Outline

• Background
  Epidemiology
• Clinical challenges
  prediction of prognosis
  noninvasive diagnosis/staging
• Treatment
Current challenges/unmet needs:

• rising prevalence of NASH
• variable prognosis/difficulty counseling patients what to expect over time
• lack of effective pharmacologic therapies
• systemic disease process with significant comorbidities (diabetes, obesity, cardiovascular disease)
Indications for liver transplantation in the United States (2001-2009)
Rising Prevalence of NAFLD in the US (NHANES data)
Spectrum of NAFLD

Steatosis

- Inflammation
- Ballooning
- Fibrosis
- Mallory’s hyaline
- Megamitochondria

Cirrhosis

- Cryptogenic
- HCC

NAFL

NASH
Perisinusoidal or portal bridging cirrhosis
## Prevalence of NAFLD/NASH

<table>
<thead>
<tr>
<th>Condition</th>
<th>NAFLD</th>
<th>NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>General adult population, US</td>
<td>17-50%</td>
<td>3-5%</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>50-70%</td>
<td>25-30%</td>
</tr>
<tr>
<td>Obese</td>
<td>70%</td>
<td>25-30%</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>90%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Musso Annals of Medicine 2011, Chalasani Hepatology 2012
Survival is decreased in NASH, but not in simple steatosis

Ekstedt Hepatology 2006
Mortality is increased in NASH compared to simple steatosis

### Table: Overall Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Odds Ratio (M-H, Fixed) 95% CI</th>
<th>Odds Ratio (M-H, Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 2005</td>
<td>5.4%</td>
<td>2.13 [0.41, 11.15]</td>
<td></td>
</tr>
<tr>
<td>Ekstedt 2006</td>
<td>14.1%</td>
<td>2.66 [1.03, 6.87]</td>
<td></td>
</tr>
<tr>
<td>Matteoni 1999</td>
<td>28.9%</td>
<td>1.36 [0.64, 2.90]</td>
<td></td>
</tr>
<tr>
<td>Rafiq 2009</td>
<td>25.2%</td>
<td>1.91 [0.90, 4.04]</td>
<td></td>
</tr>
<tr>
<td>Soderberg 2009</td>
<td>26.3%</td>
<td>1.70 [0.81, 3.59]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>100.0%</td>
<td><strong>1.81 [1.24, 2.66]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events:
- Heterogeneity: Chi² = 1.26, df = 4 (P = 0.87); I² = 0%
- Test for overall effect: Z = 3.05 (P = 0.002)

Musso Ann Med 2011
Liver-related mortality is increased in NASH compared to simple steatosis

Liver-related mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 2005</td>
<td>13.3%</td>
<td>3.71 [0.20, 70.19]</td>
<td></td>
</tr>
<tr>
<td>Ekstedt 2006</td>
<td>10.2%</td>
<td>4.21 [0.20, 89.42]</td>
<td></td>
</tr>
<tr>
<td>Matteoni 1999</td>
<td>20.4%</td>
<td>5.91 [0.71, 48.83]</td>
<td></td>
</tr>
<tr>
<td>Rafiq 2009</td>
<td>27.5%</td>
<td>7.66 [1.61, 36.52]</td>
<td></td>
</tr>
<tr>
<td>Soderberg 2009</td>
<td>28.6%</td>
<td>5.17 [1.03, 26.06]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>5.71 [2.31, 14.13]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events

Heterogeneity: Chi² = 0.27, df = 4 (P = 0.99); I² = 0%

Test for overall effect: Z = 3.77 (P = 0.0002)

Musso Ann Medicine 2011
Take home point #1

• Not all patients with fatty liver are the same-important to distinguish patients with “simple steatosis” from those with NASH
Natural History of NASH

N = 68
mean follow-up 13.7 years

16% improvement

43% stable

41% fibrosis progression

5.4% cirrhosis-related complications

Ekstedt Hepatology 2006
AASLD Liver Meeting 2013 Abstract #577 (Kleiner, et al): Natural History of Non-alcoholic Fatty Liver Disease in Adults: A Paired Biopsy Study from the NASH CRN

- n=359 patients
  - mean age 47
  - mean time between biopsies: 4.4 years (range: 1 – 17.3)

Factors associated with fibrosis progression:

- Ballooning
- Mallory-Denk bodies
- Caucasian race

**FIBROSIS CHANGE**

- No change, 128, 36%
- Regression, 103, 29%
- Progression, 128, 35%
Aim: Identify predictors of progression to advanced stage NASH

Methods:
adults enrolled in NASH CRN with paired biopsies
first biopsy fibrosis stage < 3
endpoint- progression to bridging fibrosis or cirrhosis

Compare baseline factors between progressors vs non-progressors
Abstract #602: (Brunt, et al)
Progression to bridging fibrosis in NAFLD over 4 years in the NASH CRN

• Results:  
  270 patients  
  mean 4.4 years between biopsies  
  16% with progression to bridging fibrosis/cirrhosis

• Statistically significant baseline predictors of progressors as compared to non-progressors:
  
  older age  
  higher ALT, AST, glucose  
  DM  
  metabolic syndrome
Abstract #602: (Brunt, et al)
Progression to bridging fibrosis in NAFLD over 4 years in the NASH CRN

Predictors of progression (multivariate model):

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal inflammation</td>
<td>2.14</td>
<td>1.01-4.53</td>
<td>0.047</td>
</tr>
<tr>
<td>Acidophil bodies</td>
<td>2.3</td>
<td>1.03-5.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Mallory Denk bodies</td>
<td>4.91</td>
<td>1.68-14.37</td>
<td>0.004</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>6.46</td>
<td>0.98-42.53</td>
<td>0.05</td>
</tr>
<tr>
<td>ALT</td>
<td>5.24</td>
<td>1.78-15.40</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Summary

