Everything You Need To Know About NAFLD

Bryan Rudolph, MD, MPH
Disclosure of Financial Interest

• Research contract with Echosens (FibroScan, Paris). Support is for research only

• Consultant, Alexion Pharmaceuticals
Learning Objectives

1. Recognize the clinical and histopathologic spectrum of nonalcoholic fatty liver disease (NAFLD)
2. Know which patients to screen for NAFLD and the limitations of commonly used tests
3. Be comfortable diagnosing NAFLD and know the indications for subspecialist referral
4. Understand currently available treatment options
Case: T.S.

• 18 year old obese female

• First elevated ALT (69 U/L) noted 5 years prior to GI referral
  – Multiple attempts at weight loss

• Previous testing included:
  – Normal albumin and bilirubin
  – Normal Hep A, B, C serology
Case: T.S.
Case: T.S.

- PMHx: Obesity; PCOS; insulin resistance; dyslipidemia
- FHx: No liver disease or autoimmune disease; parents both from Mexico
- Meds: None
## Case: T.S.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Normal Hgb, Plt</td>
</tr>
<tr>
<td>Coags</td>
<td>Normal INR (0.9), PT</td>
</tr>
<tr>
<td>GGT</td>
<td>71 U/L (elevated)</td>
</tr>
<tr>
<td>Ceruloplasmin</td>
<td>35.1 mg/dL (normal)</td>
</tr>
<tr>
<td>Total IgG</td>
<td>1250 mg/dL (normal)</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
</tr>
<tr>
<td>Smooth muscle antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-liver kidney microsomal antibody</td>
<td>Negative</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin phenotype</td>
<td>MM (normal)</td>
</tr>
<tr>
<td>Celiac panel</td>
<td>Negative</td>
</tr>
<tr>
<td>TSH and FT4</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Case: T.S.

Ultrasound:
Mildly enlarged liver (17.2 cm) with diffuse, increased echogenicity consistent with fatty infiltration
Case: T.S.

- Liver biopsy in December 2014 demonstrated:
  - Grade 2 steatosis
  - Grade 1 inflammation
  - Stage 2 fibrosis
Definition and Disease Spectrum

NAFLD

Steatosis ↔ NASH → Cirrhosis
Definition: Steatosis

- Macroversicular
- $\geq 5\%$ of hepatocytes
Definition: Nonalcoholic Steatohepatitis

- Steatosis
- Inflammation
  - Ballooning
- +/- Fibrosis
Definition: Cirrhosis

- Advanced fibrosis
- May be reversible
- High risk for HCC, transplant
Clinical Presentation

• Most overweight or obese

• Asymptomatic

• Associations
  – Metabolic syndrome, CVD, OSA, QOL, PCOS, hyperinsulinism/diabetes
Prevalence: SCALE

742 Children

13% with NAFLD
(9.6% adjusted)

5% of normal weight
16% of overweight
38% of obese

23% with NASH

Highest prevalence
• Higher BMI
• Hispanics
• Older children

Schwimmer et al. SCALE. Peds; 2006
Natural History

- NASH and Fibrosis have important prognostic implications
- More consistent and rapid progression to cirrhosis and simple steatosis

Steatosis \( \rightarrow \) Cirrhosis (3%) (\( > 10 \) years)

NASH/Fibrosis \( \rightarrow \) Cirrhosis (30%) (5 - 10 years)

Matteoni et al. Gastroenterology 1999
Associations: Cardiovascular Disease

• Elevated ALT is associated with increased risk of cardiovascular and all-cause mortality in adults

• Children with NAFLD are more likely to have
  • Dyslipidemia
  • Hypertension
  • Insulin resistance
  • Components of metabolic syndrome
Associations: Gender and Ethnicity

- Boys > Girls
- Prevalence varies by ethnicity:
  - High (11.8%)
    - Hispanic
  - Low (1.5%)
    - Asian
    - Caucasian
    - African American

