Updates in Outpatient Cirrhosis Management

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Learning Objectives

• Review cirrhosis epidemiology, natural history, and prognosis
• Summarize updates on current standards of care regarding management of cirrhosis complications
  – Encephalopathy treatment
  – Variceal bleeding prophylaxis
  – SBP prophylaxis
  – HCC surveillance
• Discuss indications for referral for liver transplantation

Burden of Cirrhosis

• 5.5 million persons in US have cirrhosis
• 12th leading cause of death in US
• 29,000 annual deaths
• 112,000 hospital discharges annually
• 6,500 liver transplants annually
• 13,000 patients on wait-list for liver transplant
• 10% wait list mortality

Causes of Liver Disease in US

Merion, R. Seminars in Liver Disease 2010;30:411-421.
Prevalence of HCV Complications

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV Infection</td>
<td>2.9 million</td>
<td>2.4 million</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>721,000</td>
<td>880,000</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>103,000</td>
<td>146,000</td>
</tr>
<tr>
<td>HCC</td>
<td>11,000</td>
<td>13,400</td>
</tr>
<tr>
<td>Liver-related Death</td>
<td>28,000</td>
<td>40,000</td>
</tr>
</tbody>
</table>


Cirrhosis and Mortality

Decompensated Cirrhosis

- **Ascites:**
  - Most common manifestation of decompensation
  - 50% within 10 years of diagnosis of cirrhosis
  - SBP develops in 10-30% of ascitics
- **Varices:**
  - 30% compensated, 60% decompensated
  - 7% per year rate of development of varices
  - One year rate for first variceal bleed is 12%
- **Encephalopathy:**
  - 50% including minimal and overt classifications
  - One year mortality 58%

Cirrhosis Stage and One Year Mortality Risk

Infection in Cirrhotics Results in 4 Fold Increased Risk of Mortality

Overall 30 day mortality 30%; 12 month mortality 63%

Prognostic Tool: MELD Score

Based on Bilirubin, Creatinine, and INR
Prognostic Tool: Child-Turcotte-Pugh Score

Childs Class A (5-6 points); B (7-9 points); C (10-15 points)

3 Month Mortality

<table>
<thead>
<tr>
<th>MELD Score</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 9</td>
<td>1.9</td>
</tr>
<tr>
<td>10-19</td>
<td>6</td>
</tr>
<tr>
<td>20-29</td>
<td>20</td>
</tr>
<tr>
<td>30-39</td>
<td>53</td>
</tr>
<tr>
<td>&gt;40</td>
<td>71</td>
</tr>
</tbody>
</table>

CTP Class

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
</tr>
<tr>
<td>C</td>
<td>40</td>
</tr>
</tbody>
</table>


Learning Objectives

- Review cirrhosis epidemiology, natural history, and prognosis
- Summarize updates on current standards of care regarding management of cirrhosis complications
  - Encephalopathy treatment
  - Variceal bleeding prophylaxis
  - SBP prophylaxis
  - HCC surveillance
- Discuss indications for referral for liver transplantation

Case Presentation

- Mr L is a 53 year old man with hepatitis C and alcohol related cirrhosis, MELD score 16, Childs Class B, who you are seeing as a new patient. He has been hospitalized three times in the past 6 months for confusion. He is on lactulose but continues to have day:night reversal and mild asterixis.
Hepatic Encephalopathy (HE)

- Spectrum of neuro-cognitive impairment
  - Deterioration in mental status
  - Psychomotor dysfunction
  - Impaired memory and concentration
  - Increased reaction time
  - Sensory abnormalities

- Two forms:
  - Overt: clinically diagnosable
  - Minimal: requires psychometric testing (attention, inhibition, working memory)

Grading of Overt HE

<table>
<thead>
<tr>
<th>Grade</th>
<th>Level of consciousness</th>
<th>Intellectual function</th>
<th>Neuromotor function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lack of awareness</td>
<td>Short attention</td>
<td>Incoordination</td>
</tr>
<tr>
<td></td>
<td>Personality change</td>
<td>Agitation</td>
<td>Mid asterixis</td>
</tr>
<tr>
<td></td>
<td>Day/night reversal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Lethargic</td>
<td>Disoriented</td>
<td>Asterixis</td>
</tr>
<tr>
<td></td>
<td>Inappropriate behavior</td>
<td>Bizarre</td>
<td>Abnormal reflexes</td>
</tr>
<tr>
<td>3</td>
<td>Somnolent but</td>
<td>Loss of meaningful</td>
<td>Asterixis</td>
</tr>
<tr>
<td></td>
<td>Arousable</td>
<td>communication</td>
<td>Abnormal reflex</td>
</tr>
<tr>
<td>4</td>
<td>Coma,</td>
<td>Absent</td>
<td>Decerebrate</td>
</tr>
<tr>
<td></td>
<td>Unresponsive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology

