Learning Objectives:

• Summarize the current epidemiology and natural history of Nonalcoholic Fatty Liver Disease (NAFLD)

• Identify patients at increased risk for Nonalcoholic Steatohepatitis (NASH)

• Implement algorithm for decision for liver biopsy for diagnosis and staging

• Critically assess current treatment options in NAFLD
Outline:

- Definition
- Epidemiology
- Natural History
- Treatments
**Non-alcoholic Fatty Liver Disease (NAFLD)**

1. The presence of **fat** in the liver either on imaging or histology
2. The exclusion of secondary causes

**Histology**

**Non-alcoholic Fatty Liver (NAFL)**
- Hepatic Steatosis with no evidence of hepatocellular injury (hepatocyte ballooning)
  - "Bland Steatosis" or "Simple Steatosis"

**Non-alcoholic Steatohepatitis (NASH)**
- Hepatic Steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis
## Secondary Causes of Fatty Liver

### Alcoholic Liver Disease

**Significant EtOH intake?**

- **Men:** > 21 drinks per week
- **Women:** > 14 drinks per week

*(although no consensus)*

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**TABLE 1. CAUSES OF FATTY LIVER DISEASE.**

<table>
<thead>
<tr>
<th>NUTRITIONAL</th>
<th>DRUGS*</th>
<th>METABOLIC OR GENETIC</th>
<th>OTHER</th>
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</thead>
<tbody>
<tr>
<td>Protein-calorie malnutrition†</td>
<td></td>
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<tr>
<td>Starvation†</td>
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<tr>
<td>Total parenteral nutrition†</td>
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<tr>
<td>Rapid weight loss†</td>
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<tr>
<td>Gastrointestinal surgery for obesity†</td>
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<tr>
<td>inflammatory bowel disease†</td>
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<td></td>
<td></td>
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<tr>
<td>Small-bowel diverticulosis with bacterial overgrowth†</td>
<td></td>
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<td></td>
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<tr>
<td>Human immunodeficiency virus infection†</td>
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<tr>
<td>Environmental hepatotoxins</td>
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<tr>
<td>Phosphorus‡</td>
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<tr>
<td>Petrochemicals†</td>
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<td></td>
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<tr>
<td>Toxic mushrooms†</td>
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<tr>
<td>Organic solvents</td>
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</tbody>
</table>
| *This is a partial list of agents that produce fatty liver. Some drugs produce inflammation as well. The association of fatty liver with calcium-channel blockers and valproic acid is weak, whereas the association with amiodarone is strong. Drug-induced fatty liver may have no sequelae (e.g., cases caused by glucocorticoids) or can result in cirrhosis (e.g., cases caused by methotrexate and amiodarone).  
† This factor predominantly causes macrovesicular steatosis (mostly owing to imbalance in the hepatic synthesis and export of lipids).  
‡ This factor predominantly causes microvesicular steatosis (mostly owing to defects in mitochondrial function).  
§ This factor causes hepatic phospholipidosis (mostly owing to the accumulation of phospholipids in lysosomes).|

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Angulo, Review in NEJM, 2002
Epidemiology NAFLD

• Most common cause of abnormal liver tests in the United States

• True prevalence is unknown → estimated about 20-30% of the general population

• Strong association with Metabolic Syndrome and Insulin Resistance
  – High risk groups such as obese and diabetics up to 70% prevalence

Clark, et al, 2003
Natural History

Bland Fatty Liver → NASH

Stable or Regression of Fibrosis

70%

20-30%

LNAH → Cirrhosis

Cirrhosis → Liver Failure

40-60% over 5-7 years

Liver Failure → Transplant or Death

Liver Failure → HCC

10% over 7 years

HCC → Transplant or Death

Ong et al, Clin Liver Dis, 2007
NAFLD will surpass HCV as leading indication for Liver Transplant by 2020

Charlton, Clin Gastro and Hep 2004
## Table 3. Adjusted Odds Ratios for Severe Fibrosis (Septal Fibrosis or Cirrhosis).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥45 yr</td>
<td>5.6 (1.5–21.7)</td>
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<tr>
<td>Obesity (body-mass index ≥30)</td>
<td>4.3 (1.4–13.8)</td>
</tr>
<tr>
<td>Aspartate aminotransferase:alanine aminotransferase</td>
<td>4.3 (1.5–12)</td>
</tr>
<tr>
<td>ratio &gt;1</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>3.5 (1.2–9.8)</td>
</tr>
</tbody>
</table>

*Adapted from Angulo et al. with the permission of the publisher. CI denotes confidence interval.

Angulo, Review in NEJM, 2002
Who to Biopsy?

