Hepatic Encephalopathy Treatments: Beyond Lactulose

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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
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</td>
<td>Covert 1</td>
<td>Episodic (no further HE for ≥6 months)</td>
</tr>
<tr>
<td>B (porto-systemic Bypass or shunt without cirrhosis)</td>
<td>2</td>
<td>Overt 3</td>
<td>Recurrent (further episode within 6 mths)</td>
</tr>
<tr>
<td>C (Cirrhosis)</td>
<td>4</td>
<td>Persistent</td>
<td>(never resolved)</td>
</tr>
</tbody>
</table>

EASL/AASLD Hepatic Encephalopathy guidelines Hepatology 2014

Outline

- Definition and types of HE
- Inpatient management of HE
- Outpatient management of HE
- Nutritional Therapy in HE
- FMT and its potential impact in cirrhosis and HE
Pathophysiology of HE

Overt Hepatic Encephalopathy
**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?

**Algorithm for Inpatient HE Management**

1. **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**

**HE** = hepatic encephalopathy

Bajaj JS. Aliment Pharmacol Ther 2010.
### 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></td>
<td>– Diuretic overdose</td>
</tr>
<tr>
<td></td>
<td>– GI bleeding</td>
</tr>
</tbody>
</table>

HE = hepatic encephalopathy

### 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, glyceryl phenylbutryrate)
  - 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.
PEG = Lactulose in an acute HE episode

Rahimi et al. JAMA Internal Medicine 2014

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

Sharma et al. Am J Gastro 2013
Nutrition in HE

Cirrhotic liver
- Reduced gluconeogenic capacity
- Hypermetabolism = increased protein and caloric demand
- Muscle breakdown/mobilization of skeletal muscle amino acids

Active alcoholism/substance abuse leading to poor diet
- Poverty
- Poor social support
- Inhrogenic restrictions

Loss of appetite
- Metabolic and hormonal alterations
- Medications
- Hepatic encephalopathy
- Inflammatory cytokines

Tense ascites → post prandial discomfort

Impaired gut motility with small intestinal bacterial overgrowth
- Altered digestion
- Nutrient malabsorption
Sarcopenia in cirrhosis

Log Rank, $P=0.005$

No Sarcopenia

Sarcopenia

Survival (%)

Montano-loza CGH 2012

Nitrogen therapy is associated with reduced mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Extra, d.f.</th>
<th>Total events (Treatment)</th>
<th>Total events (Control)</th>
<th>Log rank test statistic (Z)</th>
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<tbody>
<tr>
<td>Parenteral nutrition</td>
<td>Nissen 1996</td>
<td>1/26</td>
<td>1/20</td>
<td>1.06 (0.07, 4.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maghnie 1995</td>
<td>9/16</td>
<td>11/10</td>
<td>0.51 (0.03, 7.13)</td>
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<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>30</td>
<td>30</td>
<td></td>
<td>0.69 (0.08, 4.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>Calle 1998</td>
<td>12/16</td>
<td>9/19</td>
<td>0.26 (0.07, 1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>De Lisio 1997</td>
<td>19/22</td>
<td>10/10</td>
<td>1.22 (0.86, 1.70)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>59</td>
<td>61</td>
<td></td>
<td>0.48 (0.19, 1.18)</td>
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<tr>
<td>Supplements</td>
<td>Hwang 1998</td>
<td>12/16</td>
<td>10/10</td>
<td>0.48 (0.13, 1.73)</td>
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<td></td>
<td>Nembach 2010</td>
<td>3/27</td>
<td>4/22</td>
<td>0.04 (0.07, 0.23)</td>
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<tr>
<td></td>
<td>Nakaya 2007</td>
<td>1/25</td>
<td>0/23</td>
<td>0.00 (0.12, 0.86)</td>
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<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>59</td>
<td>79</td>
<td></td>
<td>0.56 (0.22, 0.93)</td>
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</tr>
</tbody>
</table>

Koretz Cochrane Review 2012
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 Therapy improves cognition in outpatients as well

- Breakfast improved cognition in cirrhotic patients
- Patients with covert HE randomized to usual therapy and to nutritional therapy (30-35 Kcal/day and 1-1.2 g/Kg/day of vegetable protein)
  - Cognitive performance and health-related quality of life was significantly better in those randomized to nutritional therapy

Vegetable proteins were better

<table>
<thead>
<tr>
<th>Period A</th>
<th>Period B</th>
<th>Period C</th>
<th>Period D</th>
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<tbody>
<tr>
<td>(asparagin + milk of Mg)</td>
<td>(40g vegetable + milk of Mg)</td>
<td>(asparagin + milk of Mg)</td>
<td>(80g vegetable + milk of Mg)</td>
</tr>
<tr>
<td>40g meat protein diet</td>
<td>40g vegetable protein diet</td>
<td>40g meat protein diet</td>
<td>80g vegetable protein diet</td>
</tr>
</tbody>
</table>

**Zinc in HE**

**Rationale for using zinc**

Is needed for the urea cycle and for muscle glutamine synthetase that fixes ammonia

