LIVER

Update on Staging of Fibrosis and Cirrhosis

Staging and Liver Fibrosis

Two important concepts for consideration:
- **Stage is more than histologic fibrosis**
  An integrated clinical/pathophysiologic approach is needed to accurately stage the disease
- **Cirrhosis is not the “end” of the story:**
  Histologic scoring may need to evolve to identify regression or remodeling of cirrhosis, and evaluate for very advanced nonreversible, or “end-stage” cirrhosis, based on degree of fibrosis

Stage is more than liver fibrosis

Clinical Modalities to Stage Chronic Liver Disease
Measurements of liver function and pathophysiology include the following among others:
- Transient elastography (Fibroscan ®)
- Clinical scores including Child-Pugh’s and MELD scores
- Serum markers and panels, such as Fibrotest ®, Hepascore®, FibroSpect®, ELF score, AAR, APRI, etc.
- Hepatic venous pressure gradient (HVPG)
Going “Beyond Cirrhosis”

Proposal from the International Liver Pathology Study Group

Concept: Cirrhosis has historically implied end-stage disease with the imminent death of patient as there was no cure and no treatment

But now, many patients remain compensated, and function improves with therapy, particularly notable in chronic viral hepatitis

Going “Beyond Cirrhosis”

Proposal: It may be time to put aside the “one-term-fits-all” approach, and stage liver disease as related to etiology and pathophysiology

Should we drop the term cirrhosis or at least recognize different “degrees of cirrhosis” for a better method of describing advanced liver injury based on etiology and patterns of injury??

Assessment of Advanced Chronic Liver Disease

Adapted from Figs 1, Beyond Cirrhosis (AJCP 2012) and Exploring Beyond Cirrhosis (Hepatol 2012, 56:779)

Patient with chronic liver disease

Clinical workup
- Assessment or reassessment of etiology, comorbidities or cofactors
- Assessment of severity
  - Laboratory tests
  - Transient elastography
  - HVPG, etc

Liver biopsy with advanced stage of chronic disease
- Activity of disease
- Features of regression
- Presence of other diseases
- Risk factors for malignancy

Clinicopathologic correlation

Final diagnosis as the sum of:
- Etiology
- Disease activity
- Risk for HCC
- Stage
  - Advanced stage with no complications
  - Advanced stage with complications
  - Advanced stage with regression
  - End stage

Staging and Liver Fibrosis

Liver biopsy is still considered an important component of staging

Questions:
- How do we use the liver biopsy in the best way?
- What are the histological aspects we need to consider?
An important starting point is the adequate biopsy!!

Current acceptable recommendations
- 5 portal areas minimum, probably >11 for optimal value
- And/or approx 2 cm core of reasonable width (17 gauge or larger)

Other considerations
- Etiology of the injury
- Pattern and degree of histological injury
- Treatment effects resulting in remodeling, or regression, of fibrosis
  - What changes are reversible?

Etiology related to fibrosis degree and patterns

<table>
<thead>
<tr>
<th>Etiology</th>
<th>HBV</th>
<th>HCV</th>
<th>AIH</th>
<th>NASH</th>
<th>ASH</th>
<th>PBC</th>
<th>PSC</th>
<th>HHC</th>
<th>WD</th>
<th>CVOO</th>
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<tbody>
<tr>
<td>Fibrosis ranking</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>NA</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>NA</td>
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<tr>
<td>Regression or remodel</td>
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<td>Centrizonal or sinusoidal</td>
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<td>fibrosis prominent pattern</td>
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<tr>
<td>Portal-based fibrosis</td>
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<td>++</td>
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Fibrosis ranking on explanted liver, 1= most fibrosis, 3= least fibrosis
AIH= autoimmune hepatitis; NASH= nonalcoholic steatohepatitis; ASH= alcoholic steatohepatitis; PBC= primary biliary cirrhosis; PSC= primary sclerosing cholangitis; HHC= hereditary hemochromatosis; WD= Wilsons disease; CVOO= primary types of chronic venous outflow obstruction
### Histological Aspects