Schwimmer et al. SCALE. Peds; 2006
Associations: Insulin Resistance

• Insulin resistance and NAFLD clearly associated

• Severity of hyperinsulinemia may correlate with degree of steatosis or NASH

• NAFLD increases risk of developing DM type 2 but may also worsen glycemic control in children with diabetes
Associations: Metabolic Syndrome (MetS)

- Prevalence of MetS significantly higher in children with elevated ALT (44.7% vs. 16.9%, p = 0.001)

### Odds Ratio for Elevated ALT According to Number of MetS Components

<table>
<thead>
<tr>
<th>Components</th>
<th>Subjects (%)</th>
<th>ALT &gt; 40 U/L (%)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>107 (14.9)</td>
<td>3 (7.9)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>1</td>
<td>234 (32.6)</td>
<td>9 (23.7)</td>
<td>2 (0.4 – 9.7)</td>
</tr>
<tr>
<td>2</td>
<td>214 (29.8)</td>
<td>9 (23.7)</td>
<td>2.5 (0.5 – 12.1)</td>
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<tr>
<td>3</td>
<td>108 (15)</td>
<td>12 (31.6)</td>
<td>7.0 (1.5 – 32.0)</td>
</tr>
<tr>
<td>4 and 5</td>
<td>20 (2.8)</td>
<td>5 (13.2)</td>
<td>17.1 (3.1 – 96.5)</td>
</tr>
</tbody>
</table>

*adjusted for age and sex

Fleet S et al, unpublished data
Associations: Obstructive Sleep Apnea (OSA)

- Nobili et al (n = 65)
  - 60% had OSA
  - OSA associated with NASH and fibrosis, even after controlling for BMI, MetS, or insulin resistance

- Sundaram et al (n = 25)
  - 15 (60%) had OSA
  - Those with OSA/hypoxemia had more advanced fibrosis

Nobili et al. Amer J Resp Cr Care. 2014
Sundaram et al. J Peds. 2014
Genetics

- Epidemiological, familial, and twins studies suggest a strong heritability for NAFLD

- NAFLD is significantly more common in the siblings and parents of children with NAFLD when compared to children without NAFLD
  - 59% siblings
  - 78% parents

Schwimmer JB et al. Gastroenterology 2009
Dongiovanni et al. Curr Pharm Des 2013
Genetic Nucleotide Polymorphisms (SNPs)

- Patatin-like phospholipase 3 (PNPLA 3)
  - Strongly associated with increased hepatic steatosis, NASH, and fibrosis (I148M variant)
  - Carrier frequency of ~50% among Hispanics in some studies
  - Variant in African Americans (S453I) is associated with decreased hepatic steatosis
Pathogenesis: *the multi-hit hypothesis*

**Constitutional risk factors**
- Age
- Gender
- Hispanic ethnicity
- Microbiome

**Genetic risk factors**
- PNPLA3 (rs738409)
- GCKR (rs126032)
- FDFT1 (rs2645424)
- PPP1R3B (rs4240624)
- LYPLAL1 (rs12137855)
- GC (rs222054)
- LCP1 (rs7324845)
- LPRR4 (rs12743824)
- SLC38A8 (rs11864146)
- APOC3 (rs2854116 – rs2854117)
- SAMM50 (rs2143571)
- PARVB (rs6006473 – rs5764455 – rs6006611)

**Modifiable risk factors**
- Sedentary lifestyle
- Visceral obesity
- Insulin Resistance
- Pubertal stage
- OSA

**Dietary risk factors**
- Carbohydrates
- Fructose
- Omega-3, omega-6
Screening

• Challenging public health question
  – 10% disease prevalence in children
  – Invasive gold-standard diagnostic test
  – Treatments limited
  – Broad differential
Recommended Screening Guidelines

AAP: Biannual screening with serum liver enzyme measurements in obese children and overweight children with additional risk factors

