Overview

• How do you diagnose cirrhosis?
• What is the natural history and prognosis of cirrhosis?
• Managing common complications
• Other issues - immunization, medications, etc in patients with cirrhosis

Natural History of Chronic Liver Disease – Old Paradigm

Chronic liver disease

20+ years
Compensated cirrhosis
5-10 years
 Decompensated cirrhosis
1-5 years
Death

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice
- HCC
Cirrhosis - Diagnosis

- Cirrhosis is a histological diagnosis
- However, in patients with chronic liver disease, various clinical, laboratory, and radiological features can suggest cirrhosis

Diagnostic Algorithm

Chronic liver disease and any of the following:
  - Variceal hemorrhage
  - Ascites
  - Hepatic encephalopathy

Physical findings:
  - Enlarged left hepatic lobe
  - Splenomegaly
  - Stigmata of chronic liver disease

Laboratory findings:
  - Thrombocytopenia
  - Impaired hepatic synthetic function

Radiological findings:
  - Small nodular liver
  - Intra-abdominal collaterals
  - Ascites
  - Splenomegaly
  - MRE > 5 kPa

Liver biopsy not necessary for the diagnosis of cirrhosis

Staging fibrosis with NFS, FIB-4, and others ...

High (>92%) NPV for advanced fibrosis
Useful in clinical practice for excluding advanced fibrosis
ELF performed only marginally better than NFS
Modest PPV – liver biopsy still necessary

McPherson, Gut 2010
Guha, Hepatology 2008
Non-invasive measurement of hepatic fibrosis

**SERUM MARKERS**
- FibroTest
- ELF Panel
- Fibromètre
- NAFLD fibrosis score

**TRANSIENT ELASTOGRAPHY**

**Transient Elastography**
- Measures elasticity using sound waves
- Stiffness determined by multiple factors
  - Degree of fibrosis
  - Degree of inflammation - not good for acute hepatitis
- Degree of steatosis
  - Not effective in morbidly obese patients >3.5 cm
- Approved in U.S. 4/2013
  - now have XL probes

*J Gastrointestin Liver Dis. 2008 Jun;17(2):155-163*

**Prediction of advanced fibrosis by transient elastography**

<table>
<thead>
<tr>
<th>Transient elastography</th>
<th>N=246</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM 7.9 kPa</td>
<td>N=146</td>
</tr>
<tr>
<td>LSM 7.9-&lt;9.6 kPa</td>
<td>N=40</td>
</tr>
<tr>
<td>LSM &gt;9.6 kPa</td>
<td>N=56</td>
</tr>
<tr>
<td>&lt;F3 (correct): 143</td>
<td>Gray zone: Liver biopsy</td>
</tr>
<tr>
<td>≥F3 (false negative): 5</td>
<td></td>
</tr>
<tr>
<td>≥F3 (false positive): 16</td>
<td></td>
</tr>
<tr>
<td>≥F3 (correct): 42</td>
<td></td>
</tr>
</tbody>
</table>

Wong, Hepatology 2010
Transmit Elastography + ELF Algorithm

MR Elastography of the Liver

Liver Stiffness Correlates With Fibrosis Stage

Yin et al. CGH 2007;5:1207-13
MRE Liver Stiffness Predicts Outcomes

Asrani et al., Journal of Hepatology. 2014 EPUB ahead of print
Transient Elastography

Shear Stiffness (kPa)

MRE

Shear Stiffness (kPa)
Clinical Interpretation of MRE Results

- \( \leq 2.9 \) kPa: Biopsy not required
- 3.0 to 4.9 kPa: Imaging features of cirrhosis
- \( \geq 5 \) kPa: Biopsy required for staging

Collagen Binding Peptide – Gadolinium Chelation

What Is the Natural History of Cirrhosis?
Prognosis in Cirrhosis

Compensated or Decompensated?

Prognosis in Compensated Cirrhosis

- Median survival 9-12 years
- Deaths: Non-liver related (Cardiovascular, stroke, etc.)
  Liver-related deaths: HCC
- Predictors of decompensation:
  MELD score HR 1.15
  Serum albumin HR 0.37

Management of Compensated Cirrhosis

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Liver transplant (LT)

Diagnosis:
- Liver biopsy
- Clinical imaging

Screen for varices (EGD):
- Large varices → beta-block/ EVL
- Small varices → EGD in 1-2 yrs
- No varices → EGD in 2-3 yrs

