Pediatric Lipid Disorders & The Role of a Lipid Clinic

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Disclosures

- None

Overview

- Discuss lipid screening and related controversies
- Review Familial Hypercholesterolemia and understanding cardiovascular risk
- The role of the Lipid Clinic

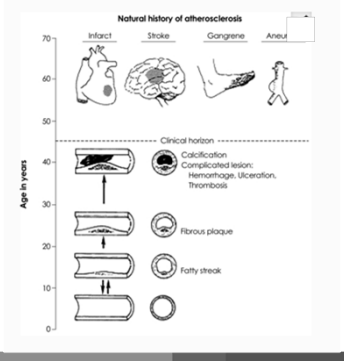
From the CDC

- During 1999–2006, there were 41,494 deaths related to congenital heart disease in the United States.
- In 2013, four vaccine-preventable diseases (measles, diphtheria, tetanus, and pertussis) resulted in 200,000 deaths worldwide
- Coronary heart disease (CHD) is the most common type of heart disease, killing over 370,000 people annually. Every year about 735,000 Americans have a heart attack.

Lipids from a Pediatric Perspective

- Atherosclerosis begins in childhood
- The people most at risk for early cardiac events can be identified and intervened on as children.

Atherosclerosis



Taco Bell Just Making Tortillas Out of Fried Chicken Now

The fast-food chain is taking its Naked Chicken Chalupa national this month

By Michael Harthorne, Newser Staff
Posted Jan 11, 2017 7:09 PM CST

39 comments

Risk factors for early cardiovascular disease in children, definitions used in pediatric dyslipidemia screening and management

Positive family history:
Premature coronary artery disease (ie, heart attack, treated angina, interventions for coronary artery disease, stroke, or sudden cardiac death) in a first- or second-degree male relative <55 years or female relative <65 years*
Known dyslipidemia (eg, familial hypercholesterolemia) or total cholesterol (TC) >240 mg/dL (6.2 mmol/L) in either parent
High-level risk factors:
Hypertension that requires drug therapy (BP ≥99th percentile + 5 mmHg)
Current cigarette smoker
Obesity with BMI ≥97th percentile
Presence of a high risk condition: • Diabetes (type 1 or type 2) • Chronic kidney disease/end-stage renal disease/post-renal transplant • Post-orthotopic heart transplant • Kawasaki disease with current aneurysms
Moderate-level risk factors:
Hypertension (defined as systolic and/or diastolic BP ≥95th percentile measured on three or more separate occasions) that does not require drug therapy
Obesity: • For children age 2 to 11 years: BMI ≥95th to <97th percentile • For adolescents ≥12 years: BMI ≥85th to <97th percentile
HDL cholesterol <40 mg/dL
Presence of a moderate risk condition: • Kawasaki disease with regressed coronary aneurysms • Chronic inflammatory disease (eg, systemic lupus erythematosus, juvenile idiopathic arthritis) • HIV infection • Nephrotic syndrome • Adolescent depressive and bipolar disorders¶

Screening Recommendations

- **When to perform lipid screening:**
- **0 – 2 years**: No lipid screening necessary
- **2 – 8 years**: No routine lipid screening necessary. Obtain a fasting lipid profile if:
  - A first or second degree relative had early angina, myocardial infarction, bypass surgery/stent or stroke (early defined as < 55 years old in males, < 65 years old in females)
  - A parent has known dyslipidemia or LDL ≥ 190 total cholesterol ≥ 24
  - The child has diabetes, hypertension, BMI ≥ 95% or smokes
  - The child has a moderate or high risk medical condition, such as chronic kidney disease, chronic inflammatory disease (i.e. JRA), or Kawasaki disease

Screening Recommendations

- **9 – 11 years**: **Universal screening**. All children should have either (a) a non-fasting, non-HDL cholesterol, or (b) a fasting lipid profile drawn.
- **12 – 16 years**: No routine lipid screening necessary. Follow guidelines for testing in 2 – 8 year old group for exceptions.
- **17 – 21 years: Universal screening**. All teens and young adults should have either (a) non-fasting, non-HDL cholesterol, or (b) fasting lipid profile drawn.

Screening Recommendations

- No where in the guidelines does it clearly state what the purpose of universal screening is:
  - To identify children and family members with Familial Hypercholesterolemia

Lipid Clinic Perspective

- Goal is to identify children with lipid disorders and identify family members based on this→ Reverse Cascade Screening
- Identify Secondary Causes of Lipid Abnormalities

Familial Hypercholesterolemia and the 2013 American College of Cardiology/American Heart Association Guidelines: Myths, Oversimplification, and Misinterpretation Versus Facts

Familial hypercholesterolemia (FH) is a genetic condition resulting in severe, lifelong elevations in low-density lipoprotein cholesterol and a marked increased risk of early-onset coronary disease. FH is treatable when identified, yet is vastly under-recognized and undertreated. Although the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of cholesterol presented a paradigm shift, we believe that there have been serious oversimplifications, misinterpretations, and erroneous reporting about the current ACC/AHA cholesterol guidelines that have contributed to suboptimal care for these subjects. In summary, the ACC/AHA guidelines place tremendous emphasis on the identification of patients with FH, the initiation of high-intensity statin therapy, the need to obtain follow-up lipid values to assess the efficacy and compliance to lifestyle and medical therapy, and the role of nonstatin drugs when needed for optimal care of the individual patient. (Am J Cardiol 2015;116:481–484)

In this editorial, we focus on 4 critical areas addressed in the ACC/AHA guidelines:

1. Screening and identification of subjects with FH as a specific high-risk patient group.
2. The importance of high-intensity statin therapy regardless of the estimated 10-year ASCVD risk or age.
3. The need for follow-up lipid values to assess response to therapy.
4. The role of nonstatin lipid-lowering medications.

