Management of Cirrhosis Related Complications

Ke-Qin Hu, MD, FAASLD
Professor of Clinical Medicine
Director of Hepatology
University of California, Irvine
Disclosure

I have no disclosure related to this presentation
Liver Biopsy and Histologic Staging

Stage 1

Stage 2

Stage 3

Stage 4
Chronic Liver Disease and Cirrhosis

- Acute liver injury
- Chronic liver disease (liv dis)
- Cirrhosis
- HCC
- Decompensation
Hepatic Elastography: A Non-Invasive Way to Diagnose Cirrhosis
Complications of Cirrhosis

• **Primary complications include:**
  - Ascites and spontaneous bacterial peritonitis
  - Hepatic encephalopathy
  - Variceal hemorrhage
  - Cholestasis/Jaundice
  - Coagulopathy

• **Other complications that can occur include:**
  - Hepatic hydrothorax
  - Hepatorenal syndrome
  - Portopulmonary hypertension
  - Hepatocellular carcinoma
  - Portal vein thrombosis

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

Analysis of Ascitic Fluid: Serum-Ascites Albumin Gradient (SAAG)

- **High SAAG (≥ 1.1):**
  - 97% accuracy in predicting PHTN
  - cirrhosis
  - AAH, HCC, cardiac ascites

- **Low SAAG (< 1.1):**
  - peritoneal carcinomatosis
  - TB peritonitis
  - peritonitis from connective tissue diseases
Approach: Ascites

- Treating underlying cause for cirrhosis
- Sodium restricted diet: 2 g NaCl/day
- No protein restriction
- Diet education of pt & care giver
- Oral diuretics: qAM dose is preferred
  - Spironolactone: 100-400 mg/d
  - Furosemide: 40-160 mg/d po
- Follow body weight & urine Na
- No NSAIDs or nephrotoxic meds
Ascites: Assessing Rx Response

• Follow body weight & urine Na/K daily
• Goal: urine Na>K
• When Ur Na>K, pt should be losing weight
• Avoid NSAIDs & nephrotoxic meds
• Avoid IV furosemide, it decreases RPF & causes azotemia in cirrhotic pts
Approach: Ascites

- Diet & dual diuretics: 90% Effective
- Refractory ascites: 10%
  - Liver transplant
  - Large-volume paracenteses q 2 wks
  - Transjugular intrahepatic portosystemic stent-shunt (TIPS)
- Peritoneovenous shunt
TIPS for Refractory Ascites

- Side-to-side radiologic shunt
- Usually converts diuretic-resistant to diuretic-sensitive
- ~25% encephalopathy but treatable
- Much better control of ascites than taps
- Possible survival advantage

NEJM 2000;342:1701-7
Gastroenterology 2002;123:1839-47
Gastroenterology 2003;124:634-41
Spontaneous Bacterial Peritonitis (SBP)

• Previously ~20% prevalence on adm
• Now much less common: prevention
• PMN ≥250 cells/cu mm ± pos cult
• *E. coli*, pneumococcus, klebsiella, etc.
• Now Increasingly Resistant Flora
• Rx: cefotaxime IV 2g q8 hrs x 5d empiric, then tailor
• Follow Local antibiogram

UpToDate
Liver Internat 2010;30:1145-6
Hepatology 2012;56:2328-35
Principles of Evaluation & Treatment for SBP

- Tap all patients with new onset, on admission, & for deterioration
- Bedside inoculation of BCB
- Treat if PMN $\geq 250$ and/or Sn or Sx of infection
- Avoid aminoglycosides
- Narrow antibiotic spectrum when possible
- Prevention with norfloxacin or Trim/Sulfa

Hepatology 2004;39:841-56
Empiric Antibiotic Choice

- Single-agent third-gen cephalosporin
- Cefotaxime: most data to support
- Ceftriaxone: suboptimal penetration
- Avoid nephrotoxic drugs
- 5 Days of Rx is usually enough

Hepatology 1985;5:457-62
Dig Dis Sci 1991;36:1782-6
AJG 2001;96:2206-10
Gastroenterology 1991;100:1737-42
Prevention of SBP – Prophylaxis

- Risk factors for development of SBP
  - Ascitic fluid protein concentration <1.0 g/dL
  - Variceal hemorrhage
  - Prior episode of SBP
- Prophylactic antibiotics