**Etiology related to fibrosis degree and patterns**

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</tr>
<tr>
<td>Regression or remodel evidence</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>NA</td>
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<td>NA</td>
</tr>
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#### Patterns of Fibrosis

**Two major patterns for early scarring of the liver**

**Portal-based Fibrosis**
- Injury begins in periportal area

**Central-based Fibrosis**
- Injury begins in centrilobular zone

Fibrosis ranking on explanted liver, 1= most fibrosis, 3= least fibrosis

AIH= autoimmune hepatitis; NASH= nonalcoholic steatohepatitis; ASH= alcoholic steatohepatitis; PBC= primary biliary cirrhosis; PSC= primary sclerosing cholangitis; HHC= hereditary hemochromatosis; WD= Wilsons disease; CVOO= primary types of chronic venous outflow obstruction

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<td>1</td>
<td>2</td>
</tr>
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<td>Regression or remodel evidence</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>NA</td>
<td>NA</td>
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#### Portal-Based Fibrosis Pattern

**Major associated lesions**

- **Chronic hepatitis**
  - Hepatitis B, C
  - Autoimmune hepatitis
  - Alpha-1-antitrypsin and Wilsons disease

- **Biliary Disease**
  - PBC, PSC, Chronic obstruction

- **Hemochromatosis**
**Portal-based Fibrosis: Chronic Hepatitis**

**Chronic Hepatitis C: Cirrhosis, rounded nodules**

**Chronic Biliary Disease**

Wider fibrous bands with more ductular reaction can occur in comparison to chronic hepatitis B or C

**Chronic Biliary Disease: Jigsaw fibrosis**
Fibrosis Scoring of Chronic Hepatitis

Practical tips and common problems

• First step: Use a system that is
  – Simple
  – Reproducible
  – Useful in clinical setting

Commonly used Grading/Staging systems

• Scheuer/Batts-Ludwig/Tsui:
  – Grade and Stage on scale 0-4
  – Simple, reproducible, validated clinically

• METAVIR:
  – Grade 0-3, Fibrosis 0-4
  – Simple, reproducible, validated clinically

• Ishak, et al:
  – Grades four categories of activity/necrosis, 0-4 or 0-6
    • Generally considered too complex, not necessary
  – Staging 0-6
    • Preferred in many clinical trials
    • Still reproducible and validated clinically

Scheuer / Batts-Ludwig / Tsui
Grading and Staging

• Simple, reproducible, validated
• Essentially same methodology so interchangeable for the most part
• Most commonly used day-to-day in USA and validated for studies as well
• #1 Recommended for typical usage for grading

Scheuer/Batts,Ludwig/Tsui
Fibrosis scoring for Chronic Hepatitis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis, normal amount of connective tissue</td>
</tr>
<tr>
<td>1</td>
<td>Portal/perportal fibrosis</td>
</tr>
<tr>
<td>2</td>
<td>Septal fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>Bridging fibrosis with architectural distortion.</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis, probable cirrhosis</td>
</tr>
</tbody>
</table>
METAVIR
2-letter, 2-number system similar to Scheuer
Used extensively in France

F = fibrosis
• F0 = no fibrosis
• F1 = portal fibrosis without septa
• F2 = portal fibrosis with rare septa
• F3 = numerous septa, not cirrhosis
• F4 = cirrhosis

Ishak, et al: Fibrosis Scoring System
(Grading system typically not used due to complexity)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Expansion of some portal areas with or without septa</td>
</tr>
<tr>
<td>2</td>
<td>Expansion of most portal areas with or without septa</td>
</tr>
<tr>
<td>3</td>
<td>Expansion of most portal areas with occasional portal to portal bridging</td>
</tr>
<tr>
<td>4</td>
<td>Expansion of portal areas with marked bridging (portal-portal and/or portal-central)</td>
</tr>
<tr>
<td>5</td>
<td>Marked bridging with occasional nodules (incomplete cirrhosis)</td>
</tr>
<tr>
<td>6</td>
<td>Cirrhosis, probable or definitive</td>
</tr>
</tbody>
</table>