1. Confirm Diagnosis:
   – Coexisting chronic liver disease cannot be excluded

2. Staging NAFLD:
   – Increased risk for steatohepatitis and advanced fibrosis
   – Important to identify those at risk for progressive liver disease to institute emerging treatment strategies
Suspected NAFLD
Chronically elevated AST/ALT (>6 months)
Exclude other causes of LFT elevations (viral, metabolic, autoimmune)

**Evaluation:** PE, Ultrasound, labs tests (glucose, lipids)

**Risk Factors for NASH/Fibrosis**

**Clinical**
- Age >45
- Obesity
- Diabetes/Insulin Resistance
- Components of Metabolic Syndrome
- Labs: Low pts, low Alb, >AST/ALT
- Imaging signs of portal hypertension

**Non-invasive assessment**
- NAFLD fibrosis score
- FIB4
- Fibroscan®

**Low Risk for NASH/Fibrosis:**
No Biopsy
Lifestyle advice and general practitioner follow up

**High Risk for NASH:**
Biopsy
Lifestyle changes, Emerging Treatment Strategies
Management

• The most common cause of death in patients with NAFLD is cardiovascular disease

• Important to treat underlying metabolic derangements:
  – Obesity
  – Hyperlipidemia – Statins are okay
  – Insulin resistance/T2DM
Therapeutics Specific for Liver

• Lifestyle intervention
  – Diet and Exercise Counseling

• Pharmacologic

• Surgical

• Future directions….
Lifestyle Intervention

• Diet:
  – Hypocaloric diet to achieve a 5-10% weight reduction
  – Consider nutritionist referral for education and counseling
  – Reduce saturated/trans fat
  – Minimize added sugars (especially fructose)
  – Minimize fast food
  – Minimize excess carbohydrates
  – Mediterranean Diet (Ryan et al, J of Hep, in press)

• Exercise
  – Exercise alone, independent of weight loss appears to reduce hepatic steatosis

Chalasani et al, AASLD Guidelines, 2012,
Zelber-Sagi et al, WJG, 2011
Pharmacologic

• No good data to support use:
  – Metformin
  – Ursodeoxycholic acid
  – Omega-3 fatty acids
  – Statin (although are safe to use for treatment HLD)

Chalasani et al, AASLD Guidelines, 2012
• **PIVENS Trial** from 2010

• **RCT** - 247 non-diabetic patients with NASH
  – Pioglitazone (30 mg/day),
  – Vitamin E (800 IU/day), or
  – Placebo

• Repeat Bx at 24 months

Sanyal, et al, NEJM, 2010
Results PIVENS

- Vit E showed improvement in NASH histology
  - (43% vs 19%, p=0.001)

- Pioglitazone showed no significant improvement in NASH histology
  - (34% vs 19%, p=0.04)*

- No significant difference in sub-analysis for improvement in fibrosis with either drug.

* Note significant p value < 0.025 given 2 primary outcomes

Sanyal, et al, NEJM, 2010
But....

- Study only in non-diabetics

- Pioglitazone
  - Safety concerns and tolerability limit use
  - Weight gain known issue (seen in PIVENS) (1)
  - Concern for risk of increased CHF (2)
  - Risk for Osteoporosis

- Vitamin E
  - Possible slight increase in all cause mortality in one analysis (3)
  - Also possible increased risk for prostate cancer (4)

Bariatric Surgery

• General Recommendations:
  – Patients with BMI of $\geq 40$
  – Patients with BMI of $\geq 35$ and features of metabolic syndrome

• But should it be done for primary indication of NAFLD/NASH?
Bariatric Surgery in NASH

• Cochrane Review in 2010 reviewed 21 prospective and retrospective cohort studies

• Pros:
  – 18 showed improved steatosis
  – 11 showed improved inflammation

• Cons:
  – 4 showed some worsening of fibrosis

• Bottom Line: No unbiased conclusion could be made on the benefit or harm of bariatric surgery in NAFLD based on lack of randomized controlled data

Chavez-Tapia et al, The Cochrane Collaboration, 2010
Future Directions:

• Awaiting Results Phase II RCT:
  – FLINT Trial from NASH CRN
  – The Farnesoid X Receptor (FXR) Ligand Obeticholic Acid in Nonalcoholic Steatohepatitis (NASH) Treatment Trial
  – Done enrolling → results out in 2014

• Currently enrolling Phase IIb RCT:
  – Novel agent GFT505 dual PPARα/δ agonist
  – University of Colorado participating site
GENFIT Trial

- Study to evaluate the efficacy and safety of GFT505 on NASH
  - GFT505 acts on several mechanisms involved in NASH pathogenesis
    - Both PPAR-alpha dependent and independent mechanisms
    - Improves insulin sensitivity
    - Lowers blood glucose
    - Improves plasma triglyceride and cholesterol profiles
- Phase IIb, Multicenter, Randomized, Double-Blind, Placebo-Controlled trial
- 52 weeks of treatment
- Liver biopsy at beginning and at end of study
- Enrollment begins ~July 2013
- PI: Kiran Bambha, MD, MSc
- Study Coordinator: Susan Hartley, RN
- Contact Information:
  303-724-1871
  susan.hartley@ucdenver.edu
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