Screen for HCC:
- Ultrasound every 6 months
- Stop alcohol
- Vaccinations
- Lifestyle changes
### Table 2: Adjusted Relative Risk of Cirrhosis According to Selected Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alcohol</th>
<th>Nonalcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.4 (1.3-1.5)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Race (white)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Smoke (current)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Smoke (former)</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (1.0-1.1)</td>
</tr>
</tbody>
</table>
| N=125,580 F/U 22 yrs

#### Notes
- Adjusted for BMI, body mass index calculated as weight in kilograms divided by the square of height in meters.
- Top three quintiles of alcohol intake (smoking, alcohol, coffee, alcohol intake), divided by quintiles of intake of each variable. Data are given as relative risk (95% confidence interval).
- p<0.05

---

### Associations between the Consumption of 4 or More Cups of Coffee per Day and Mortality

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any coffee</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Coffee alone</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Other sources</td>
<td>0.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>
| N=617,000 follow up 5,148,000 person years

---

*From: Coffee, Cirrhosis, and Transaminase Enzymes*  
Associations between the Consumption of 4 or More Cups of Coffee per Day and Mortality

Overall Hazards ratio = 0.88 (95% CI, 0.84 to 0.93)  
P<0.001

N=617,000  follow up 5,148,000 person years

Wake up and drink the coffee

Cirrhosis: Median Survival Based on Complications
- Compensated cirrhosis  9-12yrs
- Decompensated cirrhosis  2 years
  - Jaundice
  - Encephalopathy
  - Ascites
  - Variceal hemorrhage
- Hepatopulmonary syndrome  10 months
- Spontaneous bacterial peritonitis  9 months
- Hepatorenal syndrome
  - Type 2 (Refractory ascites)  6 months
  - Type 1 (Creatinine > 2.5mg/dL)  <6 weeks
Infections in Patients with Cirrhosis

Retrospective review of 178 studies

Mortality at 1, 3, and 12 months determined

Comparison with non-infected cohort

Infection-Related Risk of Death

<table>
<thead>
<tr>
<th>Study (publication year)</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dnoula (2003)</td>
<td>2.06 (1.04, 4.11)</td>
<td>46.0</td>
</tr>
<tr>
<td>Tan (1997)</td>
<td>1.06 (1.23, 2.59)</td>
<td>2.2</td>
</tr>
<tr>
<td>Shilam (1997)</td>
<td>4.16 (1.81, 9.37)</td>
<td>5.9</td>
</tr>
<tr>
<td>Tito (1999)</td>
<td>5.26 (2.24, 12.5)</td>
<td>11.5</td>
</tr>
<tr>
<td>Wang (1999)</td>
<td>3.29 (2.62, 32.3)</td>
<td>4.0</td>
</tr>
<tr>
<td>Tokosi (1999)</td>
<td>6.32 (3.61, 10.6)</td>
<td>4.6</td>
</tr>
<tr>
<td>BAC (1999)</td>
<td>2.49 (1.86, 6.79)</td>
<td>4.0</td>
</tr>
<tr>
<td>Bernard (1999)</td>
<td>1.39 (1.02, 1.93)</td>
<td>3.0</td>
</tr>
<tr>
<td>Wang (2000)</td>
<td>3.03 (1.97, 12.6)</td>
<td>3.0</td>
</tr>
<tr>
<td>Vivas (2001)</td>
<td>2.60 (1.35, 5.05)</td>
<td>1.6</td>
</tr>
<tr>
<td>Bonino (2001)</td>
<td>2.79 (1.47, 5.37)</td>
<td>9.6</td>
</tr>
<tr>
<td>Yonehara (2002)</td>
<td>3.50 (1.31, 9.41)</td>
<td>5.8</td>
</tr>
<tr>
<td>de Mattos (2002)</td>
<td>2.22 (1.16, 4.09)</td>
<td>7.5</td>
</tr>
<tr>
<td>Ploosder (2003)</td>
<td>2.89 (2.97, 29.7)</td>
<td>1.5</td>
</tr>
<tr>
<td>Ferreira (2006)</td>
<td>3.12 (1.55, 6.32)</td>
<td>7.1</td>
</tr>
<tr>
<td>Pinonista (2008)</td>
<td>0.78 (0.27, 26.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>3.76 (0.09, 4.66)</td>
<td></td>
</tr>
</tbody>
</table>

*HR=hazard ratio*

### Mortality Rate per 1000 Patients

- **6-11**
- **12-14**
- **15-17**
- **18-20**
- **21-23**
- **24-26**
- **27-29**
- **30-39**
- **40+**

**MELD**

- **24-26**
- **27-29**
- **30-39**
- **40+**

Immunizations

- Pneumococcal, influenza, and tetanus vaccines mandatory
- Hepatitis A and B vaccines after serologic testing for previous exposure
- Risk of inadequate antibody response associated with hepatic disease severity
- Live attenuated vaccines not contraindicated (CDC)

