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.
Burden of Cirrhosis and HE
US Hospital Discharges Due to Cirrhosis Are Increasing

*ICD-9-CM diagnosis codes 571.2, 571.5, 571.6; all listed diagnoses.
HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. 
Readmissions for HE: A gift that keeps on giving

HE and cognitive dysfunction adds 7 points to biological MELD score

HE does not get transplant priority so low MELD recurrent HE patients are disadvantaged

Pathogenesis of HE
Pathophysiology of HE: it takes a village

Bajaj JS Hepatology 2015, Dasarathy et al J Hepatol 2016
Gut microbiota are necessary for brain inflammation (microglial and glial) in cirrhotic mice

4 mouse groups: GF, GF made cirrhotic using CCL4 gavage, Conventional control and Conventional mice made cirrhotic using CCL4 gavage

Kang, Bajaj et al Hepatology 2016
Classification of HE
# 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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>Covert</td>
<td>Episodic</td>
<td>Precipitated (specific factor found)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>(no further HE for ≥ 6 months)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Recurrent</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Persistent</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Spontaneous</td>
<td></td>
</tr>
<tr>
<td>B  (porto-systemic Bypass or shunt without cirrhosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C  (Cirrhosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Grade 2 or lower HE is difficult to diagnose

Reuter et al
Liver Transpl
2018
Covert HE
Covert HE is associated with Poor Quality of Life

<table>
<thead>
<tr>
<th>Study</th>
<th>Instrument used</th>
<th>Poor QOL?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groeneweg 1998</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Schomerus 2001</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Bao 2007</td>
<td>Chronic liver disease Q, SF-36</td>
<td>Yes</td>
</tr>
<tr>
<td>Prasad 2007</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhou 2009</td>
<td>Chinese adaptation of QOL</td>
<td>Yes</td>
</tr>
<tr>
<td>Les 2010</td>
<td>Chronic liver disease Q, SF-36</td>
<td>Yes</td>
</tr>
<tr>
<td>Sidhu 2010</td>
<td>Sickness Impact Profile</td>
<td>Yes</td>
</tr>
<tr>
<td>Wunsch 2011</td>
<td>Chronic liver disease Q, SF-36</td>
<td>No</td>
</tr>
<tr>
<td>Bajaj 2011</td>
<td>PROMIS tools and Sickness Impact Profile</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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>
Methods for Detecting Covert HE

Neuropsychological tests¹
(Paper / pencil or computer)

PHES, NCT-A, DST, BDT, WAIS-R

Rapid automated tests²

Critical flicker frequency,
Inhibitory control test
Stroop App

Sophisticated neurophysiologic tests¹

EEG,
P300 auditory evoked potentials

NCT-A = number connection test-A; DST = digit symbol test; PSE = portosystemic encephalopathy syndrome; BDT = block design test; WAIS-R = Wechsler Adult Intelligence Scale-Revised; EEG = electroencephalographic

¹Ferenci et al, Hepatology 2002; 35: 716–21
Real-World Settings
- Apps (EncephalApp)
- QOL testing using SIP
- Inhibitory control test
- Animal naming tests
HRQOL can be used to diagnose covert/minimal HE

- SIP was used to diagnose CHE in 170 cirrhotics using paper pencil gold standard
- 93 patients (55%) had CHE when the study began.
- We developed a formula to identify patients with CHE based on age, sex, and responses to 4 SIP questions (a SIP CHE score).
- Baseline SIP CHE scores greater than 0 identified patients with CHE with 80% sensitivity and 79% specificity.
- >80% sensitivity continued at 6 month and 12 month follow-up.

<table>
<thead>
<tr>
<th>I do not maintain balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>I act irritable or impatient with myself</td>
</tr>
<tr>
<td>I am not doing any of my usual physical recreation or activities</td>
</tr>
<tr>
<td>I am eating much less than usual</td>
</tr>
</tbody>
</table>

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

Patient with potential HE

- Disoriented
- Asterixis
- Somnolence and Stupor
- Lethargy
- Coma

Setting of Assessment

- Clinical practice
- Single-center trial
- Multi-center trial

Do you know the patient well?
Do you have caregiver input?

