NEW INSIGHTS INTO HE
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# West-Haven Grading of HE

(also known as Conn Score)

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Normal examination; if impaired psychometric test; minimal HE</th>
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</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild lack of awareness&lt;br&gt;Shortened attention span&lt;br&gt;Impaired performance of addition / subtraction&lt;br&gt;Mild asterixis or tremor</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Lethargy&lt;br&gt;Disorientation&lt;br&gt;Inappropriate behaviour&lt;br&gt;Obvious asterixis; slurred speech</td>
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<tr>
<td>Grade 3</td>
<td>Somnolence but responsive to stimuli&lt;br&gt;Gross disorientation; bizarre behaviour&lt;br&gt;Muscular rigidity and clonus; hyper-reflexia</td>
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<tr>
<td>Grade 4</td>
<td>Coma (unresponsive to verbal or noxious stimuli)&lt;br&gt;Decerebrate posturing</td>
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</table>

Burden of Hepatic Encephalopathy

- Overt HE occurs in 30–45% of patients\textsuperscript{1}
- 45–80% of patients with cirrhosis may suffer from minimal HE\textsuperscript{2,3}
- HE is a criterion for decompensation and associated with poor prognosis\textsuperscript{1,4}
  - Barcelona cohort: Mortality at 1 year 58% and 77% at 3 years\textsuperscript{5}
  - Denmark population: Mortality at 1 year 64% and 85% at 5 years\textsuperscript{6}
- HE is associated with a reduced quality-of-life and has a significant burden on health economics and caregivers / family\textsuperscript{1,7}

\textsuperscript{1}Poordad FF. Aliment Pharmacol Ther. 2007;25(Suppl 1):3–9
\textsuperscript{3}Bass NM. Aliment Pharmacol Ther. 2007;25(Suppl 1):23–31
\textsuperscript{7}Bajaj JS, et al. Am J Gastroenterol. 2011;106:1646–53
Prognosis and Outcomes in Patients with HE

- 466 Danish patients with alcoholic liver disease; 1993-2005
  At diagnosis 55% had ascites and 11% HE

Mortality (%)

- HE at baseline: 85% 5-year mortality

Years after onset

- Hepatic encephalopathy (n=169)
- Ascites + variceal bleeding (n=94)
- Ascites alone (n=287)
- Variceal bleeding alone (n=45)
- No complications (n=114)

Diagnosis

- Overt HE is a clinical diagnosis; signs / symptoms include
  - Personality changes
  - Sleep disturbances
  - Confusion
  - Depression
  - Slurred speech
  - Lethargy
  - Coma
  - Asterixis
  - Ataxia
  - Foetor hepaticus; Sweet or musty odour of breath and urine believed to be due to mercaptans

- Minimal HE requires psychometric testing to identify / diagnose

Harrison, Internal Medicine. 15th Ed:p1765
Conditions Mimicking HE

The following conditions should be excluded before diagnosing HE:

- Acute alcohol intoxication
- Sedative overdose
- Delirium tremens
- Uremia
- Hyponatraemia
- Wernicke’s encephalopathy
- Korsakoff’s psychosis
- Subdural hematoma
- Meningitis
- Hypoglycaemia
- Wilson’s disease
## Diagnostic Tools for Minimal HE

### Tools for detecting HE

<table>
<thead>
<tr>
<th>Psychometric testing</th>
<th>Neurophysiologic testing</th>
<th>Neuroimaging</th>
<th>Blood ammonia levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuro-psychological assessments</td>
<td>EEG (Specialised analysis may be necessary)</td>
<td>CT scan (for exclusion of other causes)</td>
<td>Helpful in evaluation and for planning management</td>
</tr>
<tr>
<td>Computerised Tests (e.g. Vienna Determination Test, Vienna Reaction Test)</td>
<td>Critical Flicker</td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Paper and Pencil Tests (e.g. Number Connection Test, Serial Dotting Test, Line Tracing Test)</td>
<td>Evoked potentials</td>
<td>MRS (mainly for research)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitory control test</td>
<td>PET scan (research tool)</td>
<td></td>
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Morgan MY. In Sherlock’s Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011*
Pathogenesis of HE

- Ammonia is central to the pathogenesis of HE
  - Bacterial synthesis from amino acids is the major source
- Liver dysfunction results in a reduced capacity to detoxify ammonia
- Portal-systemic shunting results in increased levels in circulation
  - Ammonia readily crosses the blood brain barrier
  - Saturation of glutamine synthetase in astrocytes leads to increased intracellular levels and osmotic changes / cerebral oedema
- Oxidative stress / inflammation (cytokines) exacerbate astrocyte dysfunction

**References**
Common Precipitating Factors for HE

50-80% of patients with episodic HE have identifiable precipitant

- **Hypovolaemia/diuretics**
  - Hypokalaemia and alkalosis facilitates ammonia production
  - Dehydration may precipitate worsening mental function in previously controlled HE

