Fibrosis Assessment
End Stage Liver Disease

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UCSF
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Liver Fibrosis Assessment

- Clinical correlates- only useful in late stages
  - Cirrhosis with portal hypertension
    - Low platelets, spider nevi, splenomegaly, ascites
- Liver Biopsy
- Imaging
  - Ultrasound- only of value in cirrhosis with portal hypertension
  - Elastography
- Serum markers
METHODS TO STAGE FIBROSIS

• Liver Biopsy with Histologic Evaluation
  – Percutaneous
  – Laparoscopic
  – Transjugular

• Elastography
  – Transient elastography- FibroScan
  – Acoustic Radiation Force Impulse (ARFI)
  – MRI

• Serum Biomarkers
  – Common Tests
  – Laboratory/ Commercial tests
Liver Biopsy Size in 355 Bx: The smaller the piece the milder the disease: Colloredo J Hep 2003

<table>
<thead>
<tr>
<th>Length of specimen</th>
<th>&gt; 3cm</th>
<th>1.5 cm</th>
<th>1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td># Portal Tracts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complete</td>
<td>22.4 ± 4.9</td>
<td>10.3 ± 2.2</td>
<td>6.4 ± 1.2</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>49.7%</td>
<td>60.2%</td>
<td>86.6%</td>
</tr>
<tr>
<td>Moderate</td>
<td>38.5%</td>
<td>39.1%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Severe</td>
<td>11.8%</td>
<td>0.6%</td>
<td>0</td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (F0-1)</td>
<td>59%</td>
<td>68.3%</td>
<td>80.1%</td>
</tr>
<tr>
<td>Moderate (F2)</td>
<td>29.8%</td>
<td>24.2%</td>
<td>14.9%</td>
</tr>
<tr>
<td>Severe (F3-4)</td>
<td>11.2%</td>
<td>7.4%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>
HCV Cure: Paired Biopsy Studies
Morphometric Analysis of Fibrosis

- Follow-up CP-A patients treated with IFN-based therapy and achieved SVR
- Biopsy done a median of 61 mos (range, 48-104) post-SVR

Area of fibrosis decreased in 89%, increased in 8% and unchanged in 3%

D'Ambrosio R. Hepatology. 2012;56:532-43
Transient Elastography
Elastography: Fibroscan

2.5 kPa

- Absent or mild fibrosis (Metavir F0-F1)
- Significant fibrosis (F2)
- Severe fibrosis (F3)
- Cirrhosis (F4)
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 >3.5cm
• Approved in U.S. 4-2013
  – XL and P probes

Problems with fibroscan

False positive
• Acute inflammation
• Rejection
• Cholestasis
• Hepatic congestion
• Non fasting state
• alcohol

Hard to estimate
• Too fat
• Too thin
• Vessels
Gray scale images, what they mean & what to do

A striated liver
GOOD

B lung
Move probe
down 1 intercostal
space or scan on exhalation

C fat
Change to XL
probe

D vessel
Reposition

E Breathing
Often seen when pt
talking
Probe too low: move up
MRI Elastography

- Similar to Fibroscan but can demonstrate the liver stiffness in the WHOLE organ and is colour coded
- Small studies ~100
- Can distinguish Child-Pugh A cirrhosis from other grades to be 93% sensitive and 82% specific

Ito et al AJR Am J Roentgenol 1999; 173:591–596
Liver Stiffness Values Require Different Thresholds to Stage Fibrosis after Cure

Paired liver biopsy and liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography:

- N = 121 with SVR (5.9 y post-cure)
- N = 215 with chronic HCV

- LS values lower in SVR vs chronic HCV for each stage of fibrosis
- Higher ARFI with higher ALT
- Lower ARFI with longer time from cure

New cut-offs to defined stage in patients with SVR are needed

Tachi Y. APT. 2016;44:346-55
Noninvasive Testing after SVR

- Noninvasive tests to stage liver fibrosis have not been validated in patients after SVR
- Risk of underestimating severity of fibrosis by relying on post-SVR test results (APRI, FIB-4, LSM)
- Pending additional studies, management of patients must be based on PRE-treatment fibrosis staging
- Elastography evaluation post-SVR more useful to assess for progression than regression

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  – Laboratory/ Commercial tests
Fibrosis Tests

- Markers of liver injury ALT/AST APRI FIB-4
  - Increased with inflammation
- Markers of hepatic function
  - PT, Alb, Alfa 2 macroglobulin, haptoglobin
- Markers of Portal HTN- platelets
- Markers of matrix production or degradation
  - Procollagen, hyaluronic acid, TIMP’ S, MMP’ s, YKL- 40
  - Enhanced liver fibrosis ELF
Serum ALT Levels: An Imperfect Marker of Liver Disease Severity

- Distribution of hepatic fibrosis in 95 HCV-infected patients

Natural History of ESLD

- Increasing liver fibrosis
  - Chronic liver disease
  - Compensated cirrhosis
  - Development of HCC
  - Decompensated cirrhosis
  - Death

- HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis

Garcia Tsao CCO Hepatitis.com 2008
Survival Time from First Liver Decompensation to Death in HCV

- Death during study
  - 366/1037 HCV
  - 100/180 HIV/HCV
- Risk factors for death:
  - HIV
  - Baseline CTP
  - MELD >13
  - Age

