“NEW” CONCEPTS AND CONTROVERSIES IN CIRRHOSIS

Michael B. Fallon, MD
• Covert Hepatic Encephalopathy
• Beta Blockers in Decompensation
• Hepatic Fibrosis Therapy
• Hepatopulmonary Syndrome (HPS)
Hepatic Encephalopathy (HE)

- Neuropsychiatric syndrome
- 50% to 70% of patients
- Decreases quality of life and survival
- Spectrum of symptoms and findings
OVERT

Physical Exam
Confusion
Admission
Standard treatments

COVERT

Specialized tests
Quality of life
Driving/work
Who to treat?
<table>
<thead>
<tr>
<th>GRADE</th>
<th>INTELECTUAL</th>
<th>STAGE</th>
<th>MENTAL STATUS</th>
<th>SPECIAL TESTS</th>
<th>ASTERIXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Unimpaired</td>
<td>Not impaired</td>
<td>Normal</td>
<td>Absent</td>
</tr>
<tr>
<td>Minimal</td>
<td>Normal exam</td>
<td>Covert HE</td>
<td>Not impaired</td>
<td>Abnormal</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Work, driving problems</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>Personality changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>attention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Altered sleep-wake cycle</td>
<td>Overt HE</td>
<td>Impaired</td>
<td>Abnormal</td>
<td>Present (unless coma)</td>
</tr>
<tr>
<td></td>
<td>lethargy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>behavior cognition</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td>Altered consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>confusion</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Stupor and coma</td>
<td></td>
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</tr>
</tbody>
</table>
1) Prevention (and early therapy) of HE

- Hepatocyte dysfunction
- Gut microbiome
- NH3
- Portosystemic shunt
- ↑NH4

Precipitating Factors:
- Sedatives - Benzodiazepines
- Infection - Inflammatory cytokines
- Electrolytes disturbances - Na, K
- Diuretics
- GI bleeding
- Constipation
- Renal dysfunction

- Astrocyte swelling/brain edema
- Neurotransmitter and receptor alterations
- Brain glucose metabolism

Gut

Hepatocyte dysfunction

Hepatocyte dysfunction leads to ↑NH4, which can precipitate HE through astrocyte swelling/brain edema, neurotransmitter and receptor alterations, and brain glucose metabolism. Precipitating factors include sedatives, benzodiazepines, infection with inflammatory cytokines, electrolyte disturbances, diuretics, GI bleeding, constipation, and renal dysfunction.
CHE: Risks

Motor Vehicle accidents (%)

- MHE+
- MHE-

p=0.004

OHE free (%)

Time (Months)

HR: 4.13
p=0.0034

Bajaj et al, Hepatology 2009
Riggo et al, CGH 2011
# MHE: Clinical and Simulation Predictors of Real-Life Crashes

<table>
<thead>
<tr>
<th>Baseline simulation</th>
<th>No MHE, Mean ± SD</th>
<th>MHE, Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driving simulation</td>
<td>n=90</td>
<td>n=77</td>
<td></td>
</tr>
<tr>
<td>Crashes</td>
<td>2.5 ± 1.7</td>
<td>3.1 ± 2.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Centre of road crossings</td>
<td>11.8 ± 6.5</td>
<td>15.2 ± 10.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Road edge excursions</td>
<td>4.8 ± 5.5</td>
<td>9.4 ± 14.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Total run time (seconds)</td>
<td>1652 ± 325</td>
<td>1765 ± 324</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Navigation Simulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illegal turns</td>
<td>1.0 ± 1.4</td>
<td>2.3 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Crashes</td>
<td>0.3 ± 0.8</td>
<td>1.0 ± 1.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Total run time (seconds)</td>
<td>904 ± 163</td>
<td>1084 ± 324</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Real life driving history at baseline</strong></td>
<td>n=107</td>
<td>n=98</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle crashes in one year</td>
<td>7 (7%)</td>
<td>16 (16%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Traffic violations in one year</td>
<td>16 (16%)</td>
<td>26 (26%)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>At one year follow-up</strong></td>
<td>n=40</td>
<td>n=33</td>
<td></td>
</tr>
<tr>
<td>Motor vehicle crashes in one year</td>
<td>0 (0%)</td>
<td>6 (18%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Traffic violations in one year</td>
<td>4 (10%)</td>
<td>9 (33%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
States with reporting requirements for MDs

- California
- Delaware
- Nevada
- New Jersey
- Oregon
- Pennsylvania
- Maryland
- Georgia

Legal immunity for Reporting

Shaw et al J Clin Gastro 2017
Stroop Test

What color is the text?

