TOPICS

- Liver Injury
- Assessment of Hepatic Fibrosis
- Complications of Cirrhosis
- When to Refer to Transplant
- What to Manage Before the Hepatologist Takes Over

Hepatic Fibrosis is the Liver's Wound Healing Response to Many Chronic Injuries

- Hepatitis Viruses
- Inherited Metabolic Disorders
- Excess Vitamin A
- NASH
- Alcohol
- Drugs
- Cholestatic Disorders
- Immune Disorders
CLASSIFICATION OF INJURY PATTERNS

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Cholestatic</th>
<th>Mixed</th>
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<tbody>
<tr>
<td>ALT</td>
<td>Bilirubin</td>
<td>All with Similar Abnormalities</td>
</tr>
<tr>
<td>AST</td>
<td>Alkaline</td>
<td>GGT</td>
</tr>
</tbody>
</table>

R score: ALT/Alk Phos expressed as multiple of upper limit of normal range
R<1.25=Hepatocellular; R=1.25-4.99=Mixed; R>4.99=Cholestatic

Danan et al. J CLIN EPID, 1993

ACUTE VS. CHRONIC

• Acute
  – Resolved within 6 months of onset or
  – Resolved following drug discontinuation

• Chronic
  – Persists beyond 6 months

TOXICITY GRADES

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DEFINITION</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal-1.24 x ULN</td>
</tr>
<tr>
<td>1</td>
<td>1.25-2.5 x ULN</td>
</tr>
<tr>
<td>2</td>
<td>2.5-5 x ULN</td>
</tr>
<tr>
<td>3</td>
<td>5-9.99 x ULN</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10 x ULN</td>
</tr>
</tbody>
</table>
HY’s RULE
• Bilirubin >3 mg/dL AND AST > 20 x ULN
• When present, chance of death from fulminant hepatic failure or need for liver transplantation = 10%-50%
• Validated by Bjornsson et al (Hepatology August 2005;42(2):481-9)

THE HYPERSENSITIVITY RULE
• ALT > 2 x ULN AND Hypereosinophilia
• Defines presence of hypersensitivity (immune mediated) liver injury

Updated ALT Ranges

MEN ≥ 30
WOMEN ≥ 19
ASSESSMENT OF HEPATIC FIBROSIS

Hepatic Fibrosis

- Type of injury determines pattern
- For most diseases, distribution is homogenous
- Inflammation is transient, fibrosis is fixed
- Cirrhosis is a histological diagnosis, not a clinical diagnosis unless decompensation has occurred

Fibrosis Stages in Hepatitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ishak</th>
<th>Metavir</th>
<th>Batts-Lu</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Normal (Stage 0)
How Accurate is the Biopsy

- Will Never Overstage Disease - 50% less variation than non-invasive tests
- Highly Reliable IF Done Correctly
  - Persico et al. AM J GASTRO 2002 - Minimal variation between Paired biopsies of Left and Right lobes when bx > 25 mm
- High concordance between/within review of trained pathologists
### Pathologic Staging of Fibrosis

**Size vs Accuracy – 161 Patients**

<table>
<thead>
<tr>
<th>Be Length</th>
<th>Cirrhosis*</th>
<th>No Cirrhosis</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 cm</td>
<td>11.2%</td>
<td>68.8%</td>
<td>1.00</td>
<td>1.00</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>7.4%</td>
<td>92.6%</td>
<td>1.00</td>
<td>0.96</td>
<td>96%</td>
</tr>
<tr>
<td>1.0 cm</td>
<td>4.9%</td>
<td>95.1%</td>
<td>1.00</td>
<td>0.93</td>
<td>94%</td>
</tr>
</tbody>
</table>

*Be Length: Bx Length

**Signif Fibr***

<table>
<thead>
<tr>
<th>Be Length</th>
<th>Signif Fibr</th>
<th>No Signif Fibr</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 cm</td>
<td>41.0%</td>
<td>59.0%</td>
<td>1.00</td>
<td>1.00</td>
<td>100%</td>
</tr>
<tr>
<td>1.5 cm</td>
<td>31.6%</td>
<td>68.4%</td>
<td>1.00</td>
<td>0.86</td>
<td>91%</td>
</tr>
<tr>
<td>1.0 cm</td>
<td>19.8%</td>
<td>80.2%</td>
<td>1.00</td>
<td>0.74</td>
<td>78%</td>
</tr>
</tbody>
</table>

**HALT C Pathology Committee Concordance Study**

- **Concordance Study**
  - (Ave. AUC = 0.938)

**Slide Courtesy of Z. Goodman, MD, PhD**

- **Sensitivity vs Specificity**
  - 200 Liver biopsies
  - 70 > 1.5 cm
  - 70 < 1 cm
  - 60 fragmented
  - 12 Pathologists

**Fibrosis Concordance Study** - (Ave. AUC = 0.938)

**Transient Elastography**

- **Probe**
  - **LB = 108**
Elastography: HCV

Affected by weight, access of probe (2 cm), steatosis

MRI Elastography

- Similar to transient elastography but can demonstrate the liver stiffness in the WHOLE organ and is colour coded
- Can distinguish Child-Pugh grade A cirrhosis from other grades to be 93% sensitive and 82% specific

