Cirrhosis Update
CIRRHOSIS
Definition

- “Irreversible” fibrous scarring within the liver which has lead to the development of regenerative nodules
- Estimated 3-4 million people in the U.S. have CLD and cirrhosis!
- CLD 15-20 million
Portal Hypertension
\[ \text{Resistance} \times \text{Flow} = \text{Portal Hypertension} \]

**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**

Portal Hypertension

• Consequences of portal hypertension produce symptoms:
  – Gastroesophageal varices
  – Ascites
  – Enlarged spleen
  – Hepatic encephalopathy

Gastroesophageal Varices
Gastroesophageal Varices

- Gastroesophageal varices present in ~50% of patients with cirrhosis
  - Presence correlates with severity of liver disease
  - 40% of Child A patients have varices
  - 85% of Child C patients have varices
- Cirrhotic patients without varices develop them at a rate of 8% per year
  - Patients with small varices develop large varices at a rate of 8% per year

Gastroesophageal Variceal Hemorrhage

- Occurs at a yearly rate of 5% to 15%
- Most important predictor of hemorrhage is size of varices
- Other predictors of hemorrhage are:
  - Decompensated cirrhosis (Child B/C)
  - Endoscopic presence of red wale marks
- Associated with a mortality of ≥20% at 6 weeks
- Bleeding ceases spontaneously in ≤40% of patients

Cirrhosis Screening and Surveillance Management

Esophagogastroduodenoscopy

- **No varices**
  - Repeat endoscopy in 3 years (well compensated); in 1 year if decompensated
  - No beta-blocker prophylaxis

- **Small varices (<5 mm), Child B/C, red wales**
  - Beta-blocker prophylaxis

- **Medium or large varices**
  - Child Class A, no red wales: Beta blockers
  - Child class B/C, red wales: Beta blockers, or endoscopic band ligation

Management of Acute Hemorrhage

- Patients with suspected acute variceal hemorrhage require intensive-care unit setting for resuscitation and management.

- Acute GI hemorrhage requires:
  - Intravascular volume support
  - Blood transfusions
  - Maintaining hemoglobin of ~8 g/dL

- Institute short-term (7-day) antibiotic prophylaxis.

- Initiate therapy with somatostatin (or its analogs).

- Perform esophagastroduodenoscopy within 12 hours; treat with endoscopic band ligation or sclerotherapy.

Management of Acute Hemorrhage (Cont.)

• TIPS (transjugular intrahepatic portosystemic shunt) indicated if hemorrhage uncontrolled or recurrent bleeding despite pharmacologic and endoscopic therapy

• Balloon tamponade should be temporary measure used prior to more definitive therapy

Bacterial Infection and Variceal Bleeding

- Variceal bleeding associated with increased risk of bacterial infection
  - SBP (spontaneous bacterial peritonitis), urinary tract infection, pneumonia or bacteremia
- Develops in 20% of patients within 48 hours and in 35% to 66% of patients within 2 weeks
- Compared to patients without infection, presence of infection is associated with
  - Failure to control bleeding (65% vs 15%)
  - Early rebleeding
  - Mortality (40% vs 3%)

Antibiotic Prophylaxis During/After Acute Variceal Bleeding

- Prophylactic ofloxacin vs antibiotics only at diagnosis of infection
- ↓ infections (2/59 vs 16/61)
- Less rebleeding within 7 days
- ↓ blood transfusions for rebleeding
- Prophylactic antibiotics recommended in management of acute variceal hemorrhage

Ascites
Ascites

- Most common complication of cirrhosis
- Only occurs when portal hypertension has developed
- ~60% of patients with compensated cirrhosis develop ascites within 10 years
- 50% mortality rate within 3 years
- Patients should generally be considered for liver transplantation referral