Portal-Based Fibrosis:
Which scoring system to use?
• All three systems are reasonable
• Scheuer and Batts/Ludwig 0-4 scales works well for chronic hepatitis B and C and is simple
  — Validated by many studies

Limitations:
• Doesn’t apply to centrizonal liver disease
• Mixed etiologies (Example: Alcohol + HBV)
• Doesn’t go “beyond cirrhosis”
  — No differentiation between early, compensated versus advanced, end-stage decompensated cirrhosis
• Doesn’t evaluate for remodeling/regression

From Theise ND, Mod Pathol 2007, 20(supple 1):S3-14; Also published in MacSween’s Pathology of the Liver
CASE EXAMPLES

Practice staging using Scale 0-4

Fibrosis Stage?

1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis: Stage?
Fibrosis stage?

1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis: Stage ?
1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis stage?

1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis score?

Fibrosis: Stage?
1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis score?

1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis score?

1. Stage 1
2. Stage 2
3. Stage 3
4. Stage 4
5. Stage 0

Fibrosis: Stage ?

Fibrosis: Stage ?
Fibrosis score?

- Stage 1: 34%
- Stage 2: 56%
- Stage 3: 3%
- Stage 4: 8%
- Stage 0: 0%

Centrizonal Fibrosis Pattern

Major associated lesions
- Chronic steatohepatitis
- Nonalcoholic types (NASH)
- Alcoholic types (ASH)
- Chronic venous outflow obstruction

NASH: Centrizonal Fibrosis with focal dense scarring

Alcohol: Central vein obliteration
Alcohol: Central vein and extensive sinusoidal obliteration

Sinusoidal Fibrosis in chronic venous outflow obstruction (chronic heart failure), Trichrome

Budd-Chiari Syndrome: Centrizonal Fibrosis and Ductular Metaplasia of hepatocytes (probably an ischemic effect)

Chronic Heart Failure: Centrizonal Fibrosis
**Fibrosis Scoring (Brunt E, et al, 1999)**

Designed for NASH

<table>
<thead>
<tr>
<th>Score</th>
<th>Histologic Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Zone 3 sinusoidal, focal or extensive</td>
</tr>
<tr>
<td>2</td>
<td>Zone 3 as above and focal/extensive periportal fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>Same as 1 or 2 with bridging fibrosis from zone 3-1 with nodular change</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

**Fibrosis Scoring - NASH**

(Kleiner, Brunt et al, including Ferrell, 2005)

<table>
<thead>
<tr>
<th>Score</th>
<th>Histologic Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1a</td>
<td>Zone 3 sinusoidal, seen on trichrome</td>
</tr>
<tr>
<td>1b</td>
<td>Zone 3 sinusoidal, seen on H&amp;E</td>
</tr>
<tr>
<td>1c</td>
<td>Portal/Periportal only</td>
</tr>
<tr>
<td>2</td>
<td>Zone 3 and periportal fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>Bridging fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

Kleiner et al, Hepatol 41:1313-1321, 2005

**Central-based Fibrosis**

*Which scoring system to use?*

- Kleiner (NASH CRN) system covers broader spectrum for Stage 1 than older Brunt methodology but both cover most current demands

**Limitations**

- Problems with stage 2 with only early centrizonal scarring combined with periportal scarring: many stage 1 lesions may be higher stage clinically
- Doesn’t account for mixed portal/central lesions
- Doesn’t go “beyond cirrhosis”
- Doesn’t evaluate for remodeling

**Problem areas: Mixed etiologies could mean mixed patterns**

- Could use combination of Kleiner and Scheuer or Batts/Ludwig and Kleiner for early stages 1 and 2