### Comorbid Conditions Associated with Decision Making Regarding HCV Treatment in a Large US HMO

Retrospective study using Kaiser Permanente database to compare characteristics of those treated vs. those not treated for HCV using IFN-based therapy and to identify significant predictors of not receiving treatment

<table>
<thead>
<tr>
<th>Factors Associated with NOT Receiving Treatment</th>
<th>Odds Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0.329</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>0.775</td>
<td>0.0085</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0.569</td>
<td>0.0185</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.650</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Psychosis/Bipolar</td>
<td>0.678</td>
<td>0.0051</td>
</tr>
<tr>
<td>Severe lung disease</td>
<td>0.555</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0.542</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MELD (≥12)</td>
<td>0.385</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Nyberg LM, EASL, 2014, O67

Factors associated with receiving treatment included age 45-65, male gender, cirrhosis, HIV, NAFLD, depression, prior liver transplant

- 15% (7,945/51,984) of the total number of patients identified with HCV were treated
- 17% (5,233/32,283) of the study population were treated
- 42% of the total study population were IFN-eligible or intolerant
- 50% of the study population had a significant comorbid illness

15% were treated, 85% were not treated
### Risk of Statin Hepatotoxicity

<table>
<thead>
<tr>
<th>Statin duration (yr)</th>
<th>Normal ALT</th>
<th>Abn. ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.48 ± 0.08</td>
<td>0.48 ± 0.08</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statin discontinue</th>
<th>Normal</th>
<th>Abn. ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10.7%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>↑ AST/ALT</th>
<th>Normal</th>
<th>Abn. ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 xULN</td>
<td>1.7%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.002</td>
<td></td>
</tr>
<tr>
<td>&gt;0.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>↑ AST/ALT</th>
<th>Normal</th>
<th>Abn. ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 xULN</td>
<td>0.2%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.6</td>
<td></td>
</tr>
</tbody>
</table>

(Chalasani Gastroenterology 2004)

### Pravastatin in patients with chronic liver disease

- **Inclusion**
  - LDL > 100 mg/dl
  - Chronic liver disease: 64% NAFLD, 24% HCV, 12% other

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=160)</th>
<th>Placebo (n=160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ↓ T cholesterol</td>
<td>20%*</td>
<td>3%</td>
</tr>
<tr>
<td>% ↓ LDL</td>
<td>31%*</td>
<td>3%</td>
</tr>
<tr>
<td>% ↑ ALT &gt; 2X BL</td>
<td>7.5%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Time to ALT ↑ and cumulative % at week 36 similar

(Hepatology 2007 Nov; 46:1453)

### Advice to the National Lipid Association Safety Task Force from the Liver Expert Panel

1. Asymptomatic elevations in aminotransferases are a class effect of statins and do not indicate liver dysfunction
2. Liver failure causing death or hospitalization or requiring liver transplantation is very rare with statins
3. Current evidence does not support routine monitoring of liver enzymes and liver biochemistries in patients receiving statins
4. Presence of chronic liver disease and Child's A cirrhosis should not be considered a contraindication for statin use
5. Current evidence supports use of statins to treat hyperlipidemia in patients with nonalcoholic fatty liver disease and NASH
**Pharmacotherapy**

- Acetaminophen usually OK (< 2 grams daily)
  - Avoid use of NSAIDs, aspirin with decompensation, ascites
- Antibiotics
  - Fluoroquinolones, cephalosporin OK
- Oral hypoglycemic agents if cirrhosis is compensated; insulin if decompensated

**Nutrition**

- Protein-calorie malnutrition
- Frequent, high-calorie small meals
- Bedtime snacks
- Check fat-soluble vitamins / zinc, and replace accordingly

**Fatigue**

- Major factor in reduced quality of life
  - Can be a manifestation of encephalopathy
  - Co-morbidities (obesity, depression, sleep apnea)
- Exclude medical causes (anemia, thyroid disease)
- No effective medical therapy identified
Depression

• Prevalence rate of 30%-40%  
• Pharmacologic therapy is safe  
SSRI  
Mirtazapine

Muscle Cramps

• Major factor in poor quality of life  
  • Independent of age, disease severity, diuretic use  
• No evidence-based therapy available  
• Antioxidants ineffective

Cirrhosis: Sexual Dysfunction

Mechanisms Unclear

Sildenafil is safe in compensated cirrhosis.  
World J Gastroenterol 2008; 14(40): 6208-6212