Prognosis of Patients with Cirrhosis at Onset of Ascites

## AASLD Practice Guidelines: Ascitic Fluid Analysis

<table>
<thead>
<tr>
<th>Routine</th>
<th>Optional</th>
<th>Unusual</th>
<th>Unhelpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count and differential</td>
<td>Culture in blood culture bottles</td>
<td>Acid-fast bacteria smear and culture</td>
<td>pH</td>
</tr>
<tr>
<td>Albumin</td>
<td>Glucose</td>
<td>Cytology</td>
<td>Lactate</td>
</tr>
<tr>
<td>Total protein</td>
<td>Lactose dehydrogenase</td>
<td>Triglyceride</td>
<td>Cholesterol</td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td>Bilirubin</td>
<td>Fibronectin</td>
</tr>
<tr>
<td></td>
<td>Gram’s stain</td>
<td></td>
<td>Glycosaminoglycans</td>
</tr>
</tbody>
</table>
Management of Ascites

First-Line Therapy

Tense ascites
- Paracentesis
- Sodium restriction (<2 Gm/24 Hrs) and diuretics*

Non-tense ascites

Second-Line Therapy

Refractory Ascites 10%

- Repeated large volume paracentesis (LVP)†
- TIPS
- Liver Transplantation

*Diuretics: Spironolactone 100 mg/day, furosemide 40 mg/day or bumetanide 1 mg/day; uptitrate stepwise to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as tolerated

†Albumin infusion of 12 gm/liter of fluid removed is a consideration for repeated LVP; post-paracentesis albumin infusion may not be necessary for < 5 liters removed

Adapted from Runyon BA. Hepatology. 2009; 49:2087-2107.
Renal Dysfunction
Renal Injury in Cirrhosis

Hospitalized patients with cirrhosis

- Chronic renal failure 1%
  - Pre-renal 68%
    - Volume-responsive 66%
      - Infection
      - Hypovolemia
      - Vasodilators
      - Other
  - Intra-renal (ATN, GMN) 32%
    - Not volume-responsive
      - HRS type 1 25%
      - HRS type 2 9%
  - Post-renal (obstructive) <1%

ARF: Acute renal failure
GMN: Glomerulonephritis
ATN: Acute tubular necrosis
AKI: Acute kidney injury
HRS: Hepatorenal syndrome

Survival is Decreased with Renal Dysfunction

Survival in Cirrhosis Based on Level of Renal Dysfunction

Survival Among Patients With Cirrhosis and Hepatorenal Syndrome

Prevention of Acute Renal Injury in Cirrhotics

• Prevent/treat volume depletion or vasodilatation
  – Careful use of diuretics
  – Avoidance of diarrhea with use of lactulose
  – Use of albumin after large-volume paracentesis

• Avoid use of aminoglycosides and NSAIDs

• Aggressively treat hypovolemia/hypotension occurrence

Hepatorenal Syndrome
Hepatorenal Syndrome: Risk Factors

- Development of bacterial infections, particularly SBP, is the most important risk factor
  - Hepatorenal syndrome develops in ~30% of patients with spontaneous bacterial peritonitis
  - Treatment with albumin infusion/antibiotics reduces the risk of developing hepatorenal syndrome and improves survival

Hepatorenal Syndrome: Prognosis

- The prognosis of hepatorenal syndrome is poor
  - Average median survival ~ 3 months
  - High MELD score and type 1 hepatorenal syndrome are associated with very poor prognosis
    - Median survival of patients with untreated type 1 hepatorenal syndrome is ~ 1 month

Hepatic Encephalopathy (HE)
Treatment Goals for OHE

• Provision for supportive care

• Identification and removal of precipitating factors
  – Infection, GI bleed, dehydration

• Reduction of nitrogenous load from gut

• Correction of electrolyte abnormalities

• Long-term therapy assessment
  – Control of potential precipitating factors
  – Higher likelihood of recurrent encephalopathy
  – Assessment of need for liver transplantation

## Current Therapy 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&lt;br&gt;• Prevention and treatment of portal-systemic encephalopathy</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Non-aminoglycoside semi-synthetic, nonsystemic antibiotic</td>
<td>Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age.</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

Ferenci P. Semin Liver Dis. 2007;27(suppl 2):10-17.
Bajaj JS. Aliment Pharmacol Ther 2010;31:537-547.
Lactulose (Cont.)

