PEDIATRIC FOIE GRAS: NON-ALCOHOLIC FATTY LIVER DISEASE

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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

Disclosures
- I have nothing to disclose

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

NAFLD Pathogenesis

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

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
New NAFLD guidelines: June 2012

Grading of recommendations, evidence

- 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 (29-65)
- 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

AND 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, \( \rightarrow \) 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 trial (PRIVENS, TONIC) suggest that rrr alpha-tocopherol at 800IU/day helpful
  - Recommended daily allowance: 30 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
- 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: eicosapentaenic 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)
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

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

Liver transplant: 2001-2009 indications

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

UCSF Pediatric Gastroenterology, Hepatology, and Nutrition
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- Alex Green
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- Mel Heyman
- Sue Rhee
- Phil Rosenthal
- Susan Stritzel-Diaz
- Patrika Tsai
- Elizabeth Yen