PEDIATRIC FOIE GRAS: NON-ALCOHOLIC FATTY LIVER DISEASE

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Disclosures
- I have nothing to disclose

Foie gras

Updates on…
- New insights into NAFLD and NASH pathophysiology
- New AASLD/AGA/ACG guidelines for NAFLD and NASH, as pertains to pediatrics
- Evidence-based recommendations for NASH treatment in children
Is NAFLD really a problem in kids?

- Most common pediatric chronic liver disease in North America
- 2-9% of all U.S. adolescents
- 20% of U.S. obese adolescents
- Rates in younger children unknown

Definitions:

- NAFLD:
  - Hepatic steatosis, by imaging or histology
  - DIAGNOSIS OF EXCLUSION: No other causes for secondary hepatic steatosis
  - Includes entire disease spectrum:
    - NAFL:
      - hepatic steatosis
      - WITHOUT hepatocellular injury
      - WITHOUT fibrosis
    - NASH:
      - hepatic steatosis
      - inflammation/ballooning
      - +/- fibrosis
      - Can progress to cirrhosis, ESLD

NAFLD/NASH Progression

Histology of NASH
Pediatric NAFLD: Type 1 vs Type 2

- **Type 1 NAFLD:**
  - “Adult-type”
  - Zone 3 steatosis
  - Ballooning
  - Perisinusoidal fibrosis

- **Type 2 NAFLD:**
  - Unique to children
  - Zone 1 steatosis
  - No ballooning
  - Portal inflammation/fibrosis

Loomba et al. HEPATOLOGY 2009;50:1282-1293

NAFLD Pathogenesis

- **Two-hit hypothesis**
- **Lipotoxicity hypothesis**

Mantena SK et al. 2008
Neuschwander-Tetri BA, Hepatology 2010

Natural history of NAFLD

- Not well understood
- In adults, NASH associated with:
  - Increased overall mortality risk
  - Leading cause of death: cardiovascular disease
  - Increased liver-mortality rate
  - NASH cirrhosis: Increased HCC risk (but lower than Hep C cirrhosis)
- In children: 1 retrospective single center study
  - 66 children
  - 5 with serial biopsies, 4 with fibrosis progression

Which of the following groups is protected from NAFLD?

- A) African Americans
- B) Asian Americans
- C) Hispanic Americans
- D) None of the above
Demographic Predictors of NAFLD

- Overweight/obesity
- Adolescents
- Males > Females: Estrogen protective?
- Ethnicity:
  - Hispanics, Asians AT RISK
  - African Americans PROTECTED
- Family history: obesity, insulin resistance/DM, NAFLD


Guidelines

New NAFLD guidelines: June 2012

Hepatology

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

Diagnosis of Nonalcoholic Fatty Liver Disease in Children and Adolescents: Position Paper of the ESPGHAN Hepatology Committee

- Strength of Recommendation: factors include evidence quality, importance to patient outcomes, and cost
  1. STRONG
  2. WEAK

- Quality of Evidence
  - High (A): Further research unlikely to change confidence in the estimate of the clinical effect
  - Moderate (B): Further research may change confidence in estimate of the clinical effect
  - Low (C): Further research very likely to impact confidence on the estimate of clinical effect
AASLD: NAFLD screening?

- Not recommended in adult primary care clinics or high-risk specialty clinics (diabetes, obesity) (1, B)
- Not recommended in overweight/obese children:
  - “Due to a paucity of evidence, a formal recommendation cannot be made with regards to screening for NAFLD in overweight and obese children despite a recent expert committee recommendation for biannual screening.” (1, B)
- Not recommended for family members of people with NAFLD or NASH (1, B)
  - 18% of NASH patients have a first degree relative with NASH

AAP Guidelines for NAFLD Screening

- Starting at 10 years of age, every 2 years
- AST/ALT in pediatric patients with:
  - BMI>85th percentile for age/gender WITH risk factors OR
  - BMI>95th percentile for age/gender, regardless of risk factors
- Risk factors:
  - Family history of obesity-related diseases, including hypertension, early cardiovascular deaths, and strokes
  - Patient history of elevated blood pressure, hyperlipidemia, or tobacco use.

What are “normal” LFTS?

- Screening ALT for Elevation in Today’s Youth (SAFETY)
- U.S. children’s hospitals:
  - Median ALT (range):
    - ALL: 53 (30-90)
    - BOYS: 50 (30-70)
    - GIRLS: 40 (29-85)
- NHANES: 12-17 yrs w/o liver disease
  - 95th percentile ALT:
    - BOYS: 25.8 U/L
    - GIRLS: 22.1 U/L

Initial evaluation

- AST/ALT
  - Does NOT correlate well with presence or severity of NASH
- Medication history
- Family history
- Alcohol screen for adolescents

Table 1: Laboratory workup in children with suspected NAFLD

- Metabolic function and iron tests
- Basic profile: Standard liver function tests, fasting glucose and insulin, and cholesterol, triglycerides, ferritin, ALT
- Lipid profile: Total, HDL, triglycerides
- Liver biopsy: Standard liver biopsy
- Genetic tests: Mutations in mitochondrial disorders
- Viral hepatitis:
  - Hep A total Ab
  - Hep B Sag, Cab, SAb
  - Hep C Ab

Evaluation of incidental hepatic steatosis

- History, clinical exam, LFTs

- Signs/symptoms liver disease and/or abnormal LFTs:
  - Suspected NAFLD, → further workup (1, A)

- NO signs/symptoms liver disease AND normal LFTs:
  - Assess for metabolic risk factors (obesity, DM, dyslipidemia) (1, A)
  - NO liver biopsy recommended (1, B)

MRI steatosis “color mapping”

When to biopsy adults for NAFLD?