Barlow SE et al. Peds 2007; 120; S164-192
Recommended Screening Guidelines

- AGA/ACG/AASLD
  - No formal recommendations due to a “paucity” of data

- ESPGHAN
  - Serum liver tests and ultrasound in all obese children

Vajro et al. JPGN 2012; 54(5): 700-713
Recommended Screening Guidelines: NASPGHAN

- “Consider” at 9 – 11 years old in obese children and overweight children with additional risk factors (central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, OSA, of family history of NAFLD/NASH)
  - Earlier screening if risk factors (obesity, Hispanic ethnicity, insulin resistance, pre-diabetes, diabetes, dyslipidemia)
Recommended Screening Guidelines: NASP GHAN

• Screen with ALT (not US)
  – If ALT elevated > 3 months, evaluate for chronic hepatitis
  – Repeat every 2 – 3 years if normal, or sooner if new risk factors

• Consider biopsy if increased risk of NASH/fibrosis

• Annual diabetes screening

• Hep A/B vaccinations
Diagnostic Tests: ALT

- Aminotransferase levels marginally reliable
  - ALT levels fluctuate
  - ALT can be normal in advanced disease
  - Upper limit of normal often set too high
What is a Normal ALT?

• Screening ALT for Elevation in Today’s Youth (SAFETY)
  – ALT of 53 U/L
    • Sensitivity: 32% (boys) and 36% (girls)
    • Specificity: 92% (boys) and 96% (girls)
  – ALT of 22.2 U/L in girls
    • Sensitivity: 80%
    • Specificity 79%
  – ALT of 25.8 U/L in boys
    • Sensitivity: 92%
    • Specificity: 85%

Schwimmer et al. Gastro 2010
Fibrosis with a “Normal” ALT

- A “normal” or “mildly elevated” ALT does NOT rule out possibility of significant disease

Molleston et al. J Peds 2014
Diagnostic Tests: Ultrasound

- Used in standard practice

- Limitations
  - Echogenic changes only when > 30% of liver is steatotic
  - Operator dependent
  - Difficult in obese patients
  - Limited yield
Diagnostic Tests: Advanced Imaging

- **MRI**
  - Most sensitive method for fat quantification
  - Expensive
  - Sedation

- **CT**
  - More sensitive than US
  - Radiation

*Schimmer et al, Hepatology 2014*
New Diagnostic Tests

- Transient elastography (FibroScan)
  - Shear wave
- Acoustic Radiation Force Impulse (ARFI)
  - Ultrasound
- LiverMultiScan
  - MR-based
- MR Elastography
- Biomarkers
Gold Standard: Liver Biopsy

