Management of Complications of Cirrhosis: Hepatic Encephalopathy and Thrombocytopenia

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Gross and Microscopic Image of a Normal and a Cirrhotic Liver

Normal

Cirrhosis

Irregular surface

Nodules

Nodules surrounded by fibrous tissue
Prevalence of Cirrhosis

- ~5.5 million people in the United States have cirrhosis
- 5th leading cause of adult deaths
- Ranks 8th in economic cost among major illnesses
Asymptomatic vs Symptomatic Cirrhosis

• Asymptomatic (Compensated)
  • Subtle clues may be overlooked
    • Thrombocytopenia
    • Muscle wasting
    • AST>ALT without alcohol consumption
    • Liver enzymes may not be abnormal
  • Etiology may be remote
    • Prior alcohol use
    • Uncontrolled diabetes mellitus and obesity

• Symptomatic (Decompensated)
  • Portal Hypertension: Ascites, hepatic encephalopathy, variceal bleeding
  • Hepatic failure: Jaundice, coagulopathy

• Child-Turcotte-Pugh (CTP) classification used to stratify patients
  • CTP-A: Compensated
  • CTP-B/C: Decompensated
Non-Invasive Markers

- Platelet count $<100 \times 10^9/L$
- Indirect biomarkers (e.g., APRI, FIB4)
- Direct biomarkers (e.g., Fibrotest, Fibrosure)
- Transient elastography (FibroScan)
- Clinically obvious cirrhosis does not require confirmation
Portal Hypertension

**Increased Resistance**
(Architectural changes secondary to fibrous tissue formation; active vasoconstriction due to decrease in formation of endogenous NO)

**Increased Blood Flow**
(Splanchnic arteriolar vasodilation)

**Increased Portal Pressure**
- Shunting (encephalopathy)
- Increased salt and water retention (ascites)
- Variceal formation (bleeding)

Portal Hypertension

• Consequences of portal hypertension produce symptoms:
  • Gastroesophageal varices
  • Ascites
  • Enlarged spleen
  • Hepatic encephalopathy
Hepatic Encephalopathy (HE)
Definition of Hepatic Encephalopathy (HE)

- HE is a 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
Characterization of HE Stages

Categorization is often arbitrary and varies between raters.

**Simple Clinical Diagnosis**

**Worsening cognitive dysfunction**

**West Haven Criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No abnormalities detected</td>
</tr>
<tr>
<td>I</td>
<td>Trivial lack of awareness; Euphoria or anxiety; short attention span; Impairment of addition or subtraction</td>
</tr>
<tr>
<td>II</td>
<td>Lethargy or apathy, Disorientation for time, Obvious personality change, Inappropriate behavior</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence to semi-stupor, Responsive to stimuli, Confused, Gross disorientation, Bizarre behavior</td>
</tr>
<tr>
<td>IV</td>
<td>Coma, unable to test mental state</td>
</tr>
</tbody>
</table>

Importance of Overt Hepatic Encephalopathy

- Associated with a poor prognosis
- Retrospective review of 111 cirrhotic patients for 12-17 months following first episode of acute OHE:
  - 82 (74%) died during follow-up period
- Survival probability
  - 42% at 1 year
  - 23% at 3 years

Diagnosis of Overt HE

- Limited to no role for serum ammonia levels
- Clinical recognition of the distinctive neurologic features of HE
- Knowledge that underlying cirrhosis is present
- Exclusion of all other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Portal-systemic encephalopathy score (PSE score; Conn score) to evaluate overall severity
General Principles of Management of OHE

• Acute HE in patients with cirrhosis is reversible in the majority of patients

• A precipitating cause of OHE, rather than worsening of hepatocellular function can be identified in most episodes

• Management of the precipitating events typically leads to prompt improvement

• Clinicians should simultaneously identify and resolve precipitating events while instituting pharmacologic therapy
# Treatment Options for HE

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactulose</td>
<td>Poorly absorbed disaccharide</td>
<td>Decrease blood ammonia concentration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention and treatment of portal-systemic encephalopathy</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Non-aminoglycoside semi-synthetic, non-systemic antibiotic</td>
<td>Reduction in risk of overt hepatic encephalopathy (HE) recurrence</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Aminoglycoside antibiotic</td>
<td>Not to be used, renal and ototoxic risk</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Synthetic antiprotozoal and antibacterial agent</td>
<td>Not approved for HE</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Aminoglycoside antibiotic</td>
<td>Not approved for HE</td>
</tr>
</tbody>
</table>
Lactulose

• Currently the mainstay of therapy of HE; ~70% to 80% of patients with acute and chronic HE improve with lactulose treatment

• Mechanism of action:
  • A non-absorbable disaccharide that is fermented in the colon
  • Metabolism by the bacterial flora in the colon to lactic acid lowers the colonic pH
  • Cathartic effect can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume

