Fatty Liver Disease in Children
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<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Disclosure</th>
<th>Resolution</th>
</tr>
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<tbody>
<tr>
<td>Rohit Kohli</td>
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<td>Research Grant Site Principal Investigator for Raptor &amp; Shire Pharmaceuticals</td>
<td>Restricted to best available evidence and ACCME content validation statement</td>
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<td>Speaker Bureau for Alexion, and Scientific and Medical Advisory Bd. Member for Takeda</td>
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<tr>
<td>Stephanie H. Abrams</td>
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Pediatric Nonalcoholic Fatty Liver Disease (NAFLD)
# The NAFLD Umbrella

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Details</th>
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<tbody>
<tr>
<td>NAFLD</td>
<td>Fatty infiltration of the liver &gt;5% by imaging or histology</td>
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<tr>
<td></td>
<td>No significant alcohol intake</td>
</tr>
<tr>
<td></td>
<td>No genetic disease</td>
</tr>
<tr>
<td></td>
<td>No Medications that cause steatosis</td>
</tr>
<tr>
<td>NAFL</td>
<td>Bland steatosis</td>
</tr>
<tr>
<td>NASH</td>
<td>Steatosis with inflammation, ± hepatocellular injury (ballooning), ± fibrosis</td>
</tr>
<tr>
<td>NAFLD with fibrosis</td>
<td>NAFL or NASH with periportal, portal, sinusoidal or bridging fibrosis</td>
</tr>
<tr>
<td>NAFLD with cirrhosis</td>
<td>Cirrhosis in the setting of NAFLD</td>
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</table>

Spectrum of Pediatric NAFLD in NASH Clinical Research Network

176 children from 8 clinical sites in US, mean age 12 (6-17 years)

- 20% Not NASH
- 36% Definite NASH
- 43% Borderline NASH
- 80% NASH

% with Fibrosis

Notably, mean BMI 33 ± 5, (range 18-58)
BMI percentile 99.1 ± 0.8 %

Clinical Features Associated with More Severe Pediatric NASH

- Abdominal obesity - ↑ waist circumference
- Insulin resistance, prediabetes, diabetes mellitus T2
- Race/ethnicity: Hispanic > White > Black
  - Genetic polymorphisms (PNPLA3)
- ↑ Age (peri and post-pubertal)
- ↑ ALT (>80 U/L), plus ↑AST and GGT
- Dyslipidemia (↑ triglycerides)

What are Future Implications for Children with NASH?

- NASH-related cirrhosis in the United States alone has increased 6 fold over the last decade in adults
  - Now 2nd leading cause for liver transplantation (LT) in adults
  - Most rapidly growing indication for LT related to HCC

- Although long-term outcome of children with NASH remains unknown, these trends in adults are worrisome

Wong RJ et al. Hepatol 2014;59:2188.
Natural History NASH vs. NAFL

NASH also associated with **significant increase in mortality in adults**

Pediatric NAFLD

Prevalence
NAFLD – Prevalence in Children

• NAFLD is the most common cause of pediatric liver disease

• There are no studies describing the incidence of NAFLD in children

NAFLD – Prevalence in Children

Continued

• Prevalence of NAFLD parallels obesity
• 2.7 fold increase 1980’s to current era

NAFLD – Prevalence in Children

Continued

• The prevalence of NAFLD varies with the age of the child, gender, race/ethnicity, and body mass index (BMI)

• There is an increased prevalence of NAFLD in children with certain risk factors such as pre-diabetes, type 2 diabetes, OSA and hypopituitarism
NAFLD – Prevalence in Children

Continued

• Prevalence of NAFLD depends on:
  – the population being screened (general population vs. high risk population)
  – the screening method used (ALT, imaging, liver biopsy)

NAFLD – Prevalence in Children

Continued

- 2-4 years - 0.7%
- 15-19 - 17.3%
- Obese children by ALT elevation - 29-38%

NAFLD – Prevalence in Children

Continued

- 11-22 years - 4-fold increased risk for Hispanic children
- 10.2% in Asian children
- 8.6% in white children
- 1.5% in black children

NAFLD – Prevalence in Children

Comorbidities Associated with Higher Risk/Severity of NAFLD

- Children with type 2 diabetes had a 48% prevalence of elevated ALT
- Obstructive sleep apnea (OSA) was associated with NASH in two pediatric studies, independently of BMI and standard metabolic risk factors
- Children with hypopituitarism have an increased risk of NAFLD/NASH and even cirrhosis

Summary - Prevalence

- The prevalence of pediatric NAFLD parallels the growing prevalence of obesity in children.
- The prevalence of NAFLD varies with the population screened, level of risk, and modality used to detect NAFLD.
- The prevalence of pediatric NAFLD is higher in certain sub-populations:
  - Overweight/ obese children
  - Males > Females
  - Ethnicity: Hispanics > Asian > Caucasian > Black
  - Pre-diabetes or type 2 diabetes
  - Obstructive sleep apnea (OSA)
  - Hypothalamic dysfunction/ hypopituitarism
Pediatric NAFLD