Treatment of HE

- Treatment reduces nitrogenous load in gut by decreasing colonic bacterial activity and increasing elimination
- Nonabsorbable disaccharides: lactulose
- Nonabsorbable antibiotics: rifaximin
- Protein restriction promotes protein degradation and, if maintained for long periods, worsens nutritional status and decreases muscle mass
  - No longer recommended

Bass, N Alim Pharm Ther 25:23-31
Non-absorbable Disaccharides


Non-absorbable Antibiotics


Rifaximin Decreases HE and Hospitalization Rates

Bass, N et al. NEJM 362;12:1076

The NEW ENGLAND JOURNAL of MEDICINE

Established in 1812 MARCH 25, 2010 VOI. 362 NO. 12

Rifaximin Treatment in Hepatic Encephalopathy

- Rifaximin 550 mg po BID vs placebo for 6 months
- Outcome: recurrent HE, hospitalizations
- Inclusion Criteria: History of HE but in remission at study entry, MELD < 26
- 90% on lactulose
- 80% study drug compliance
- No difference in adverse events
**Triggers of HE**
- Infection
- Bleeding
- Dehydration
- Electrolyte Imbalance
- Medications
- Constipation
- Portal vein thrombosis

**Should patients with HE Drive?**
- Minimal HE difficult to diagnosis but results in impaired reaction time and navigational skills
- Patients with minimal HE have higher risk of driving offenses and crashes
- Even after overt HE resolves, evidence suggests residual cognitive impairment
- DMV does not specifically list HE or liver disease as condition requiring automatic reporting in any state

**Required Conditions to Be Reported by MD**

**HE and Driving Recommendations**
- No national guideline or law exists
- Patients with MHE and their caregivers should be told about risk of decreased driving scores and incidents
- Patients with MHE may benefit from on-road test for driving fitness
- Patients with overt HE (ie cognitive impairment/lapse of consciousness) should not drive


Case

- During the patient’s last hospitalization for HE, he underwent a diagnostic paracentesis which showed 550 PMNs per cubic mm and he was diagnosed with SBP. He was treated with IV cefotaxime for five days. He has well controlled, minimal ascites on diuretics.

All of the following patients should receive SBP prophylaxis except:

- 1) Prior episode of SBP
- 2) Ascitic protein of < 1.5 g/dl and at least one of the following: Creatinine > 1.2, BUN > 25, sodium < 130, bilirubin > 3, CPT > 9
- 3) Active GI bleed
- 4) Cirrhotics undergoing routine colonoscopy

SBP Prophylaxis Decreases Mortality

RR 0.65 (95% CI, 0.48-0.88) for overall mortality (16% vs 25%)

N= 600 pts (8 studies)

**SBP Prophylaxis in Low Protein Ascites (< 1.5 g/dl)**

OR 0.60 (95% CI, 0.37-0.97)


**RCT: SBP Primary Prophylaxis Improves Mortality**

- Inclusion criteria included:
  - Ascitic protein level < 1.5 g/dl
  - CPT score > 9 and total bilirubin > 3
  - Creatinine > 1.2, BUN > 25, sodium < 130
- 3 mo mortality 94% vs 62% (p < .003)
- SBP episodes 61% vs 7% (p < .001)
- Hepatorenal 41% vs 28% (p=.02)

Fernandez, J et al. Gastroenterology (2007); 133:818-824

**SBP Prophylaxis in Setting of GIB**

Overall mortality 15% vs 24%


**SBP Prophylaxis Medications**

- Norfloxacin 400 mg po QD
- Ciprofloxacin 250 mg po QD
- Septra DS 1 tablet QD 5D per week
- Ciprofloxacin 750 po Qweek

Runyon, B. Hepatology (2009); 49 (6): 2087-2107.
Case Presentation

• You begin SBP prophylaxis. You also discuss with the patient the importance of a low salt diet, need for abstinence lifelong from alcohol, the warning signs for bleeding, and risk of HCC development in HCV cirrhosis.

All of the following should receive primary prophylaxis for variceal bleed, except:

• 1) Large varices, Childs Class A
• 2) Small varices, Childs Class C
• 3) No varices, Childs Class C
• 4) Medium varices, Childs Class A

Primary Prophylaxis for VB

• Recommendations suggest EGD at cirrhosis diagnosis to survey for presence of varices
  – If none, repeat EGD every 2-3 years
• Treatment dependent on size of varices and degree of decompensation
• Two treatment options are equivalent at preventing first variceal bleed:
  – Nonselective beta-blockade (NSBB)
  – Endoscopic Band Ligation
• Practice variation on preferential use of NSBB vs Ligation

Primary Prophylaxis for VB

<table>
<thead>
<tr>
<th>Varices</th>
<th>Childs Class</th>
<th>Prophylaxis</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Any</td>
<td>None</td>
<td>NSBB do not prevent variceal development</td>
</tr>
<tr>
<td>Small</td>
<td>A</td>
<td>NSBB optional</td>
<td>Low overall risk of bleed 6 week post bleed mortality 0%</td>
</tr>
<tr>
<td>Small</td>
<td>B/C</td>
<td>NSBB</td>
<td>6 week post bleed mortality 30%</td>
</tr>
<tr>
<td>Medium/Large</td>
<td>Any</td>
<td>NSBB or Ligation</td>
<td>NSBB side effects 15-20% NSBB may also reduce SBP</td>
</tr>
</tbody>
</table>

Garcia-Tsao, G. et al. NEJM (2010); 362 (9): 823-832.