• Administered orally or through a nasogastric tube or via retention enemas
• Dose: 45 to 90 g/day, titrated to achieve 2 to 3 soft stools per day with a pH below 6
• Main side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence

Rifaximin

• Oral minimally absorbed (<0.4%) antibiotic
• Broad-spectrum *in vitro* activity against aerobic and anaerobic enteric bacteria
• No drug interactions
• No dosing adjustment required in patients with liver disease or renal insufficiency
• Can be used long-term with or without lactulose
• Approval of 550 mg tablets was granted March 24, 2010 for reduction in risk of HE recurrence and was based on a large, double-blind, placebo-controlled, Phase 3 trial published in *The New England Journal of Medicine*

Management Goals for HE

- Provision for supportive care
- Identification and removal of precipitating factors (e.g., infection, GI bleed, dehydration)
- Correct electrolyte abnormalities
- Diet: daily energy intake between 35-40 kcal/kg ideal body weight, daily protein intake of 1.2-1.5 g/kg/day (do not restrict protein), small meals/liquid nutritional supplements throughout the day with late-night snack
- Assessment of the need for long-term therapy
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of the need for liver transplantation
- Difficult on the caregiver so assure necessary support
Managing Thrombocytopenia in the Cirrhotic Patient
Liver Disease and Thrombocytopenia

- Liver disease impacts all aspects of “clotting” including hemostasis, coagulation and fibrinolysis
- Thrombocytopenia, defined as platelet count <100 x 10^9/L, is estimated to affect up to 70% of patients with cirrhosis
  - Worsens with the severity of portal hypertension and cirrhosis
- Higher risk of bleeding
- May be deemed ineligible for elective surgical or diagnostic procedures
Procedures, Thrombocytopenia and Chronic Liver Disease (CLD)

- CLD patients require 1-3 procedures annually
- Different procedures are associated with different risks of bleeding
- Thrombocytopenia can lead to serious uncontrolled bleeding in these patients negatively impacting clinical care
  - Prolonged hospitalizations
  - Serious complications
  - Poor clinical outcomes
- Until recently, platelet transfusions were the recommended option for platelet counts <50 x 10^9/L

Relative Bleeding Risk Associated With Common Medical Procedures Performed in Patients With Chronic Liver Disease

<table>
<thead>
<tr>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Thoracentesis</td>
<td>• Liver biopsy</td>
<td>• Biliary interventions</td>
</tr>
<tr>
<td>• Paracentesis</td>
<td>• Bronchoscopy ± biopsy</td>
<td>• Dental procedures</td>
</tr>
<tr>
<td>• Endoscopy</td>
<td>• Ethanol ablation</td>
<td>• Transjugular intrahepatic portosystemic shunt</td>
</tr>
<tr>
<td>• Upper GI endoscopy</td>
<td>• Chemoembolization for HCC</td>
<td>• Laparoscopic interventions</td>
</tr>
<tr>
<td>- ± biopsy</td>
<td></td>
<td>• Nephrostomy tube placement</td>
</tr>
<tr>
<td>- ± variceal banding ± sclerotherapy</td>
<td></td>
<td>• Radiofrequency ablation</td>
</tr>
<tr>
<td>• Colonoscopy ± polypectomy biopsy</td>
<td></td>
<td>• Renal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vascular catheterization</td>
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New Option: Thrombopoietin Receptor Agonists

- Both avatrombopag and lusutrombopag were approved in 2018
- Oral meds which are dosed for a few days prior to scheduled procedure
- Can be used instead of platelet transfusion
- Platelet levels gradually decrease to pretreatment level
Avatrombopag in Chronic Liver Disease Patients Undergoing Scheduled Procedures

- Significantly reduced the need for platelet transfusion prior to undergoing invasive procedure
- Safe and well tolerated

![No Platelet Rescue Procedure Required](chart)

### ADAPT-1
- Platelets <40 x 10^9/L: 23% (Avatrombopag; 66%), 35% (Placebo)
- Platelets 40-<50 x 10^9/L: 38% (Avatrombopag), 33% (Placebo)

### ADAPT-2
- Platelets <40 x 10^9/L: 23% (Avatrombopag), 35% (Placebo)
- Platelets 40-<50 x 10^9/L: 38% (Avatrombopag), 33% (Placebo)

**P-values:**
- P<0.0001
- P=0.0006
- P=0.0001
Lusutrombopag in Chronic Liver Disease Patients Undergoing Scheduled Procedures

- Significantly reduced the need for platelet transfusion prior to undergoing invasive procedure
- Safe and well tolerated
Managing the Cirrhotic Patient...

- Recognize signs of hepatic encephalopathy
- Assure liver cancer screening
- Recognition of ascites
- Life style and nutrition counseling
- Assure thrombocytopenia managed when elective procedures required
- Intervene early when decompensation first recognized in order to minimize morbidity and mortality