- Yes
  - Grade II and higher should be considered overt HE
  - Overt HE
  - Treat patient for OHE
  - Consider further specialized testing

- No
  - Single-center trial

Soriano, Bajaj Hepatology 2017
Overt HE

- Acute Episode
- Prevention of Recurrence
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?
- 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, sleep aids, opioids)
- **Electrolyte disorders** (hyponatremia and hypercalcemia)
- **Intracranial bleeding and stroke**
- Neurological infections
- Nonconvulsive epilepsy
- Psychiatric disorders
- Severe medical stressful events (organ failure and inflammation)
All that is altered is not HE: Clues against HE

- New focal deficits
- Excitatory motor activity, especially seizures
- Current/recent alcohol use
- Current/recent illegal or legal sedating drug use
- Other situations in which HE is unlikely
Carefully go over medications especially sleep aids and pain medications.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potency†</th>
<th>Active metabolite formed</th>
<th>Bioavailability in cirrhosis</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1×</td>
<td>Yes</td>
<td>Increased 100%</td>
<td>Reduce dose and frequency by half</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>75–125×</td>
<td>No</td>
<td>Unchanged (CP A or B)</td>
<td>Usually none for single dose‡</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>500–1000×</td>
<td>?</td>
<td>Unchanged</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>250×</td>
<td>?</td>
<td>Unchanged</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Meperidine (pethidine)</td>
<td>0.1×</td>
<td>Yes</td>
<td>Increased up to 80%</td>
<td>Generally avoid using, or reduced dose and avoid chronic use§</td>
</tr>
<tr>
<td>Codeine (methylmorphine)</td>
<td>0.1 ×</td>
<td>Yes</td>
<td>Reduced</td>
<td>Poor analgesic effect and should be avoided</td>
</tr>
<tr>
<td>Methadone</td>
<td>1×</td>
<td>No</td>
<td>Largely unaffected‡</td>
<td>None needed in compensated cirrhosis</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>7×</td>
<td>No</td>
<td>Increased 16–128× fold</td>
<td>Reduce dose in impaired renal function</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1×</td>
<td>Yes</td>
<td>Increased 50–95%</td>
<td>Reduce dose to prevent accumulation</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>6–10×</td>
<td>Yes</td>
<td>Limited data</td>
<td>Limited data</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>&lt;1×</td>
<td>?</td>
<td>Increased</td>
<td>Avoid in cirrhosis**</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.1×</td>
<td>Yes</td>
<td>Increased two to threefold</td>
<td>Consider alternative agents††</td>
</tr>
</tbody>
</table>

Lewis et al Aliment Pharmacol Ther 2013
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.
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
Prevention of HE Recurrence
Overt HE: Important questions at the time of discharge

• How can we prevent this from happening again?
• Is the patient able to perform all activities of daily living and instrumental activities of daily living?
• 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
Adverse effect management

Patient education

Therapy titration

Counseling of family members
Patients whose HE recurred (%)

Prevention of Overt HE recurrence: Rifaximin

- 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
The Majority of Overt HE Patients Do Not Receive Proper Management Therapy After Discharge

- It was determined that >60% of patients did not receive ongoing prophylactic therapy to reduce the risk of HE recurrence after discharge

- Within an analysis of medical and hospital claims among outpatients who had 1 or more overt HE episodes from 2009 to 2011 during a 3-year period

Saab S. *Int J Gen Med.* 2015; Neff GW, Frederick RT. *Hepatology.* 2012;56(suppl 1):945A.
Systematic changes directed towards HE can reduce readmissions

A Association between intervention phase and 30-day readmission

B Reasons for 30-day readmission by intervention phase

How can we make this better?

A. Improving the set-up
B. Reducing risks for recurrence and
C. Encouraging newer therapies
Work the body

Exercise intervention

Aerobic training
- Cycling
- Jogging
- Walking
- Light swim

Resistance training
- Weights (1-2lb)
- Chair dips
- Resistance band
- Squats

Balance & strength
- Side/back leg raise
- Sit-to-stand reps
- Go around chair
- Toe stand

Dietary intervention

Mechanism

- Increase cardiopulmonary endurance

Target

- Improve physical fitness
- Halt/reverse sarcopenia
- Reverse frailty

Outcome

- Metabolic complications
- Complications from portal hypertension
- Health-related quality of life
- Wait-list survival
- Posttransplant complications

Declining functional status

Nutritional therapy

- Improve malnutrition

Duarte-Rojo et al Liver Transpl 2017
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.*
Caregivers are important
HE Disrupts Caregiver’s Lives