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>Dose /Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>400 mg/day orally</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1g/day IV for 7 days</td>
</tr>
<tr>
<td>Double-strength</td>
<td>5 doses/week</td>
</tr>
<tr>
<td>sulfamethoxazole/trimethoprim</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>750 mg as single oral dose/week</td>
</tr>
</tbody>
</table>

- Intermittent dosing of prophylactic antibiotics may select resistant flora; daily dosing preferred

Albumin Plus ABx for SBP

- RCT of 126 pts with SBP: ABx vs ABx + Alb
- 1.5 g/kg in 6 Hrs & 1 g/kg on day 3
- 29% vs 10% mortality (p=0.01)
- Lowest mortality ever reported
- Survival advantage persisted at 3 months

NEJM 1999;341:403-9
Hepatic Encephalopathy (HE)

- 2nd Most common complication: 28% 10 yr
- Reversible metabolic confusion
- Drowsiness
- Dx: asterixis, trail test, not ammonia
- FHF: brain edema
  - Rx: Liver Transplant
- Cirrhosis: no brain edema
  - Rx: Lactulose, No Protein Restriction, Rifaximin

References:
- NEJM 1998;337:473-9
- BMJ 1999;318:1391
- NEJM 2010;362:1071-81
Hepatic Encephalopathy (HE)

- Most Commonly Intermittent
  - Precipitated By
    - Dehydration
    - Infection
    - GI Bleeding
    - Narcotics, Benzos
    - Hypokalemia

- Chronic Severe
  - Post-TIPS
  - Post Portosystemic Shunt
## Current Therapy Options for HE

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug Class</th>
<th>Indication</th>
</tr>
</thead>
</table>
| Lactulose | Poorly absorbed disaccharide | • Decrease blood ammonia concentration  
• Prevention and treatment of portal-systemic encephalopathy |
| Rifaximin | Non-aminoglycoside semi-synthetic, nonsystemic antibiotic | Reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥ 18 years of age. |
| Neomycin | Aminoglycoside antibiotic | Not to be used, renal and ototoxic risk |
| Metronidazole | Synthetic antiprotozoal and antibacterial agent | Not approved for HE |
| Vancomycin | Aminoglycoside antibiotic | Not approved for HE |

Rifaximin Treatment in HE: Time to First Breakthrough Episode (Primary End Point)

Hazard ratio with rifaximin, 0.42 (95% CI, 0.28-0.64)  
\[ P < 0.001 \]

Treatment Approach for Acute Overt Hepatic Encephalopathy: Lactulose + Rifaximin vs. Lactulose

172 Cirrhotic Patients Screened

120 Patients Enrolled

Randomization

Lactulose (30-60 mL tid) + Rifaximin (one 400 mg capsule tid)  
$n=63$ (10 grade 2, 20 grade 3, 33 grade 4)

Lactulose (30-60 mL tid) + Placebo (one sugar capsule tid)  
$n=57$ (12 grade 2, 20 grade 3, 25 grade 4)

Treatment Approach for Acute Overt HE: Lactulose + Rifaximin vs. Lactulose

- Treatment was given through nasogastric tube and continued until recovery of HE or a maximum of 10 days.
- Hospital stay was shorter with Lactulose + Rifaximin than with Lactulose + Placebo (5.8 ± 3.4 vs. 8.2 ± 4.6 days, \( P=0.001 \)).

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

Rx: Variceal Hemorrhage

- Octreotide IV in ICU (? Terlipressin)
- PRBC to keep Hb 7-9 g/dL
- FFP to keep INR <1.5 (Tradition)
- Ceftriaxone 1g IV, then norfloxacin 400 mg/day x 7 d
- Early endoscopy for banding, repeat
- Rarely, balloon tube needed
- Refractory: shunt surgery or TIPS
### MELD Score and Timing for Tx Eval

**What is MELD score**

R = \( (0.957 \times \log_e(\text{creatinine mg/dl}) + 0.378 \times \log_e(\text{total bilirubin mg/dl}) + 1.120 \times \log_e(\text{INR}) + 0.643)) \times 10 \)

**Why MELD score**

**What MELD for considering referral for OLT evaluation and listing**

<table>
<thead>
<tr>
<th>MELD</th>
<th>90 Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>2-8%</td>
</tr>
<tr>
<td>10-19</td>
<td>6-29%</td>
</tr>
<tr>
<td>20-29</td>
<td>50-76%</td>
</tr>
<tr>
<td>30-39</td>
<td>62-83%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>100%</td>
</tr>
</tbody>
</table>