Primary Prophylaxis Treatments

Carvedilol 6.25-12.5 mg QD is an alternative NSBB test in RCT

Garcia-Tsao, G. et al. NEJM (2010); 362 (9): 823-832
Tripathi, D et al Hepatology (2009); 50:825-833.

Etiology of Cirrhosis and HCC Risk

Five year cumulative risk of HCC development in cirrhosis


AASLD HCC Screening Guidelines

- High risk groups with prevalence of HCC exceeding 1.5%/year should be in surveillance program (Level I)
- Patients awaiting transplant should be screened (Level III)
- US is test of choice, and should be done every 6 months (Level II)
- AFP alone should not be used for screening (Level II)
- If US not available or of poor quality, consider AFP or no screening at all

High Risk Populations for HCC

- Hepatitis B carriers
  - Asian males ≥ 40 years
  - Asian females ≥ 50 years
  - All chronic hepatitis B carriers
- Family history of HCC
- African or age ≥ 20
- For non-Caucasian hepatitis B carriers not listed above; the risk of HCC varies depending on the severity of the underlying liver disease, and current and past hepatitis inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity remain at risk for HCC.
- Non-hepatitis B cirrhosis
- Hepatitis C
- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis
- Although the following groups have an increased risk of HCC no recommendations for or against surveillance can be made because a lack of data precludes an assessment of whether surveillance would be beneficial.
- Alpha-fetoprotein deficiency
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis


RCT: US Screening Led to Improved HCC Mortality in Asian HBV Patients

HR HCC Death
0.63 (95% CI 0.41, 0.98)

Screening Led to Earlier Stage and Increased Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screening group (88)</th>
<th>Control group (67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>32(37.5%)</td>
<td>68(49.3%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>30(34.1%)</td>
<td>25(18.9%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>5(5.7%)</td>
<td>3(2.2%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60(68.2%)</td>
<td>48(64.4%)</td>
</tr>
</tbody>
</table>

- Adherence in Screening Group

Table 2 Stage distribution, treatment, and survival of patients with HCC in the screened and control groups (TACE: transarterial chemoembolization, PEI: percutaneous ethanol injection)


HCC Surveillance Practice Patterns in US

- Retrospective analysis of SEER-Medicare database of 1873 HCV cirrhotic patients with HCC
  - 17% had routine surveillance (most commonly US + AFP)
  - 38% inconsistent surveillance

- Retrospective analysis of VA database of 13,002 HCV cirrhotic patients
  - 12% had routine surveillance (two studies within 2 years)
  - 58% inconsistent surveillance

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  - SBP prophylaxis
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Liver Transplant Referral

- Does the patient need a transplant?
- Does the patient want a transplant?
- Are there significant medical co-morbidities or psychosocial reasons that make liver transplant too high risk for the patient?

Does the Patient Need a Transplant?

- Development of Decompensated Disease by symptoms, or worsening of MELD > 10, CPT > 7
- Hepatocellular Carcinoma
- Impaired quality of life issues:
  - chronic encephalopathy
  - hepatic hydrothorax
  - hepatopulmonary syndrome
  - portopulmonary hypertension
  - Refractory itching
  - Persistent recurrent cholangitis
Risk of Transplant Outweighs Benefit with MELD < 15

Summary of Cirrhosis Prognosis
• Transition to decompensated cirrhosis: 5% to 7% per year
• 1 year mortality
  – 1% in compensated
  – 20% in decompensated with ascites
  – 57% in decompensated with varices
• Infection, MELD and CPT scores are important predictors of death in cirrhotics

Liver Transplant Survival

Summary of Cirrhosis Management
• Rifaximin 550 mg po BID reduces recurrent HE and hospitalizations
• Prophylaxis for SBP reduces mortality in patients with history of SBP, low protein ascites and active GI bleed
• Method of primary prophylaxis for first variceal bleed is dependent on size of varices and Childs Class
• HCC surveillance with US should be performed in high risk patient groups
  – Benefits optimized in patient interested in/ can tolerate HCC treatment and compliant with long-term surveillance protocols

Merion et al. AJT (2005); 5: 307-313.
Wolfe R AJT (2009); 9: 869-878.