Natural History
Natural History: A Retrospective Look

5 pediatric subjects
Initial liver Biopsy
Mean Fibrosis Stage: 0.2

5 subjects
Increased fibrosis on repeat liver biopsy
Mean fibrosis Stage: 2

41 +/- 28 months

18 pediatric subjects
Biopsy proven NASH

28 months

No change in fibrosis: 8/18 (44%)
Progression of fibrosis: 7/18 (39%)
Regression of fibrosis: 3/18 (17%)

Natural History: A Prospective Look

TONIC trial
Vitamin E vs. Metformin vs. Placebo

Placebo control (n=47)
Nutrition and Physical Activity

NASH resolution (28%)
Mean change -0.2

Fibrosis improvement (40%)

Steatosis improvement (40%)
Mean change -0.4

Lobular inflammation improvement (43%)
Mean change -0.3

Histologic improvements based on change in NAS activity score
Mean change in ALT: -35

Lavine JE et al. JAMA 2011;305(16):1659-68.
Increased Mortality in Pediatric NAFLD

- 66 children (mean age 13.9 years)
  - Mean follow up: 6.4 years (Range 0.05-20 years)
  - Total of 409 person years follow up
  - 4 events
    - 2 patients died, 2 liver transplant
    - Observed vs. expected survival - \( p < 0.001 \)

Increasing Mortality in Pediatric NAFLD

- 229 adults with biopsy proven NAFLD compared to National Registry of Population Data

- NAFLD mortality:
  - Increased overall (HR 1.29)
  - Cardiovascular (HR 1.55)
  - HCC (HR 6.55)
  - Infectious (HR 2.71)
  - Cirrhosis (HR 3.2)

Fibrosis and Increased Mortality

- No increase in mortality with NAS 5-8
- No increase in mortality with fibrosis stage 0-2
- Fibrosis stage 3-4, irrespective of NAS with increased mortality (HR 3.3)

# Pediatric NAFLD: An Aggressive Phenotype?

Comparison of severely obese adults vs. adolescents at bariatric surgery (BMI $\geq 40$)

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Severely obese adults (n=24)</th>
<th>Severely obese adolescents (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive NASH</td>
<td>25%</td>
<td>63%</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean NAS</td>
<td>2.5</td>
<td>3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Presence of fibrosis</td>
<td>29%</td>
<td>83%</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean fibrosis score</td>
<td>0.4</td>
<td>1.3</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Select adolescents with NAFLD have more advanced disease than comparable adults

Summary-Natural History

• Limited data, from small series

• Extrapolation of adult natural history studies may be insufficient
  – Early onset of obesity
  – Increased severity of obesity
  – In utero exposure to maternal obesity and insulin resistance

• Delineation of clinical outcomes of pediatric NAFLD will require long term follow up of affected children into adulthood
Pediatric NAFLD

Screening
Upper Limit for ALT?

- Regional laboratories use local population for norms
  - Do not exclude overweight/obese or other causes of liver disease
  - Median ULN at children’s hospitals 53 U/L (range 30-90)
- 95 percentile for ALT in healthy weight, metabolically normal, liver disease free, NHANES adolescent group (12-17 yrs)

ALT 25.8 U/L for BOYS
ALT 22.1 U/L for GIRLS

Limitations of ALT

• Poor correlation with histology
  – Some studies suggest AST, GGT better correlated with fibrosis
  – ALT changes even with placebo!

• Fluctuations over time

• Cannot always differentiate between

NASH  NAFL
Ultrasound

- **Pros:**
  - Non-invasive

- **Cons**
  - Low sensitivity/specificity particularly lower degrees of steatosis
    (not recommended for screening in NASPGHAN Guidelines)
  - Cannot differentiate between NASH and NAFL

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Advanced Imaging

- Newer imaging techniques
  - Ultrasound based
    - Shear wave
    - Radiofrequency impulse
  - Magnetic Resonance based
    - Elastography
    - Spectroscopy

- Not widely available

Recommendations-Screening

- Screening should be considered between 9 and 11 years for:
  - Children (BMI ≥ 95th percentile)
  - Children (BMI ≥ 85th and 94th percentile) with additional risk factors
    - Central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/NASH
Recommendations-Screening

Continued

• Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH, or hypopituitarism

• Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD
Recommendations-Screening

Continued

• Best test currently- ALT
  - Sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys)
  - Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD
  - ALT of >80 U/L warrants increased clinical concern and timely evaluation
Recommendations-Screening

Continued

• Clinically available routine ultrasound is not recommended as a screening test for NAFLD