1. Establish diagnosis
2. Rule out competing diagnoses
3. Prognosis
4. Treatment
### Differential for Hepatic Steatosis

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<th>Nutritional</th>
<th>Systemic</th>
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<td>α1-antitrypsin deficiency</td>
<td>Anorexia nervosa</td>
<td>Acute fatty liver of pregnancy</td>
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<tr>
<td>Alper’s syndrome</td>
<td>Cachexia</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Alström syndrome</td>
<td>Obesity</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>Rapid weight loss</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Bile acid synthesis defects</td>
<td>Starvation</td>
<td>Diabetes Type I</td>
</tr>
<tr>
<td>Cantú syndrome</td>
<td>Total Parenteral Nutrition</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Cholesterol ester storage disease</td>
<td></td>
<td>Hypothalamo-pituitary disorders</td>
</tr>
<tr>
<td>Cohen syndrome</td>
<td></td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Congenital disorders of glycosylation</td>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
<td>Polycystic ovarian syndrome</td>
</tr>
<tr>
<td>Dorfman-Chanarin syndrome</td>
<td>Pharmacologic</td>
<td>Reye’s syndrome</td>
</tr>
<tr>
<td>Dysbetalipoproteinemia</td>
<td>Calcium-channel blockers</td>
<td>Systemic lupus erythematosis</td>
</tr>
<tr>
<td>Fatty acid oxidation defects</td>
<td>Cocaine</td>
<td>Thyroid disorders</td>
</tr>
<tr>
<td>Familial hyper-lipoproteinemia</td>
<td>Coralgil</td>
<td></td>
</tr>
<tr>
<td>Fructosemia</td>
<td>Estrogens</td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Glucocorticoids</td>
<td></td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>HAART</td>
<td></td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>L-asparaginase</td>
<td></td>
</tr>
<tr>
<td>Lipodystrophies</td>
<td>MDMA (ecstasy)</td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Perhexiline</td>
<td></td>
</tr>
<tr>
<td>Shwachman Diamond syndrome</td>
<td>Tamoxifen</td>
<td></td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Toxins (alcohol, pesticides, others)</td>
<td></td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
<td>Valproate</td>
<td></td>
</tr>
<tr>
<td>Weber-Christian syndrome</td>
<td>Vitamin A toxicity</td>
<td></td>
</tr>
<tr>
<td>Wilsons Disease</td>
<td></td>
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Laboratory Work-Up: NASPGHAN

- **Exclusion of Other Diseases:**
  - Ceruloplasmin or 24 hour urinary copper
  - ANA, Anti-LKM Ab, Anti-SM Ab, IgG
  - Celiac panel (tTG and IgA)
  - α1-Antitrypsin phenotype
  - LAL enzyme activity level
  - Hep A/B/C antibodies
  - Viral serology (EBV, CMV, etc.)

- **Metabolic Function:**
  - Liver tests, GGT, INR
  - CBC
  - Fasting glucose, insulin, OGTT, Hgb A₁C
  - Fasting lipids
  - TFTs

Vajro et al. Position Paper of the ESPGHAN Hepatology Committee. JPGN; 54 (5) 2012
Laboratory Work-Up: ESPGHAN

• Exclusion of Other Diseases:
  – Lactate, uric acid, iron, ferritin, pyruvate
  – Serum copper, ceruloplasmin, 24 hour urinary copper
  – ANA, Anti-LKM Ab, Anti-SM Ab, IgG
  – Celiac panel
  – α1-Antitrypsin phenotype
  – Serum organic acids
  – Free FA and acyl carnitine
  – Urinary steroid metabolites
  – Hep A/B/C antibodies
  – Sweat test
  – CPK

• Metabolic Function:
  – Liver tests, GGT, INR
  – CBC
  – Chem 10
  – Fasting glucose, insulin, OGTT, Hgb A₁C
  – Fasting lipids
  – TFTs

Vajro et al. Position Paper of the ESPGHAN Hepatology Committee. JPGN; 54 (5) 2012
Elevated ALT or increased echogenicity on ultrasound

Thorough history and physical

NAFLD likely if:
- Asymptomatic, other than right upper quadrant abdominal pain
- Overweight/obese
- Normal bilirubin/INR
- Older patients (> 3 years)
- ALT ≤ 100 U/L
- Evidence of metabolic syndrome

Total parenteral nutrition, hepatotoxic medications, drugs, or alcohol use?

No

Lifestyle modification, weight loss, and repeat liver tests

If repeat ALT remains elevated, perform right upper quadrant ultrasound and test for the following:
1) Full hepatic panel: INR, GGT, platelet count
2) Viral hepatitis: HBsAg, HCV Ab
3) α-1 antitrypsin deficiency: A1A phenotype
4) Celiac disease: total IgA, tTG IgA
5) Muscle disorders: CPK
6) Wilson’s disease: serum ceruloplasmin
7) Autoimmune hepatitis: ANA, anti-smooth muscle Ab, liver kidney microsomal Ab, total IgG

Screening tests negative

Referral for possible liver biopsy

NAFLD less likely if:
- Symptomatic
- Normal/underweight
- Elevated bilirubin/INR
- Younger patients (< 3 years)
- ALT > 100 U/L
- Signs/symptoms of underlying liver disease

