td>15.6 ± 4.1</td>
<td>17.8 ± 3.7</td>
<td>0.006</td>
</tr>
<tr>
<td>- Entrapment</td>
<td>13.4 ± 6.5</td>
<td>17.3 ± 8.3</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Bajaj et al Am J Gastroenterol 2011
Cirrhotic patients need more caregiving

Cirrhotic
- Informal: 60%
- Formal: 31%
- None: 9%

Non-Cirrhotic
- Informal: 79%
- Formal: 16%
- None: 5%

Informal | Formal | None
---|---|---
60% | 31% | 9%
79% | 16% | 5%

Rakoski et al, Hepatol 2012
HE and Cirrhosis: Burden on patients and caregivers

• Patients’ burden
  – Medical/Physical: high risk of death and hospitalization
  – Financial: higher unemployment and poor performance
  – Psycho-social: poor HRQOL and higher dependence on caregivers

• Caregiver’s burden
  – Medical/Physical: higher rate of death
  – Financial: worse employment and income
  – Psycho-social: effects on mood and cognition

Overt HE prevention of recurrence take-home points

• Re-evaluate the ability of caregivers to handle the multiple issues

• Excellent evidence regarding pharmacological intervention
  – After the 1\textsuperscript{st} episode: Lactulose therapy is indicated
  – After the 2\textsuperscript{nd} episode: Rifaximin in addition to lactulose is recommended

• Evaluate patient for recurrent precipitating factors and for liver transplant suitability
What Should a Physician do When Faced with a Potentially Impaired Driver?

- Follow the applicable local laws on mandatory reporting (only for overt HE as of now)
- Inform the patient and their family of the potential impairment
- Do not treat only if the ammonia levels are high; many false positive results
- Where possible, recommend a fitness-to-drive evaluation by a driving instructor trained in detecting driving impairment
- The driving agencies have the ultimate authority to determine fitness to drive and not us!

<table>
<thead>
<tr>
<th>HE and Traffic Safety</th>
<th>All</th>
<th>Europe</th>
<th>Americas</th>
<th>Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finds it difficult to deal with traffic issues and HE</td>
<td>75%</td>
<td>75%</td>
<td>86%</td>
<td>62%</td>
</tr>
<tr>
<td>Obtains traffic history in &gt; 60%</td>
<td>21%</td>
<td>17%</td>
<td>29%</td>
<td>14%</td>
</tr>
<tr>
<td>Are aware of local driving laws in relation to HE</td>
<td>47%</td>
<td>50%</td>
<td>32%</td>
<td>57%</td>
</tr>
<tr>
<td>Thinks recent OHE impacts driving skills</td>
<td>99%</td>
<td>99%</td>
<td>98%</td>
<td>96%</td>
</tr>
<tr>
<td>Will restrict driving in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent OHE</td>
<td>79%</td>
<td>80%</td>
<td>79%</td>
<td>76%</td>
</tr>
<tr>
<td>Prior, currently controlled HE</td>
<td>48%</td>
<td>42%</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>Recommended driving restrictions in &gt; 60% of cases of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent OHE</td>
<td>20%</td>
<td>15%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td>Currently controlled HE</td>
<td>7%</td>
<td>6%</td>
<td>0%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Lauridsen et al *J Hepatol* 2015
Patient with Cirrhosis

Altered mental status

YES

Evaluate for alternative diagnosis.

Treat

- Non-focal neurological disease
- Asterixis, disorientation, stupor or coma

4 pronged approach
- Initiation of care.
- Evaluate alternative etiologies.
- Identify precipitating factors and correct.
- Initiation of empirical therapy.

Impaired on at least 2 tests compared to normal.

- CHE diagnosis confirmed and needs closer monitoring for OHE and negative outcomes.
- Consider trial of treatment

Unimpaired patient

Monitor and consider retesting in 6 months.

Consider liver transplant candidacy

NO

Patient employed? Is patient a driver? Is patients QOL poor? Obvious cognitive disabilities?