**Limitations**

- Doesn’t account for more advanced lesions scored in 3-4 range or “beyond cirrhosis”
**NASH + HCV or HBV**

**NOTE Pattern of disease locations**

**PORTAL**: favors chronic hepatitis
- Portal-based chronic inflammation, fibrosis, and interface hepatitis
- HBV or HCV markers

**CENTRAL**: favors steatohepatitis
- Centrizonal fat, fibrosis, ballooned cells, inflammation associated with fat
- Risk factors for NASH/ASH

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**NASH and HCV**

Centrizonal and Periportal fibrosis

**How to stage?**

- **Stage separately for earlier stages if possible**
  - **NASH**: Brunt or Kleiner stage
    - Case example
      - if all fibrosis due to NASH, Stage 2 NASH
      - If periportal likely due to HCV, then Stage 1 NASH
  - **Viral hepatitis**: Do not include central fibrosis
    - Scheuer or Batts/Ludwig stage 1 or 2
    - Note prominent pattern or combination of patterns as centrizonal or portal if possible
NASH + HCV or HBV STAGING

- **Later stages:** *Stage combined etiologic patterns as bridging or cirrhosis*
  - NASH stage 3 or 4 or Scheuer 3 or 4
- Note if both centrizonal, portal patterns are present, and if possible, most prominent pattern
- Note any difficulties of determining etiologic cause of all fibrosis to communicate the message that both entities could have contributed to stage

NEW: Modified Laennec Scoring System

**Features:**
- Does not use portal-based versus central-based pattern of scarring as a primary definition so could be used for mixed lesions
- 6 stages and 6 scores
  - 3 for pre-cirrhotic conditions as in the 0-4 methodologies
  - Adds 2 more stages and scores for cirrhosis.
- Makes a distinction between stage and score
Modified Laennec Scoring System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Name</th>
<th>Criteria (as slightly modified by LF)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
<td>No definite fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Minimal fibrosis</td>
<td>No septa or rare thin septum; may have portal expansion or mild sinusoidal fibrosis</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Mild fibrosis</td>
<td>Occasional thin septa; may have portal expansion or mild sinusoidal fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Moderate fibrosis</td>
<td>Moderate thin septa; up to incomplete cirrhosis (thin bridging OK)</td>
<td>3</td>
</tr>
<tr>
<td>4A</td>
<td>Cirrhosis, mild definite, or probable</td>
<td>Marked septation with rounded contours or visible nodules</td>
<td>4</td>
</tr>
<tr>
<td>4B</td>
<td>Cirrhosis, moderate</td>
<td>At least 2 broad septa, but no very broad septa and &lt;1/2 of biopsy length composed of minute nodules (micronodules)</td>
<td>5</td>
</tr>
<tr>
<td>4C</td>
<td>Cirrhosis, severe</td>
<td>At least 1 very broad septum or &gt;1/2 of biopsy length composed of micronodules</td>
<td>6</td>
</tr>
</tbody>
</table>

Adapted from Table 2 in: Kim, et al. on staging reference list

Modified Laennec Scoring System

- Recognizes that all cirrhoses are “not equal” in that the degree of fibrosis may be related to clinical stage
- Limitations
  - Newest methodology: validated only on limited basis for cirrhosis scores
  - Doesn’t address etiology
  - Doesn’t evaluate remodeling/regression
  - Problem with the 3-4 scale as overlapping features of focal thin or thicker septa could be seen in 3 or 4b

Problems universal to all fibrosis scoring systems

- Limitation by sample size
- Mixed ETIOLOGIC lesions not addressed directly (which may relate to therapy)
- No system recognizes remodeling changes

QUESTIONS

- What lesions are potentially reversible and can remodel/regress?
- What lesions suggest remodeling/regression?