• Follow up screening recommended
  – Repeating ALT every 2 to 3 years if risk factors remain unchanged
  – Consider repeating screening sooner if clinical risk factors of NAFLD increase
Pediatric NAFLD

Diagnosis
# Diagnosis of Exclusion

Other causes of hepatic steatosis need to be excluded

<table>
<thead>
<tr>
<th>Genetic/Metabolic disorders</th>
<th>Medications</th>
<th>Dietary causes</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAL-D</td>
<td>Corticosteroids</td>
<td>Alcohol</td>
<td>Hepatitis C (genotype 3)</td>
</tr>
<tr>
<td>FACD, citrin deficiency</td>
<td>Amiodarone</td>
<td>Rapid weight loss e.g., surgical</td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Methotrexate</td>
<td>Parenteral nutrition</td>
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</tr>
<tr>
<td>Lipodystrophies</td>
<td>Antipsychotics</td>
<td>Protein-energy malnutrition</td>
<td></td>
</tr>
<tr>
<td>Abeta-/hypobetalipoproteinemia</td>
<td>Antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled diabetes</td>
<td>HAART</td>
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</table>
How to Diagnose?

NAFLD diagnosis

Imaging modalities

Serum markers/scores

Liver biopsy
Portal Predominant NASH in Many Pediatric Patients, Rarely in Adults

“Pediatric” pattern

Zone 1 - portal inflammation (often no ballooning)

Typical adult pattern

Zone 3 centered injury, more ballooning

Portal and periportal fibrosis

Sinusoidal Fibrosis

Assessment of Steatosis

• Liver biopsy
  – Traditionally used to quantify steatosis
  – Steatosis in >5% of hepatocytes is abnormal
  – NAFLD Activity Score (NAS)
    • Research: steatosis grading 0-3

• Imaging
  – Investigative ultrasonography
  – MR-based technologies

Cost and availability limit their use

Diagnosing NASH

Cannot distinguish NAFL from NASH

- Obesity severity
- Degree of metabolic dysregulation
- Bloodwork (ALT, keratin 18, etc.)

Can confirm NASH

- Liver biopsy

- NASH more common in those with ALT > 80 U/L
- Panhypopituitarism, T2DM associated with NASH

- >2 cm length ↑ likelihood of accurate classification
- NAS score (research) used to rate severity

Liver Biopsy Considerations

- Safe in children, even if overweight
  - Extreme obesity: consider involving interventional radiology

- Optimal timing of biopsy
  - Not established
  - Shared decision with family
  - Biopsy can be helpful to identify:
    - Other liver diseases
    - Advanced NAFLD

May trigger pursuit of more intensive treatment strategies.

## Determining the Presence of Fibrosis - Biomarkers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALT for &gt;F2</th>
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<tbody>
<tr>
<td>Pediatric NAFLD fibrosis score</td>
<td>0.74</td>
</tr>
<tr>
<td>Pediatric NAFLD fibrosis score</td>
<td>0.62</td>
</tr>
<tr>
<td>Enhanced liver fibrosis</td>
<td>0.96</td>
</tr>
<tr>
<td>PNFI + ELF</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>any fibrosis</td>
</tr>
</tbody>
</table>

- ALT≥ 80 predicts advanced fibrosis (F3/F4)
  - sensitivity 76%; specificity 59%
- AST/PLT; hyaluronic acid; other biomarkers: remain to be validated in children

Benefits and Limitations of Each Diagnostic Approach

**Liver Biopsy**
- Differentiates NAFL from NASH
- Excludes other liver diseases
- Clinical reference for diagnosis

**Liver Biopsy**
- Invasive
- Samples a small fraction of the liver

**Serum Biomarkers**
- Non-invasive
- Cheap

**Serum Biomarkers**
- Often have low sensitivity/specificity
- Some remain to be validated

**Imaging Modalities**
- Non-invasive
- Imaging of entire liver
- Can exclude certain conditions
- Cost varies

**Imaging Modalities**
- U/S has low sensitivity/specificity
- CT exposes to radiation
- MRI/MRS: diagnostic cutoffs unclear

Determining the Presence of Fibrosis - Imaging

- Pediatric literature limited
  - Small sample size
  - Few patients with advanced fibrosis

- Transient Elastography
  - ROC = 0.79-1.00 to predict ≥F2

- Magnetic Resonance Elastography
  - ROC = 0.92
    - Scanner and reader dependent

Further validation studies are required

Recommendations

- Exclude other liver diseases when evaluating a patient with suspected NAFLD
- Consider liver biopsy in children at risk of NASH and/or advanced fibrosis
- Ultrasound is not recommended to determine or quantify steatosis due to poor sensitivity/specificity
- CT not recommended for quantification of steatosis due to exposure to radiation
Pediatric NAFLD