Consider evaluation for CHE.

Algorithm to approach OHE & CHE Patidar, Bajaj CGH 2015.
Other uses and benefits of rifaximin
RIFAXIMIN AND PROPRANOLOL COMBINATION THERAPY IS MORE EFFECTIVE THAN PROPRANOLOL MONOTHERAPY IN THE HEPATIC VENOUS PRESSURE GRADIENT RESPONSE AND PROPRANOLOL DOSE REDUCTION – A PILOT STUDY

Soon Koo Baik*1, Yoo Li Lim1, Youn Zoo Cho1, Moon Young Kim1, Yoon Ok Jang2, Ki Tae Suk3, Gab Jin Cheon4, Young Don Kim4, Dae Hee Choi5

1Internal Medicine, 2Cell Therapy and Tissue Engineering, Wonju Christian Hospital, Wonju, 3Internal Medicine, Chuncheon Sacred Heart Hospital, Chuncheon, 4Internal Medicine, Kangneung Asan Hospital, Kangneung, 5Internal Medicine, Kangwon University School of Medicine, Chuncheon, Korea, South
Background and Aims

• Nonselective beta blocker is first line therapy to decrease portal hypertension.

• Anti-portal pressure effect is often insufficient and side effects limit use in many patients.

• Gut bacterial translocation and production of endotoxin are known to increase portal pressure in cirrhosis.

• Aim: investigate the effect of adding gut decontamination via rifaximin to nonselective beta blocker, propranolol, in lowering the hepatic venous gradient (HVPG)
Methods

• 65 patients with advanced cirrhosis randomized
  – Propranolol monotherapy (n=48)
    • Titrated to max 320 mg/day with target of 25% heart rate (HR) reduction
  – Propranolol + rifaximin therapy (n=17)
    • 25% HR reduction: max propranolol 160 mg/day + rifaxamin 1200 mg/day

• HVPG measured at
  – Baseline and 3 months after randomization

• Response defined as HVPG reduction by ≥20% or to less than 12 mmHg

• Mean blood pressure (MBP), HR, side effects and other serologic data were also collected.
## Results

<table>
<thead>
<tr>
<th></th>
<th>Propranolol Monotherapy (N=48)</th>
<th>Propranolol + Rifaximin (N=17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal pressure decline mmHg</td>
<td>17.0 ±3.9 to 13.5 ± 4.1</td>
<td>16.7±3.6  to 10.9±4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HVPG response (%)</td>
<td>50</td>
<td>82</td>
<td>0.018</td>
</tr>
<tr>
<td>Mean reduction in HVPG mmHg</td>
<td>3.5 ± 3.9</td>
<td>5.8 ± 3.8</td>
<td>0.038</td>
</tr>
<tr>
<td>Mean dose Propranolol mg/day</td>
<td>152 ± 59.3</td>
<td>127.0 ± 32.4</td>
<td>0.033</td>
</tr>
<tr>
<td>Decrease in HR (%)</td>
<td>20.5 ± 13</td>
<td>7.4 ± 15.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Decrease in mean BP mm Hg</td>
<td>3.1 ± 11.7</td>
<td>4.4 ± 12.3</td>
<td>0.695</td>
</tr>
</tbody>
</table>

Summary

- HE is a prevalent disorder in cirrhosis
- Ammonia and inflammation form the patho-physiological basis for HE
- Covert HE is epidemic in patients with cirrhosis and need specialized testing for diagnosis
- It is associated with often disabling cognitive dysfunction
- Rapid diagnostic tests are available and treatment could help improve quality of life
- Treatment of Overt HE as an inpatient and outpatient is largely dependent on gut milieu modification, with lactulose as the first line
- There are several alternatives to lactulose such as rifaximin
- Prevention of Overt HE recurrence is a clinically relevant goal that has implications on the patients, caregivers and the healthcare system
Acknowledgements:

• Jas Bajaj
• Kevin Mullen
• Michele Mendler
• Buddy Sussman

• UCLA radiology team
• USC hepatology