Remodeling/Regression changes

- Remodeling could be the sequelaes of necrosis, so is a broader concept than regression
- Regression is noted by decrease in fibrous tissue, so can include remodeling patterns
  - Regression is usually associated with improvement of clinical status, but can be variable in degree of improvement depending on reversibility of the liver damage
**Case Example of Remodeling in Setting of Necrosis to Fibrosis**

- Acute necrosis followed by fibrosis and chronic hepatitis
- Patient was later shown to have LKM antibody, thought to be type 2 AIH
- Responded to steroids and azothiaprine
- Liver biopsy 15 months later: shows features of thin septa

**Biopsy in acute stage with confluent centrizonal and periportal necrosis**

**Followup biopsy 15 months later with minimal inflammation and thin septa**

**Case Example of Regression**

73 year old woman
- History of Hepatitis B cirrhosis by history
- Had received antiviral therapy
  - No evidence of active viral hepatitis
Example of Regression

**Trichrome: Thin septa**
Can be difficult to identify without collagen stain

**Trichrome: Perforated septa**
Plates lined up irregularly

Should we develop a scoring system for these changes?

Example of Regression

**Reticulin:** irregular architecture includes sinusoidal changes

**Orcein for Elastic:** remnants of remote dense scarring

Regression occurs if changes are reversible.

*What is not reversible?*

- Extensive scar with elastosis and/or parenchymal extinction is unlikely to regress
  - Elastosis occurs in later stages of scarring
  - Often seen with nondegradable forms of highly-complexed collagen (such as Type III)
  - Nondegradable forms of collagen and elastosis seen in parenchymal extinction
- Extensive vascular remodeling may limit reversibility of liver function regardless of regression of fibrosis

Irreversible lesions: What is Elastosis?

**Elastosis = extensive deposits of elastic fibers**

**Trichrome Stain:** Cirrhosis, pale areas of elastic fibers

**EVG Stain:** Cirrhosis, bundles of elastic fibers
What is Parenchymal Extinction?

Parenchymal Extinction = Extensive scar

- Dark, dense fibers predominate = highly complexed collagen
- Indicates a late stage in the fibrotic process as in Laennec stage 4c
- Much of the extensive scarring probably related to either venous outflow or arterial inflow alterations and chronic ischemic effects in advanced “end-stage” cirrhosis

Vascular Alterations in Cirrhosis

Vascular collaterals/modifications develop in fibrosis and cirrhosis.
Fibrosis leads to intraparenchymal vascular resistance
Micro- and Macrocirculatory changes occur in conjunction with alterations in hepatic flow dynamics

Microcirculatory Remodeling

Example: Arterialization of Centrizonal Scars
- Increased arteries and microvessels in centrizonal scars
- Increased CD34 staining of sinusoidal endothelial cells as effect of loss of fenestrations (“capillarization”)
- Occurs prior to cirrhosis, but most prevalent in fibrosis score 4-6 by ISHAK

Arrows point to Arteries

Vascular Alterations in Cirrhosis

Vascular thrombosis secondary to cirrhosis
- Commonly seen in decompensated cirrhosis
- Organized, obliterative lesions likely not reversible!

Obliteration of portal vein

Conclusions:
- Fibrosis score requires an adequate biopsy
- Current 0-4 systems of fibrosis scoring good for chronic viral hepatitis and fatty liver when used for single etiology
- Recognize limitations of current scoring systems for mixed lesions and advanced stage of cirrhosis
- Correlate biopsy scores with clinical findings

Questions:
- Should we consider findings of advanced cirrhosis? (parenchymal extinction, elastosis)
- Should we consider identification of remodeling, or regression changes?

The real Tom Sawyer was from San Francisco

Other complications

• Ductopenia
  – PBC
  – PSC

PBC: Portal area with interface hepatitis and ductopenia

PSC: Hyaline scar at duct site

PSC: Sclerosis of large duct in hilum resulting in a large circular scar at the site of the former bile duct