- Administered orally, by mouth 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
- Principal side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence
- Systematic review of clinical studies found insufficient evidence to support or refute the use of lactulose for HE

Ferenci P. Semin Liver Dis. 2007;27(suppl 2):10-17.
Bajaj JS. Aliment Pharmacol Ther 2010;31:537-547.
Rifaximin

• Minimally absorbed (<0.4%) oral antibiotic
• Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria
• No clinical drug interactions reported
• No dosing adjustment required in patients with liver disease or renal insufficiency
• Approved for overt recurrent HE risk reduction in patients ≥18 years of age
• In registration trials, 91% of patients were given lactulose concomitantly

Rifaximin Trial:
Time to First Breakthrough HE Episode Primary End Point

- Proportion of Patients Without Breakthrough HE (%)
  - Rifaximin*: (77.9%)
  - Placebo*: (54.1%)

*Rifaximin 550 mg or placebo twice daily

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)

P<0.001

Rifaximin Trial:
Time to First HE-Related Hospitalization
Key Secondary End Point

Proportion of Patients Without HE-Related Hospitalization (%)

Days Since Randomization

*Rifaximin 550 mg or placebo twice daily
Hazard ratio with rifaximin, 0.42 (95% CI, 0.28–0.64)
\( P<0.001 \)

Rifaximin Trial: Rifaximin Improves Health-Related Quality of Life

CLD, Questionnaire Domain Scores: Differences in least square means of time-weighted average values and 95% CI intervals, rifaximin (n=101) vs. placebo (n=118) groups

<table>
<thead>
<tr>
<th>Domain</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>0.0087</td>
</tr>
<tr>
<td>Abdominal symptoms</td>
<td>0.0090</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>0.0160</td>
</tr>
<tr>
<td>Activity</td>
<td>0.0022</td>
</tr>
<tr>
<td>Emotional function</td>
<td>0.0065</td>
</tr>
<tr>
<td>Worry</td>
<td>0.0436</td>
</tr>
<tr>
<td>Overall</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

Rifaximin Trial: Side Effects Similar to Placebo

- Incidence of adverse events did not differ significantly between 2 study groups ($P>0.05$ for all comparisons)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rifaximin (n=140)</th>
<th>Placebo (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event, n (%)</td>
<td>112 (80.0)</td>
<td>127 (79.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (14.3)</td>
<td>21 (13.2)</td>
</tr>
<tr>
<td>Diarrhea</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 edema</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>
</tbody>
</table>

Hepatocellular Carcinoma (HCC)
HCC Incidence Tripled Over the Last Three Decades

AASLD recommends surveillance using AFP + US every 6-12 months for at-risk patient groups:

- Hepatitis B carriers
  - Asian males >40 years
  - Asian females >50 years
  - All cirrhotic hepatitis B carriers
  - Family history of HCC
  - Africans >20 years
  - Non-cirrhotic hepatitis B carriers with high HBV DNA levels or more severe current/past levels of inflammatory activity

- Cirrhosis due to hepatitis C, alcohol, or other causes
Imaging Studies

- **AASLD Criteria - HCC**
  - Nodules > 1 cm (previously ≥ 2 cm) **both early arterial enhancement and rapid venous/late phase wash out** with on dynamic contrast CT/MRI
  - Any other findings require biopsy or interval growth for HCC diagnosis
Liver Biopsies of HCC Are Rarely Needed!

**Risks**
- Pain
- Bleeding
- Needle Tract Seeding
- Mis-diagnosis
Health Maintenance of the Cirrhotic Patient

- Vaccinations
- Bone disease screening, surveillance and management
- HCC Screening and Surveillance
- Varices Screening and Surveillance
- Nutritional Support
  - Vitamin assessment for Vit A and D deficiency
  - Mineral assessment: Zinc and Mg++
- Review Medication List