- Overt episodes of HE are debilitating, can render the patient incapable of self-care\(^1\)
- HE caregivers report greater disruptions compared to cirrhosis caregivers\(^2\)

**Complications of Cirrhosis\(^3\):**
- Encephalopathy
- Ascites
- Varices, Bleeds
- Coagulopathy
- Malnutrition
- HCC
- HPS/HRS

**Complications of Aging:**
- COPD
- CVA
- DM
- Arthritis
- Cancer
- Dementia
- CHF
- CAD
- MI

ADL, activities of daily living; IADL, instrumental activities of daily living; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; GI, gastrointestinal; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; MI, myocardial infarction

Patients with HE are a significant burden on their caregivers because they need attention.

<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>Impact on schedule</td>
<td>11.9 ± 7.0</td>
<td>16.1 ± 6.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Impact on health</td>
<td>15.6 ± 4.1</td>
<td>17.8 ± 3.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Sense of entrapment</td>
<td>13.4 ± 6.5</td>
<td>17.3 ± 8.3</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Assessed by: Perceived Caregiver Burden Scale, Zarit Burden Interview-short form, Beck Depression Inventory, Beck Anxiety Inventory and Interpersonal Support Evaluation list-Short Form

Bajaj JS et al. Am J Gastroenterol. 2011;106:1646–53
Work the mind of Patients and Caregivers

In cirrhotic patients with depression, depression, Sleep, QOL and Caregiver burden improve after Mindfulness

Bajaj JS et al Clin Transl Gastro 2017
Management of “refractory HE”

• Incorrect diagnosis of HE
  – Go over differential diagnosis carefully

• Incorrect detection of precipitating factors
  – The same person can have different or multiple precipitating factors during different admissions for HE

• Insufficient treatment of precipitating factors
  – MDR organisms, abscesses, fungi

• Persistent shunting
  – Embolization in patients with a major shunt and low MELD score

• Dysbiosis and ammonia generation
  – Investigational therapies
    • Fecal microbial transplant
    • Ammonia scavengers

Persistent and Recurrent HE
Persistent HE may be associated with shunts

Embolization of these shunts can improve the course of HE especially with low MELD <11 and a single shunt

Case Report of FMT in the management of hepatic encephalopathy

A Taxonomy at family level

B Principal Coordinate Analysis (PCoA) of β-diversity

Kao et al Hepatology 2015
Healthy patients ➔ HE patients ➔ Train HE Classifier to rank donors ➔ OpenBiome donors ➔ Classify and rank donors

Material from one stool sample from the donor with highest Lachnospiraceae/Ruminococcaceae used for the FMT-assigned group

RCT of FMT enema vs. standard of care with safety as primary endpoint ➔ Outpatient cirrhosis and recurrent HE

Patients divided into standard of care or FMT group with 150 day follow-up

IN THE FMT GROUP COMPARED TO STANDARD OF CARE:
- Reduced hospitalizations
- Improved cognition
- Reduced HE episodes
- Recovery of antibiotic-associated collapse in microbial diversity

Bajaj et al
Hepatology 2017
Take-home messages

• HE is a spectrum from covert to overt
• Covert HE can impair daily function and early diagnosis using point-of-care tests are important
• Overt HE staging along 4 axes to improve treatment and prevent readmissions is important
• Appropriate use of therapies to prevent recurrence, improving nutrition, encouraging exercise and treating the etiology is needed
• Taking care of the caregivers is also important
• In refractory cases, alternative diagnoses, embolization and consideration for future therapies are needed.
Acknowledgements

- Arun J Sanyal, MD
- Douglas M Heuman, MD
- Richard K Sterling, MD
- Mitchell Schubert, MD
- R Todd Stravitz, MD
- Velimir Luketic, MD
- Michael Fuchs, MD
- Muhammad S Siddiqui, MD
- Scott C Matherly, MD
- William M Pandak, MD
- Patrick M Gillevet, PhD
- James B Wade, PhD
- Leroy R Thacker, PhD
- HoChong Gilles, NP
- Melanie B White, RN
- Nicole A Noble, BS
- Ariel Unser, BS
- Pamela Monteith, RN
- Janet Starkey, RN
- Jane McCarthy, BS
- Edith Gavis, RN