Workup and referral as indicated
Liver biopsy might be indicated

Screening tests positive

Rudolph and Kogan. JCOM 2016
# Yield of Diagnostic Tests in Suspected NAFLD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Laboratory Tests</th>
<th>Abnormal Value</th>
<th>Positive Tests</th>
<th>Diagnosis Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Unknown, probably ~1:200,000 in adults</td>
<td>-</td>
<td>ANA ≥1:20</td>
<td>8/90</td>
<td></td>
<td>0/93*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-SM Ab Positive</td>
<td>2/75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-LKM Ab ≥ 25 units</td>
<td>0/66</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total IgG &gt;1912 mg/dL</td>
<td>1/27</td>
<td></td>
<td></td>
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<tr>
<td>α-1 Antitrypsin Deficiency</td>
<td>1:1,600 – 1:2,000</td>
<td>-</td>
<td>A1A phenotype ZZ</td>
<td>0/37</td>
<td></td>
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</tr>
<tr>
<td>Celiac Disease</td>
<td>1:104</td>
<td>-</td>
<td>tTG ≥ 21 EU/mL</td>
<td>0/22</td>
<td></td>
<td>0/22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-endomysial Ab Positive</td>
<td>0/22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Variable</td>
<td>-</td>
<td>CMV IgM Positive</td>
<td>0/19</td>
<td></td>
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</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>Variable</td>
<td>-</td>
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<td>0/41</td>
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<td>Muscle Disorder</td>
<td>Variable</td>
<td>-</td>
<td>CPK ≥ 200 U/L</td>
<td>11/48</td>
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<td>1/48</td>
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<tr>
<td>Wilson’s Disease</td>
<td>1:30,000</td>
<td>-</td>
<td>Copper &lt; 75 µg/dL (low)</td>
<td>1/14</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ceruloplasmin &lt;15 mg/dL</td>
<td>0/70</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24 hour Urine Copper &gt; 100 µg</td>
<td>0/3</td>
<td></td>
<td></td>
</tr>
</tbody>
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Yield of Laboratory Screening:
- Sensitivity N/A
- Specificity 97%
- Positive Predictive Value 5%
- Negative Predictive Value N/A

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<th>Disease</th>
<th>Prevalence</th>
<th>Incidence</th>
<th>Laboratory Tests</th>
<th>Abnormal Value</th>
<th>Positive Tests</th>
<th>Diagnosis Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Unknown, probably ~1:200,000 in adults</td>
<td>-</td>
<td>ANA</td>
<td>≥1:20</td>
<td>8/90</td>
<td>0/93*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-SM Ab</td>
<td>Positive</td>
<td>2/75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-LKM Ab</td>
<td>≥ 25 units</td>
<td>0/66</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total IgG</td>
<td>&gt;1912 mg/dL</td>
<td>1/27</td>
<td></td>
</tr>
<tr>
<td>α-1 Antitrypsin Deficiency</td>
<td>1:1,600 – 1:2,000</td>
<td>-</td>
<td>A1A phenotype</td>
<td>ZZ</td>
<td>0/37</td>
<td>0/37</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>1:104</td>
<td>-</td>
<td>tTG</td>
<td>≥ 21 EU/mL</td>
<td>0/22</td>
<td>0/22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anti-endomysial Ab</td>
<td>Positive</td>
<td>0/22</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Variable</td>
<td>-</td>
<td>CMV IgM</td>
<td>Positive</td>
<td>0/19</td>
<td>0/19</td>
</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>Variable</td>
<td>-</td>
<td>EBV IgM</td>
<td>Positive</td>
<td>0/41</td>
<td>0/41</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Variable</td>
<td>-</td>
<td>Hep A IgM</td>
<td>Positive</td>
<td>0/62</td>
<td>0/62</td>
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<tr>
<td>Hepatitis B</td>
<td>Variable</td>
<td>-</td>
<td>Hep BsAg</td>
<td>Positive</td>
<td>0/98</td>
<td>0/98</td>
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<tr>
<td>Hepatitis C</td>
<td>2:1,000 in 6-11 years 4:1,000 in 12-19 years</td>
<td>-</td>
<td>Hep C Ab</td>
<td>Positive</td>
<td>0/101</td>
<td>0/101</td>
</tr>
<tr>
<td>Muscle Disorder</td>
<td>Variable</td>
<td>-</td>
<td>CPK</td>
<td>≥ 200 U/L</td>
<td>11/48</td>
<td>1/48</td>
</tr>
<tr>
<td>Wilson’s Disease</td>
<td>1:30,000</td>
<td>-</td>
<td>Copper</td>
<td>&lt; 75 µg/dL (low)</td>
<td>1/14</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ceruloplasmin</td>
<td>&lt;15 mg/dL</td>
<td>0/70</td>
<td>0/71*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>24 hour Urine Copper</td>
<td>&gt; 100 µg</td>
<td>0/3</td>
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</tr>
</tbody>
</table>