Pineda, Hepatology 2005
Natural history of ESLD

• Transition to decompensated cirrhosis: 5% to 7% of patients per year.
• Best predictor of decompensation: hepatic venous pressure gradient (HVPG) > 10 mm Hg
• HCC
  – can trigger decompensation
  – predictor of death in decompensated cirrhosis
• Tools for predicting disease severity and death in decompensated cirrhosis
  – Child-Turcotte-Pugh (CTP) score
  – Model for End-Stage Liver Disease (MELD) score

D’Amico 2006
### Child-Pugh-Turcotte Score

<table>
<thead>
<tr>
<th>Points</th>
<th>1 (normal)</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>slight</td>
<td>mod</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>PT</td>
<td>&lt;4 secs ↑</td>
<td>4-6 secs</td>
<td>&gt;6 secs</td>
</tr>
<tr>
<td>or INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

A: 5-6; B: 7-9; C: > 9
MELD: Model for End-Stage Liver Disease

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>MELD</td>
<td>10</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>
Risk of Bleeding from Esophageal Varices

Cirrhosis

Prevalence
35%-80%

Risk of Bleeding
25%-40%

Survive
50%-70%

Die
30%-50%

Rebleed
70%
Variceal Surveillance

All cirrhotics require 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
- Nonselective Beta-blocker prophylaxis

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

HVP to Predict Portal Hypertension

Robic J Hep 2011: 100 pts followed for 2y: ETOH 38; v hep 28: 75 F3-4

71 events in 41 patients
LS to predict Portal Hypertension

No need for EGD if
- <20 kPa
- Platelets >150k
Treatment of ascites

• Diuretic-responsive ascites
  – Sodium restriction
  – Spironolactone (75-100 mg) and furosemide (20-40 mg)

• Refractory ascites
  – Large volume paracentesis with 25% albumin (50 cc/L)
  – TIPS- higher OLT free survival, higher PSE
  – TIPS HVP <12 mm Hg
  – Albumin, midodrine and octreotide- vasoconstriction

• Hyponatremia
  – Fluid restriction, vasopression 2R antagonists, midodrine
6 mos Survival with Sodium <135

![Survival curve for serum sodium levels](image)

Jenq J Clin Gast 2010: 126 cirrhotics
Hepatorenal syndrome (HRS)

- Acute renal failure occurs in 14% to 25% of hospitalized patients with cirrhosis
- Most commonly prerenal failure (accounting for 60% to 80% of the cases)
  - HRS is a form of prerenal failure
- Then acute tubular necrosis (20% to 40%)
Hepatorenal syndrome

- results from vasodilatation and marked reduction in effective arterial blood volume leading to renal vasoconstriction
- occurs in patients with refractory ascites and/or hyponatremia.
- **Type 1 HRS**: rapidly progressive renal failure in 2 weeks
  - with doubling of serum creatinine to a level > 2.5 mg/dL
  - or halving creatinine clearance to < 20 mL/min
  - Prognosis: < 50% survival at 1 month
HRS-contd

• **Type 2 HRS**: slowly progressive
  – increase in serum creatinine level to > 1.5 mg/dL
  – a creatinine clearance of < 40 mL/mi
  – or a urine sodium < 10 mEq/d
  – associated with ascites that is unresponsive to diuretic medications
  – median survival: ~ 6 months
Spontaneous bacterial peritonitis (SBP)

- Most common type of bacterial infection in hospitalized cirrhotic patients
- Clinical suspicion:
  - unexplained encephalopathy, jaundice
  - worsening renal failure
  - <50%: fever, abdominal pain or tenderness, and leukocytosis
- Diagnose: tap ascites: WCC>500, PMN > 250 cells/mm$^3$
  - Place ascites in blood culture bottles
- Start treatment immediately before culture results
Hepatic Encephalopathy

• Precipitants
  – Infection - especially SBP or UTI
  – Bleeding
  – Electrolyte imbalance
  – Portal vein thrombosis
  – Worsening liver disease
  – HCC
Hepatic Encephalopathy

- Treatment aims to reduce production of ammonia from the colon through
  - nonabsorbable disaccharides
    - lactulose, lactitol, and lactose
  - nonabsorbable antibiotics
    - neomycin, rifaximin
  - Protein restriction promotes protein degradation and, if maintained for long periods, worsens nutritional status and decreases muscle mass
    - No longer recommended
Indications for Liver Transplantation

- Development of decompensation (synthetic dysfunction, MELD >12, ascites, variceal, HE) in patients with cirrhosis
- Decompensation is associated with a median survival of only 1.5 years
- HCC that is confined to the liver by Milan criteria: 1 lesion <5 cm or 3 lesions < 3 cm
  - UCSF criteria ≤6.5 cm total
- Adherent, no drug use, alcohol, adequate support
- No extrahepatic disease
Summary

- Monitor for varices in cirrhosis
  - Elastography to assess severity of fibrosis/cirrhosis
  - Monitor varices with EGD
- HCC monitor every 6 months imaging and AFP
- Consider OLT when first decompensation occurs
  - Ascites and hyponatremia
  - Hepatorenal syndrome
  - Hepatic encephalopathy