Treatment
Goals of Treatment

1. Regression of NAFLD
   - Defined as decrease in steatosis, inflammation, or fibrosis

2. Resolution of NASH
   - These goals are defined and determined by liver histology
Liver Histology

• Assessment of change in fibrosis over time is reasonable as a treatment outcome in children over longer time periods (≥ 2 years) and currently requires a liver biopsy for staging

Surrogate Markers of Treatment Response

• ALT
  – Decrease in ALT is associated with improvements in NAFLD, but how much of a change is meaningful for a given individual is still to be determined

Surrogate Markers: Imaging

- **Ultrasound**
  - Not reliable

- **MRI**
  - Promising
  - Needs validation as a measure of change
Other Treatment Goals

- Decrease in adiposity
- Improvement
  - Dyslipidemia
  - Insulin resistance
  - Blood pressure
Potential Treatment Options

- Lifestyle
- Dietary supplements
- Medications
- Surgery
Lifestyle Modifications

- Lifestyle modifications to improve diet and increase physical activity are 1st-line treatments for all children with NAFLD

Lifestyle Targets

- Avoid sugar-sweetened beverages
- Healthy, well-balanced diet
- Moderate to vigorous exercise
- Limit screen time to < 2 hours per day

Medications for NAFLD

• No currently available medications or supplements are recommended to treat NAFLD

• Bariatric surgery may be considered for selected adolescents with
  – BMI ≥ 35 kg/m², who have
  – non-cirrhotic NAFLD
  – Absence of other serious comorbidities
Pediatric NAFLD

Extrahepatic Associations
Cardiovascular Disease (CVD)

• Adult studies:
  – CVD is the leading cause of mortality in patients with NAFLD
  – NAFLD associated with CVD independent of BMI and other metabolic syndrome components

Pediatric Data

- Dyslipidemia is common
  - Suggestive of insulin resistance ($\uparrow$TG, $\downarrow$HDL)

- Early atherosclerosis seen in adolescents with NAFLD using surrogate markers and/or autopsies

Impact of Treatment

- Treating dyslipidemia in the context of NAFLD:
  - No data on hepatic impact of dyslipidemia treatment

- Treating NAFLD – impact on dyslipidemia:
  - TONIC: NASH resolution associated with improvement in cholesterol, not TG
  - DHA superior to placebo for TG improvement
  - Low fructose diet improved oxidized LDL

Screening for Dyslipidemia

- As per published guidelines:
  - 2-8 years old
    - If risk factors exist
    - If family history of dyslipidemia/CVD
  - 9-11 years old
    - Universal screening

Hypertension

- Increased risk of hypertension in children with NAFLD and obesity vs. obesity alone

- Treatment recommendations as per guidelines for overweight children

CVD Recommendations

• Children with NAFLD:
  – Should be screened for dyslipidemia at diagnosis and periodically, as per published guidelines
  – Should have their blood pressure monitored
Insulin Resistance and Diabetes Mellitus

• Increased risk of NASH if NAFLD with:
  – Insulin resistance (OR: 1.8)
  – Diabetes mellitus (OR: 2.6)

• Correlation between hepatic fat and prevalence of insulin resistance

• Baseline fat content predicts long-term (~2y) insulin sensitivity

Diabetes Recommendations

- Screen annually or sooner if clinical concern
- Screen using:
  - Fasting glucose
  - HgbA1c
  - OGTT if above suggest pre-diabetes
Obstructive Sleep Apnea (OSA)

- OSA affects > 50% of children with NAFLD
- Independent of BMI and metabolic syndrome, OSA is associated with:
  - NASH
  - Advanced fibrosis
- Increased % of time with $\text{SaO}_2 \leq 90\%$ relates to:
  - Hepatic necroinflammation and steatosis
  - Elevated transaminase levels
Pediatric NAFLD

Unanswered Questions and Research Priorities
Unanswered Questions and Research Priorities

- Natural history of NAFLD starting in childhood
- Risk factors in childhood NAFLD that predict progression to cirrhosis and HCC
- Non invasive diagnostics
- Longitudinal studies of biomarkers and imaging

Unanswered Questions and Research Priorities

• Treatment questions:
  – Role of dietary interventions
  – Type and duration of exercise
  – Validation of promising therapeutics
  – Role of weight loss surgery

• Cost effectiveness and public health questions:
  – Effective prevention strategies
  – Cost effectiveness of screening, diagnosis and follow up
Future Directions

• Improvement in understanding of the disease will lead to improved outcomes

• As pediatricians, prevention is a priority but not yet a focus for funding

• Collaborative efforts exist nationally and internationally
  – NASPGHAN NAFLD Scientific Advisory Board
  – The Liver Forum
  – NIH sponsored NASH Clinical Research Network
  – Industry supported Natural History studies

• These are all opportunities to get involved!