# # # #

Red

Green  Blue  Red

Green  Blue  Red

6.325

12.722
2) Diagnosis

- Clinical (overt)

- Ammonia (specificity, diagnostic level)
  - GI bleeding
  - Muscular exertion
  - Tourniquet use
  - Delayed processing/cooling
  - Drugs: alcohol, barbiturates, diuretics, narcotics
  - Smoking

- Neurocognitive tests (covert)
  - PHES
  - STROOP
  - CNS-VS
  - SIP-CHE
Diagnosis of covert encephalopathy

SIP-CHE
- Age
- Sex
- 4 questions:
  - Balance
  - Irritability, impatience
  - Doing typical activities
  - Eating

STROOP Test
- >190 sec on+off time

Bajaj et al, CGH 2014

ROC curve
3) Treatment

- No role for protein restriction
- Non-compliance with lactulose 40%
- Probiotics for “early” PSE
Probiotics and HE

Yogurt 12 oz q day for 2 months

VSL#3 one TID for at least 6 months

Bajaj, Am J Gastro, 2008

Lunia et al, Clin Gastroenterol Hepatol. 2014
Meta-analysis: the effects of gut flora modulation using prebiotics, probiotics and synbiotics on minimal hepatic encephalopathy
MHE Screening algorithm

Care Giver Concern
Work Difficulties (interpersonal)
Recent ETOH discontinuation
Prior MVA or violation last 6 mo
Age >60

Inform patient and family
EncephalApp

On-off <190 sec
On-off>190 sec

Re-test q 6 mos
Treat and re-test
Report as required
Hepatic encephalopathy

- Focus on covert and prevention (QOL, driving, apps)
- Screen for CHE and treat if positive
- Preventive therapy with probiotics
Non-Cardioselective β–blockers in Cirrhosis

Detrimental

- Sersté
  - n=151
  - ↑mortality
  - ↑PPCD

- Mandorfer
  - n=607
  - ↑AKI and mortality

Beneficial

- Refractory Ascites
- Large Volume Paracentesis
- Spontaneous Bacterial Peritonitis
- LT list (refractory ascites or not)
- ↓mortality