Magnetic Resonance Elastography

FIBROSIS MARKERS
Predictive Model

Imbert-Bismut, LANCET, 2001

FIB-4

• Uses easily acquired information
  – Age
  – Platelet Count
  – AST
  – ALT
• Formula
  – AGE x AST
  – PLT x ALT
• Interpretation: <1.45 is F0/1 or >3.25 is F3/4
  with 65% Positive Predictive value

Sterling RK et al, HEPATOLOGY 2006

MISCLASSIFICATION RATE
Non-Invasive Tests

Boursier J et al. LIVER INT, 2009
Rapid Progression of Liver Disease in HIV/HCV-Coinfected Patients

- Prospective study of fibrosis progression in 67 coinfected patients
- 2 biopsies; median time between biopsies was 2.84 years

Patients with Mild Fibrosis (F1) on First Biopsy

- >25% of patients with mild fibrosis on initial biopsy had ≥2 stage progression in fibrosis score

Change in Ishak Score From First to Second Biopsy

Fattovich et al., Gastroenterology 1997; 112:463
HEPATIC DECOMPENSATION

- Ascites
  - Hepato-Renal Syndrome (HRS)
  - Hepatic Hydrothorax
  - SBP
- Encephalopathy
- Bleeding Varices
- Coagulopathy (PT >3 seconds>control)

Clinical Staging of Cirrhosis:
Child-Turcotte-Pugh Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Bilirubin (mg/dL)</th>
<th>Albumin (g/dL)</th>
<th>PT (INR)</th>
<th>Hepatic Encephal.</th>
<th>Ascites (grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;2</td>
<td>&gt;3.5</td>
<td>&lt;1.7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2.0–3.0</td>
<td>2.8–3.5</td>
<td>1.8–2.3</td>
<td>1–2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>&gt;3</td>
<td>&lt;2.8</td>
<td>&gt;2.3</td>
<td>3–4</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Child Class
- A: 5–6
- B: 7–9
- C: >9


MELD

- MODEL FOR END-STAGE LIVER DISEASE
  - Bilirubin
  - Creatinine
  - INR
- Used to predict mortality and time for OTL Tx
  - Example: Creatinine 1.6; Bill 1.4; INR 1.6
  - MELD=17
  - Estimated 3 month mortality: 18%
LIVER TRANSPLANTATION
When to Refer

- Any hepatic decompensation
  - Ascites
  - Encephalopathy
  - Variceal bleeding
- MELD >10
- HCC
WHEN TO TAP ASCITES

- First time ascites discovered
- Every time patient is admitted to hospital
- With all changes in status

Management of Ascites

First-Line Therapy
- Tense ascites
  - Refractory Paracentesis
  - Sodium restriction (<2 gm/24 hrs) and Diuretics
  - Non-tense ascites

Second-Line Therapy
- Repeated Large volume Paracentesis (LVP)
- TIPSS
- Liver Transplantation

Treatments for refractory ascites:
- Spironolactone 50 mg/day, furosemide 20 mg/day or bumetanide 1 mg/day
- Titrate stepwise to a maximum of 400 mg spironolactone/day or 160 mg furosemide/day or 4 mg bumetanide/day, as long as it is tolerated at 2-WEEK INTERVALS
HEPATIC HYDROTHORAX

VARICES

Cirrhosis Prevalence 35%-80%
Risk of Bleeding 25%-40%
Die 30%-50%
Survive 50%-70%
Rebleed 70%
Risk of Bleeding: Esophageal Varices
VARICEAL SURVEILLANCE

- **EGD**
  - No varices
  - Small varices (<5 mm)
    - Child B/C
  - Medium or large varices
    - Non-selective beta-blocker prophylaxis
    - Child Class A: no red wales beta blockers
    - Child class B/C: red wales beta blockers, or band ligation

Repeat endoscopy in 3 years (well compensated); in 1 year if decompensated.

No beta-blocker prophylaxis.

Small varices (<5 mm), child B/C

Medium or large varices

- Non-selective beta-blocker prophylaxis
- Child Class A: no red wales beta blockers
- Child class B/C: red wales beta blockers, or band ligation

HEPATIC ENCEPHALOPATHY

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

- **Rifaximin**
  - Placebo

Proportion of Patients Without Breakthrough HE (%)

- Rifaximin: 77.9%
- Placebo: 54.1%


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

P<0.001
MHE: Associated With Motor Vehicle Crashes
Predictive Accuracy of Diagnostic Testing

Percentage of patients with crashes by SELF-REPORT according to MHE status and diagnostic test (n=120)

Percentage of patients with crashes by DOT according to MHE status and diagnostic test (n=167)

P=0.0004
P=0.4
P=0.004
P=0.37

Positive
Negative
Positive
Negative


HCC SURVEILLANCE

• Ultrasound
  – Every 6 months
  – Subjective, experience matters

• AFP and related markers
  – Not recommended by AASLD
  – Used by most hepatologists

SUMMARY

• HCV is ALSO a Liver Disease
  – Ask Whether Advanced Fibrosis is Present
  – If Yes, Start Surveillance for
    • Varices (EGD)
    • Ascites (US)
    • HCC (US)

• CONTACT HEPATOLOGIST EARLY WHEN ANY SIGN OF DECOMPENSATION IS PRESENT
• MANAGE THE COMPLICATIONS!!