Yield of Laboratory Screening:
- Sensitivity N/A
- Specificity 97%
- Positive Predictive Value 5%
- Negative Predictive Value N/A

Treatment: Lifestyle Modifications

• Exercise
  – Goal of 60 minutes 5 days a week

• Limit fructose
  – Associated with steatosis, inflammation, and possibly fibrosis

• Well-balanced, iso-caloric diet limited in simple carbohydrates along with significant exercise
Treatment: Lifestyle Modification

• Weight loss vs. weight maintenance?

• How much weight loss?
  – 5 % decrease = improvement in ALT
  – 10% decrease = histologic change

• How fast?
Question

You are considering therapy for your 16 year old patient with NASH who has failed lifestyle therapy. Which of the following is the next best step in management?

a) Metformin
b) Milk thistle
c) Vitamin E
d) Ursodiol
e) Bariatric surgery
f) Probiotics
Second Line Treatment: Bariatric Surgery

- Improvement in histology
- Data lacking in adolescents
- Worsening of liver disease with rapid weight loss
Treatment: Probiotics

- Review of nine animal studies
  - Steatosis improved in 44%
  - Liver enzyme levels, serum cholesterol and triglycerides were reduced in 22%
  - Fibrosis improved in 22%

- Few human studies. Clinical use warrants additional trials with larger sample size and long-term follow up
TONIC Trial

• Multicenter, double-masked, double-placebo, randomized clinical trial of metformin or vitamin E versus placebo
  – 1º endpoint: sustained reduction in ALT
  – 2º endpoint: improvement in histology

• 173 children with biopsy proven NASH

• Re-biopsied at 96 weeks

Lavine et al, JAMA, 2011
TONIC Trial

ALT

Change (U/L)
-80
-60
-40
-20

Weeks

0 4 12 24 48 72 96

Vitamin E
Metformin
Placebo

Lavine et al, JAMA, 2011
TONIC Trial

- Vitamin E reduces NASH

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E (n=43)</th>
<th>Placebo (n=38)</th>
<th>Metformin (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolved (%)</td>
<td>58%</td>
<td>28%</td>
<td>41%</td>
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<tr>
<td>P-value</td>
<td><strong>0.006</strong></td>
<td>---</td>
<td>0.23</td>
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</table>

Lavine et al, JAMA, 2011
Summary

• NAFLD is the most common liver disease in the U.S., both for adults and children

• NAFLD is a spectrum of disease which can progress

• Liver biopsy remains the gold standard for diagnosis, but imaging and biomarkers are in development
Summary

• Screening guidelines vary

• ALT thresholds are set too high to reliably detect disease

• Weight loss is the most effective management
  – Vitamin E with biopsy proven disease
Questions?