Leithead
- N=322
HRS

Classic criteria
Very high mortality
Delayed therapy

AKI

New criteria
Mortality increased
Focus: early detection
reversible causes

How to treat?
NCSBB and Survival in ACLF: Canonic Study

Mookerjee et al, J. Hepatol 2015

Logrank test p-value: 0.011
<table>
<thead>
<tr>
<th>Study</th>
<th>NSBBs Events</th>
<th>NSBBs Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk ratio (M-H, Random, 95% CI)</th>
<th>Risk ratio (M-H, Random, 95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Mazhar 2013</td>
<td>43</td>
<td>619</td>
<td>167</td>
<td>941</td>
<td>10.6%</td>
<td>0.39 [0.28, 0.54]</td>
<td></td>
</tr>
<tr>
<td>Robins 2012</td>
<td>18</td>
<td>36</td>
<td>59</td>
<td>78</td>
<td>10.5%</td>
<td>0.66 [0.47, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Leithhead 2014</td>
<td>35</td>
<td>159</td>
<td>47</td>
<td>163</td>
<td>10.3%</td>
<td>0.76 [0.52, 1.12]</td>
<td></td>
</tr>
<tr>
<td>Escorsell 2002</td>
<td>7</td>
<td>19</td>
<td>11</td>
<td>23</td>
<td>7.8%</td>
<td>0.77 [0.37, 1.59]</td>
<td></td>
</tr>
<tr>
<td>Kimer 2014</td>
<td>15</td>
<td>23</td>
<td>26</td>
<td>38</td>
<td>10.3%</td>
<td>0.95 [0.66, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Lo 2004</td>
<td>5</td>
<td>17</td>
<td>6</td>
<td>20</td>
<td>6.1%</td>
<td>0.98 [0.36, 2.65]</td>
<td></td>
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<tr>
<td>Mandorfer 2014</td>
<td>239</td>
<td>245</td>
<td>355</td>
<td>362</td>
<td>11.6%</td>
<td>0.99 [0.97, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Borroni 2002</td>
<td>23</td>
<td>25</td>
<td>21</td>
<td>27</td>
<td>11.1%</td>
<td>1.18 [0.94, 1.49]</td>
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</tr>
<tr>
<td>Shah 2014</td>
<td>10</td>
<td>33</td>
<td>6</td>
<td>32</td>
<td>6.7%</td>
<td>1.62 [0.67, 3.93]</td>
<td></td>
</tr>
<tr>
<td>Serste 2010</td>
<td>63</td>
<td>77</td>
<td>34</td>
<td>74</td>
<td>10.9%</td>
<td>1.78 [1.36, 2.33]</td>
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<tr>
<td>Cholongitas 2006</td>
<td>14</td>
<td>101</td>
<td>2</td>
<td>33</td>
<td>4.0%</td>
<td>2.29 [0.55, 9.54]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1354</td>
<td>1791</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.95 [0.67, 1.35]</td>
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</tr>
</tbody>
</table>

Total events 472 734

Heterogeneity: Tau² = 0.28; Chi² = 155.49, df = 10 (P < .00001)
I² = 94%; Test for overall effect: Z = 0.28 (P = .078)
Nonselective β-blockers do not affect mortality in cirrhosis patients with ascites: Post Hoc analysis of three randomized controlled trials with 1198 patients

Non-Cardioselective β–blockers in Cirrhosis

Outpatients:

- Titrate NCSBB for increased hypotension or AKI
- Not clearly deleterious in refractory ascites/LVP
- ? Concern with combined beta/alpha-1 (carvedilol)

Admitted with Cirrhosis complications:

- Hold with infection or AKI
- maintain or restart when BP stable and/or ACLF improving
Hepatic fibrosis

Chronic injury
- Viral infection
- Alcohol
- NASH
- Autoimmune disorders
- Cholestatic disorders
- Metabolic diseases

Genetic polymorphisms
- Epigenetic marks
- Cofactors (such as obesity and alcohol)

5–50 years

Liver transplant

Liver failure
Portal hypertension

Hepatocellular carcinoma

Resolution
- Removal of underlying cause
- Anti-fibrotic drug or cell therapy

Regression
- Disrupted architecture
- Loss of function
- Aberrant hepatocyte regeneration

Inflammatory damage
- Matrix deposition
- Parenchymal cell death
- Angiogenesis

Normal liver

Early fibrosis

Cirrhosis
Fibrosis

Cirrhosis

Treat disease
Little focus on mechanisms
Implications unclear

Disease controlled
Mortality increased
Therapy increases survival?
Fibrosis mechanisms
# Fibrosis and HCV treatment

% reduction in fibrosis in the liver as measured by change in fibrosis scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Tsubota N = 93</th>
<th>Reichard N = 26</th>
<th>Dufour N = 8</th>
<th>Scheuer Score</th>
<th>Knodell Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3</td>
<td>1.9</td>
<td>3.3</td>
<td>-35%</td>
<td>-76%</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>-47%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% of patients that showed improvement in fibrosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Marcellin N = 80</th>
<th>George N = 116</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Study: Tsubota, Reichard, Dufour, Marcellin, George.
Cirrhosis reversibility

Hepatitis B

Schiff et al. CGH 2011
Cirrhosis reversibility

Du et al. J. Viral Hepatitis 2013
Cirrhosis reversibility

Autoimmune hepatitis

Primary biliary cirrhosis

ETOH cirrhosis
Cirrhosis reversal

- Termination of chronic damage
  - GS4997: ASK1 inhibitor

- Shifting cellular bias from inflammation to resolution
  - PRI-724: Wnt inhibitor
  - Obeticholic acid: FXR agonist