- “Should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis” (1, B)
  - Metabolic syndrome
  - NAFLD Fibrosis Score

- “Patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded” (1, B)
When to biopsy children for NAFLD?

- AASLD:
  - “where the diagnosis of NAFLD is unclear”
  - “where there is possibility of multiple diagnoses”
  - “before starting potentially hepatotoxic medications”
  - “prior to starting pharmacologic therapy for NASH”

- ESPGHAN:
  - “no present consensus or evidence base to formulate guidelines”
  - “to exclude other treatable disease”
  - “in cases of clinically suspected advanced liver disease”
  - “before pharmacologic/surgical treatment”
  - “as part of a structured intervention protocol or clinical research trial”

Approach to NAFLD workup and biopsy

Which of the following is not an effective treatment for NAFLD?

- A) Weight loss
- B) Exercise
- C) Vitamin E
- D) Metformin
### Lifestyle modification to treat NAFLD:
- Weight loss through lifestyle modification:
  - 3-5%: reduced hepatic steatosis (1, B)
  - 10%: reduced necro-inflammation (1, B)
  - Improved steatosis, lobular inflammation, ballooning, and NAFLD activity score
- Exercise alone, even without weight loss
  - Can significantly decrease hepatic steatosis (1, B)
  - 2-3 sessions/week, 30-60 minutes, 6-12 weeks
- In children and adults, no evidence to definitively recommend a specific diet or exercise plan

### Pediatric NAFLD
- Treatment:
  - Lifestyle modification (2, B)
  - Vitamin E:
    - **TONIC trial (NASH CRN):** RCT of Vitamin E vs. metformin vs. placebo x 96 weeks
      - NO difference between groups in primary outcome: sustained ALT reduction
      - Vitamin E did significantly decrease NAS and improve NASH resolution
    - **Recommendation:** 800 IU rrr alpha-tocopherol daily for children with biopsy-proven NASH or borderline NASH (1, B)

### Vitamin E in adults:
- **Vitamin E:** Recommended at 800 IU/day for biopsy-proven, non-diabetic ADULTS as first line therapy (1, B)
  - Anti-oxidant
  - Improves steatosis, inflammation, ballooning, NASH resolution
  - Does NOT improve fibrosis
  - NASH CRN trials (PIVENS, TONIC) suggest that rrr alpha-tocopherol at 800IU/day helpful
  - Recommended daily allowance: 22.5 IU/day
  - 2 previous meta-analyses failed to show histologic benefits
  - ?Increases all-cause mortality
    - Conflicting data from meta-analyses
    - Recent trial of 400 IU/day associated with increased prostate cancer risk
  - NOT recommended in NASH + DM, NAFLD w/o liver biopsy, NASH cirrhosis, cryptogenic cirrhosis, (1, C) NAFLD/NASH with other chronic liver disease co-existing (1, B)

### Medications for NAFLD/NASH:
- **Metformin:** Not recommended (1, A)
  - RCT data for both adults and children
  - No effect on AST/ALT or liver histology
  - No effect regardless of diabetes as co-morbidity
- **Rosiglitazone:** Not recommended
  - Increased risk coronary events
  - Less data than for pioglitazone, but does not seem to improve inflammation or fibrosis (maybe AST/ALT, steatosis?)
- **Pioglitazone:** Recommended in biopsy-proven, non-diabetic ADULTS (1, B)
  - Meta-analysis (Vernon G et al, 2011):
    - Improves steatosis: OR 4.05, 95% CI 2.58-6.35
    - Improves inflammation: OR 3.53, 95% CI 2.21-5.64
    - **Does NOT** improve fibrosis: OR 1.40, 95% CI 0.87-2.24
    - Causes weight gain
Medications for NAFLD/NASH:

- **UDCA**: Not recommended (1, B)
  - Several small studies, 1 large RCT: no benefit

- **Omega-3 fatty acids**: Use to treat hypertriglyceridemia in NASH patients, but not specifically to treat NAFLD/NASH (1, B)
  - Large multicenter study ongoing: eicosapentanoic acid
  - Other studies small, flawed

- **Statins**: Use to treat dyslipidemia in NAFLD/NASH patients (1, B), but NOT as specific treatment for NAFLD/NASH (1, B)

CyNCH trial

- Cysteamine bitartrate delayed-release for treatment of NASH
  - Children 8-17 years of age with histologically proven NASH
  - Double-blind, placebo-controlled RCT
  - 52 weeks of treatment, 24 week post-treatment follow-up
  - 6 follow-up visits
  - Post-treatment liver biopsy

Bariatric surgery and NASH:

- NAFLD/NASH not a contraindication (1, A)
- No RCTs evaluate bariatric surgery as a treatment for NAFLD/NASH
- In cohort studies, availability of histologic outcomes variable, BUT
  - 2 meta-analyses:
    - *Mummadi et al.*: bariatric surgery improves steatosis, steatohepatitis, fibrosis
    - *Cochrane Review*: lack of RCT data prevents definitive assessment of bariatric surgery as NASH treatment
- Safety and utility in NASH cirrhosis not established (1, B)
- No recommendations on specific types of bariatric surgery for NAFLD/NASH population
Summary

• NAFLD is the most common pediatric chronic liver disease in North America
• NAFLD can progress to fibrosis and ultimately require liver transplant
• Initial evaluation consists of AST and ALT
• Further evaluation may include liver biopsy
• Weight loss and exercise even without weight loss reduce NAFLD
• Vitamin E is recommended for biopsy-proven NASH

References