- **Renal failure**
  - Reduced clearance of ammonia, acid-base imbalance and other nitrogenous products

- **Upper GI bleed**
  - Blood in GI tract leads to increased ammonia and nitrogen absorption

- **Infection**
  - Tissue catabolism
  - Impaired renal function
  - Inflammation
  - Increased blood ammonia

- **Constipation**
  - Increases ammonia

- **Psychoactive medication**
  - Worsen symptoms of HE

- **TIPS**
  - HE is the most common complication of TIPS
  - Related to portal hypoperfusion and increased availability of ammonia and toxins

- **Hyponatraemia**
  - Contributes to astrocyte swelling

- **Additional liver injury**
  - Worsens hepatic function and reduces ammonia metabolism

After: Morgan MY. In Sherlock's Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011
After: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537–47
Lactulose for Secondary Prophylaxis (ITT)

- Patients recovering from HE; existing therapy continued and randomised to lactulose or placebo
  - Mean MELD score 21.8 and 20.6 respectively at baseline.
  - Median 14 (1–20) months’ follow-up (n=140 entered – 15 lost to follow-up)

![Bar chart showing breakthrough HE (%)](chart)

*\(p=0.001\)

Lactulose Tolerability

- Patients taking lactulose / lactitol require education regarding adverse events:
  - Excessive sweet taste
  - Flatulence and bloating
  - Electrolyte imbalance
    - Hypernatraemia which can deteriorate the patient’s mental status
  - Lactitol better tolerated than lactulose
- Abdominal cramping
- Diarrhoea
  - May worsen HE and risk of hypovolaemia and hypernatraemia
- Dose should be carefully titrated to maintain 2–3 stools/day without diarrhoea
- In patients with acute liver failure caution due to risk of colonic distension, particularly if surgery planned

Morgan MY. In Sherlock's Disease of the Liver and Biliary System, 12th ed: Blackwell Publishing Ltd; 2011
Rifaximin for Secondary Prophylaxis of HE: Results

- 91% of study patients were receiving lactulose

**Time to HE breakthrough**

Free from HE (% of patients)

- Hazard ratio: 0.42 (95% CI, 0.28–0.64)
- p<0.001

**Time to HE-related hospitalisation**

Not hospitalised (% of patients)

- Hazard ratio: 0.50 (95% CI, 0.29–0.87)
- p=0.01

- 58% relative risk reduction (NNT=4 over 6 months)
- 50% relative risk reduction (NNT=9 over 6 months)

Rifaximin for Secondary Prophylaxis of HE: Most Common Events

- *Clostridium difficile* infection reported in 2 patients
  - Multiple risk factors for *C. difficile* (advanced age, frequent recent hospitalisations with multiple courses of antibiotics, PPI therapy)
  - Resolved with treatment (rifaximin continued)

- 9 deaths in rifaximin group and 11 in placebo, most attributed to conditions associated with disease progression

<table>
<thead>
<tr>
<th>Event</th>
<th>Rifaximin (n=140)</th>
<th>Control (n=159)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>20 (14.3)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15 (10.7)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17 (12.1)</td>
<td>18 (11.3)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>21 (15.0)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Ascites</td>
<td>16 (11.4)</td>
<td>15 (9.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (12.9)</td>
<td>13 (8.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10.0)</td>
<td>17 (10.7)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (9.3)</td>
<td>11 (6.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>13 (9.3)</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (8.6)</td>
<td>13 (8.2)</td>
</tr>
</tbody>
</table>

Nutritional Advice in Patients with Cirrhosis: Protein Intake

- Maintain protein intake 1.2–1.5g/kg
- Protein restricted diets seldom have any place in management / prevention of HE
  - Vegetable or casein protein may be better tolerated
- Frequent meals (6 or more a day)
  - Complex, not simple, carbohydrate
  - Nocturnal feeding
- Balanced diet of 30 kcal/kg body weight
  - Corrected or ideal body weight in patients with ascites
  - 30–35% of calories consumed as fat
  - 50–55% of calories consumed as carbohydrate

Adapted from:
HE: General Considerations

- HE is common in patients with cirrhosis
  - Therefore, testing for HE should be part of routine evaluation of cirrhotic patients

- Early identification of lower grades of HE allows intervention to be initiated
  - Reduces risk of developing more severe grade HE
  - May potentially avoid longer term cognitive deficit

- Options for treatment include lactulose
- Rifaximin in addition to lactulose prevents recurrence
- Albumin dialysis (MARS) may reduce HE severity in patients who do not respond to treatment

- Patient follow-up is important
  - Ensure on-going compliance with therapy
  - Patient and family / caregiver education

- HE is a decompensation event
  - Consider evaluation for transplantation
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