- Myofibroblast deactivation
  - siRNA for collagen chaperone protein

- Matrix degradation
  - Simtuzumab: LOXL2 collagen remodeling
Hepatic fibrosis

- Increasing recognition that cirrhosis reverses
- HCV, HBV and NASH therapy will increase pool
- Major focus on use of antifibrotics ongoing
HPS

HPS common (30%)

10% with severe hypoxemia
Cirrhosis
Hepatic injury
Portal hypertension

HPS

LUNG

POPH

Vasodilatation and Angiogenesis in microvasculature

Vasoconstriction and remodeling in resistance vessels
HPS: SURVIVAL

Survival (%) vs. Time (Months)

Non HPS (n=146), Fallon et al. Gastro.2008
HPS (n=72, p=0.013), Fallon et al., Gastro.2008
HPS (N=57), Iyer et al., Hepatol 2013
HPS (n=37, p=0.003), Swanson et al. Hepatol, 2005
HPS (n=27, p=0.018), Schenk et al. Gastro.2003
Portal Hypertension
Cirrhosis
Portosystemic shunting

Contrast TTE
Sensitive
Specific
Other cardiac data

Abnormal ABGs
HPS

MAA scan
Quantitative
Standardization

HPS Treatment

No clearly effective drug therapy for HPS

MELD exception available
**HPS MELD Exception criteria**

**Initial Request**
Clinical evidence of portal hypertension

- Evidence of a shunt by
  - contrast ECHO
  - Lung Scan

- PaO2 < 60 mmHg (room air, at rest)

- No evidence of underlying primary pulmonary disease

**Renewal Request (increase 3 points)**
Resubmit above every 3 months
A randomized, double-blind, placebo-controlled parallel trial of 50 subjects with hepatopulmonary syndrome

To determine whether sorafenib affects alveolar-arterial oxygen gradient (AaPO$_2$) at 12 weeks

Field Centers:

- Penn (Goldberg)  
- UT- Houston (Fallon)  
- Mayo Clinic-Rochester (Krowka)  
- Columbia University (Brown)  
- University of Alabama (Simpson)  
- Northwestern University (Levitsky)  
- Mayo Clinic-Arizona (Vargas)

Data Coordinating Center: Penn (Ellenberg, Kawut)  
Echo Core: Mayo Clinic (Lin, Oh)  
PFT Core: Mayo Clinic (Scanlon, Mottram)  
Lab Core: University of Vermont (Tracy)
Hepatopulmonary syndrome (HPS)

Overview of HPS

Liver disease

Pulmonary vasodilation
- Pulmonary vasodilation
- Angiogenesis

Constriction

Dilation

HPS 5~32%

Pulmonary microvasculature

Normal

Alveolar type II cell alterations
- Surfactant protein reductions
- AT2 cell apoptosis

PERFUSION

Abnormal gas exchange ($AaPO_2 \uparrow / PO_2 \downarrow$)

Hepatopulmonary syndrome (HPS)

VENTILATION

Yang et al. AASLD 2015
AT2 cell alterations in experimental HPS

Common bile duct ligation (CBDL)

Control:SP-C

CBDL:SP-C

AT2 cell apoptosis

CBDL:TUNEL

CBDL:TUNEL&SP-C

SP reduction

Control

CBDL

Pro-SP-C

GAPDH

Alveolar airspace (Lm) decrease

Yang et al. AASLD 2015
Summary

- **HE**
  Focus on covert (QOL, driving, probiotics, apps)

- **NCSBB in Decompensation**
  Balance between effects on translocation, variceal pressure and renal perfusion/AKI
  No formal guidelines: inpatients vs outpatients, carvedilol?

- **Hepatic Fibrosis**
  Cirrhosis is reversible
  More patients living with advanced fibrosis
  Therapies in clinical trials

- **HPS**
  Common, increased mortality, clinical trials, ?alveolar involvement