Correlates inversely with ammonia

**Studies**

<table>
<thead>
<tr>
<th>Author and date</th>
<th>Study design</th>
<th>Duration</th>
<th>Patients (n)</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Reding <em>et al.</em> (1984)</td>
<td>Randomized; placebo-controlled</td>
<td>7 days</td>
<td>22</td>
<td>Zn acetate 600 mg/day</td>
</tr>
<tr>
<td>Schölmerich (1987)</td>
<td>Randomized; placebo-controlled</td>
<td>3 months</td>
<td>12</td>
<td>Zn sulphate 135 mg/day</td>
</tr>
<tr>
<td>Schölmerich (1987)</td>
<td></td>
<td></td>
<td>12</td>
<td>Zn histidine 45 mg/day</td>
</tr>
<tr>
<td>Riggio <em>et al.</em> (1991)</td>
<td>Randomized; placebo controlled; cross-over</td>
<td>10 days</td>
<td>15</td>
<td>Zn sulphate 600 mg/day</td>
</tr>
<tr>
<td>Marchesini <em>et al.</em> (1996)</td>
<td>Open; controlled</td>
<td>3 months</td>
<td>16</td>
<td>Zn sulphate 600 mg/day</td>
</tr>
<tr>
<td>Rössle <em>et al.</em> (1997)</td>
<td>Open; controlled</td>
<td>3 months</td>
<td>42</td>
<td>Zn hydrogen aspartate 100 mg/day</td>
</tr>
<tr>
<td>Takuma et al (2011)</td>
<td>Open controlled carnosine</td>
<td>6 months</td>
<td>79</td>
<td>Zinc 225 mg/day+</td>
</tr>
</tbody>
</table>
**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

Amodio et al Hepatol 2013.
AASLD EASL 2014 Guidelines Hepatol/ J Hepatol.

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**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

Laleman et al Hepatol 2013.

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

![Graph showing the efficacy of Lactulose compared to Placebo in preventing Overt Hepatic Encephalopathy recurrence.](image-url)
Adverse effect management
Patient education
Therapy titration
Counseling of family members

High HE recurrence rate due to lactulose in clinical practice after the first HE episode

Bajaj et al Aliment Pharmacol Ther 2010
Prevention of Overt HE recurrence: Rifaximin

Patients whose HE recurred (%)

- Rifaximin 550 mg bid (n=140)
- Placebo (n=159)

\[ p < 0.0001 \]

*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

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Prevention of re-hospitalization with VSL#3

There remains a population of patients that experiences recurrent HE, despite being on standard of care.
A brief history of FMT

Directed Donors → Standardized Universal Donors

Eiseman, 1958
Van Nood, 2013

Hong, 380s
Hamilton, 2012

Enforcement Discretion, 2013

Medical & Public Stakeholders Comment on Draft Guidance, 2014
Enforcement Discretion Remains

Smith, 2014

The mechanics of FMT

Healthy gut microbial ecosystem

Cirrhosis severity, Decreased Bile Acids, Antibiotics, Immune dysfunction

Etiological Rx

Repeated episodes, more antibiotics

Dysbiosis

Worsening Dysbiosis
4 D’s of FMT

- Decision - Patient Selection
- Donor Model
- Delivery Modality
- Discharge & Follow-Up
Particular challenges of FMT in HE

- Generally a much more advanced population
- Prone to potentially life-threatening infections, including those that are initiated from the gut
- Avoiding antibiotics post-FMT may not be feasible
- Many are already on rifaximin and SBP prophylaxis
- Directed donor vs. universal donor?

Case Report of FMT in the management of hepatic encephalopathy

Kao et al. Hepatology 2015
**Rational Donor selection**

- Randomized open-label trial under FDA
- 19 patients have been enrolled
- Results expected soon

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**ClinicalTrials.gov**

4 studies found for: Hepatic Encephalopathy and fecal transplant

<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recruiting</td>
<td>Fecal Transplant in Recurrent Hepatic Encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Hepatic Encephalopathy; Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Biological Fecal transplant</td>
</tr>
<tr>
<td>2</td>
<td>Active, not recruiting</td>
<td>Fecal Microbiota Transplantation (FMT) in the Management of Hepatic Encephalopathy (HE): a Pilot Study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Hepatic Encephalopathy; Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention: Biological Fecal Microbiota Transplant</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td>Randomized Controlled Trial Comparing the Efficacy and Safety of FMT in Hepatitis B Reactivation Leads to Acute on Chronic Liver Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions: Acute on Chronic Liver Failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interventions: Drug Treatment; Drug Fecal Microbiota Transplantation (FMT)</td>
</tr>
</tbody>
</table>

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* example: “heart attack” AND “Los Angeles”
### Summary

- Hepatic encephalopathy remains an important issue in our cirrhotic patients from an inpatient and outpatient perspective.
- Lactulose is the mainstay of therapy but can have several issues.
- Rifaximin is the best alternative/additive therapy.
- Nutritional therapy is an excellent resource that needs to be applied.
- Many other options are being developed.
- FMT may be a promising future option but current data is very limited.

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### Thank you..questions?
## Acknowledgements

**VCU and Richmond VA**
- Douglas Heuman
- Arun Sanyal
- Edith Gavis
- Melanie White
- Andrew Fagan
- Dinesh Ganapathy

**Institute for Liver Diseases, London**
- I Jane Cox
- Roger Williams

**Imperial College, London**
- Mark McPhail
- Simon D Taylor-Robinson

**George Mason University**
- Patrick Gillevet
- Masoumeh Sikaroodi
- Naga Betrapally

**OpenBiome**
- Zain Kassam
- Mark Smith

**University of California, Davis**
- Oliver Fiehn
- Dmitry Grapov
- Sili Fan

**MIT**
- Thomas Gurry
- Eric Alm