- Patients with NASH have a variable prognosis
- Older age, metabolic syndrome, DM, and elevated ALT correlate with progression to advanced fibrosis
- Baseline histologic features aid in prediction of fibrosis progressors
- Consider liver biopsy in patients with these high risk clinical features for fibrosis staging and prognosis estimation
Diagnosis
Clinical Presentation

Asymptomatic

- liver enzyme elevation
- fatty liver on imaging
- hepatomegaly
- fatigue

Symptomatic

- Decompensated cirrhosis
- Hepatocellular carcinoma
Clinical Approach:

Abnormal LFTs

1. Rule out other causes (viral, ETOH, autoimmune)

2. Imaging: ultrasound

Fatty liver on imaging

Assess for insulin resistance (HOMA) and metabolic syndrome
rule out secondary causes of fatty liver

Consider liver biopsy for diagnosis and staging
Challenges in the Diagnosis of NASH

- Imaging does not distinguish between simple steatosis and NASH
- Aminotransferases not reliable
- Liver biopsy subject to sampling variability
- Noninvasive tests for diagnosis and staging of NASH under investigation
Noninvasive diagnosis of steatosis

**Ultrasound**
- Sensitivity 83-89%
- Specificity 93-100%

**CT**
- Sensitivity 86%
- Specificity 87%
Noninvasive diagnosis of steatosis

Magnetic Resonance Spectroscopy

A.

Transient Elastography - CAP

Sensitivity > 90%
Controlled Attenuation Parameter

A. Steatosis quantification using CAP

B. Steatosis quantification using $^1$H-MR spectroscopy

Karlas PLOS One 2014
Magnetic Resonance Elastography

Simple steatosis  inflammation without fibrosis  fibrosis

Chen Radiology 2011
MR Elastography for distinguishing NASH vs simple steatosis

<table>
<thead>
<tr>
<th>Threshold (kPa)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>2.74</td>
<td>94</td>
<td>73</td>
<td>85</td>
<td>89</td>
</tr>
<tr>
<td>2.90</td>
<td>83</td>
<td>82</td>
<td>88</td>
<td>75</td>
</tr>
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</table>

AUC = 0.93

Chen Radiology 2011
Figure 2. Distribution of fibrosis and MR elastography readings for the entire cohort.
Sensitivity: 0.86 (0.65-0.97)
Specificity: 0.91 (0.83-0.96)
PPV: 0.68 (0.48-0.84)
NPV: 0.97 (0.91-0.99)
Noninvasive scoring systems

1. NAFLD Fibrosis score (http://nafldscore.com)
   - age, BMI
   - hyperglycemia
   - platelet count, albumin
   - AST/ALT ratio

2. APRI
   - AST/platelet ratio index

3. FIB-4 score
   - age, AST, platelets, ALT

4. BARD score
   - BMI, AST, ALT, DM
Treatment
Published randomized controlled treatment trials for NASH

- **Insulin sensitizers**
  - Pioglitazone  
    - Belfort NEJM 2006
    - Sanyal NEJM 2010 (PIVENS)
  - Rosiglitazone  
    - Ratziu Gastro 2008 (FLIRT)
    - Ratziu Hepatol 2010 (FLIRT-2)
  - Rosiglitazone + Metformin  
    - Torres Hepatol 2011

- **Vitamin E**  
  - Sanyal NEJM 2010 (PIVENS)

- **Pentoxifylline**  
  - Zein Hepatol 2011
Meta Analysis:
Insulin sensitizing agents for NASH

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<td>0.96 [0.25, 3.72]</td>
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<td>3.1%</td>
<td>1.00 [0.05, 18.57]</td>
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Test for overall effect: Z = 1.39 (P = 0.17)

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<td>Shields 2009</td>
<td>16.3%</td>
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Heterogeneity: Chi² = 2.62, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)

Musso Hepatology 2010
Challenges in identifying pharmacologic treatment for NASH

- Rebound effect after discontinuation of treatment
- Long term safety concerns:
  - Rosiglitazone (Rosen NEJM 2010)
  - Vitamin E (Miller Ann Int Med 2005)
  - Klein JAMA 2011
- Identification of appropriate therapeutic targets
  - insulin resistance
  - inflammation
  - altered lipid metabolism
  - obesity
  - fibrosis
- Validation of noninvasive markers of disease activity and staging
Current management approach

• Lifestyle modification
  weight loss
    (3-5% improves steatosis
     >9% improves necroinflammation)
  exercise
diet

• Diagnose and manage any comorbid features of metabolic syndrome
NAFLD: proposed clinical approach

- Fatty Liver
  - NAFL
    - observe
  - NASH
    - Minimal fibrosis
      - Low risk for progression
    - Advanced fibrosis
      - High risk for progression
      - Clinical trials
      - HCC screening if cirrhotic
      - Lifestyle modification

- Lifestyle modification
Summary

• Patients with NASH have a variable risk for disease progression
• Older age, DM, metabolic syndrome and elevated ALT are associated with advanced fibrosis
• Effective pharmacologic treatments are still lacking
• Target higher risk individuals for staging liver biopsy, aggressive lifestyle modification, and therapeutic clinical trials
• Don’t overlook comorbid metabolic syndrome in patients with NASH- cardiovascular disease remains the leading cause of mortality in patients with NASH