Arguments Against Screening and Treatment in Childhood

- Cost/benefit
  - Cost of treating identified cases efficient ($5-9K/LY)
    - In the United States interventions that cost less than $50,000 to $60,000 per life year gained are considered reasonably efficient.
  - Cost of identifying cases high if universal screening is the approach
- What is the incremental benefit of identification at age 10 vs 20 years?

Controversy USPSTF Screening 2016

- USPSTF reaffirms 2007 position that the evidence for cholesterol screening in childhood is insufficient to make recommendations regarding benefits and harms
- National Heart, Lung, and Blood Institute and the American Academy of Pediatrics recommend universal screening for blood cholesterol levels at ages 9 to 11 years and 17 to 21 years.
- Why are these conclusions disparate?

Why Cholesterol Testing Matters:

Gidding, JAMA Cardiol. 2016;1(8):859-861

- *Evidence gaps identified by the USPSTF:*
  - *lack of knowledge regarding the relationship of childhood lipid levels to adult outcomes*
  - *consistent but imperfect observational data*
  - ***randomized trial data with surrogate rather than primary end points and limited 2-year follow-up.***
- *NHLBI/AAP*
  - *"Recommendations of the 2011 panel were driven by the consistency of the evidence relating severely elevated cholesterol levels to premature development of atherosclerosis as well as the impossibility and ethical limitations of conducting a 40-year randomized trial to prove that lowering low-density lipoprotein (LDL) cholesterol in childhood prevents CVD events."*

The Effect:

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians

Sarah D. de Ferranti, MD, MPH[1], Angie Mae Rodday, PhD, MS[1,2], Susan K. Pa... PhD[3], Karen G. O'Connor, BS[4], Stephen R. Daniels, MD, PhD[5], and Lau...

Controversy USPSTF Screening

Objectives To determine pediatricians' practices, attitudes, and barriers regarding screening for and treatment of pediatric dyslipidemias in 9- to 11-year-olds and 17- to 21-year-olds.
Study design American Academy of Pediatrics (AAP) 2013-2014 Periodic Survey of a national, randomly selected sample of 1627 practicing AAP physicians. Pediatricians' responses were described and modeled.
Results Of 614 (38%) respondents who met eligibility criteria, less than half (46%) were moderately/very knowledgeable about the 2008 AAP cholesterol statement; fewer were well-informed about 2011 National Heart, Lung, and Blood Institute Guidelines or 2007 US Preventive Service Task Force review (both 26%). Despite published recommendations, universal screening was not routine: 68% reported they never/rarely/sometimes screened healthy 9- to 11-year-olds. In contrast, more providers usually/most/all of the time screened based on family cardiovascular history (61%) and obesity (82%). Screening 17- to 21-year-olds was more common in all categories ($P < .001$). Only 58% agreed with universal screening, and 23% felt screening was low priority.
Pediatricians uniformly provided lifestyle counseling but access to healthy food (81%), exercise (83%), and adherence to lifestyle recommendations (96%) were reported barriers. One-half of pediatricians (55%) reported a lack of local subspecialists. Although 62% and 89% believed statins were appropriate for children and adolescents with high low-density lipoprotein cholesterol (200 mg/dL) unresponsive to lifestyle, a minority initiated statins (8%, 21%).
Conclusions US pediatricians report lipid screening and treatment practices that are largely at odds with existing recommendations, likely because of lack of knowledge and conflicts among national guidelines, and concern about treatment efficacy and harms. Education regarding pediatric lipid disorders could promote guideline implementation.
(J Pediatr 2017;185:99-105).

William

- Unknown family history
- Cholesterol "high as a teen." Never followed in his 20s
- First MI at age 38

Marie

- Cholesterol First Checked at age 25
- Total Cholesterol 410. No intervention.
  - Active, healthy, no other risk factors
- Angina in her early 30s
- CABGx3 at age 50

Familial Hypercholesterolemia

HetFH

Why Cholesterol Testing Matters:

Gidding, JAMA Cardiol. 2016;1(8):859-861

- Heterozygous Familial Hypercholesterolemia (FH)
- Individuals with FH have a lifetime risk of CHD of about 90%
  - **Prevalence of FH estimated 1 in 200**
  - **Presence of an FH gene triples the likelihood of CHD at any given LDL cholesterol**
  - **FH clinical phenotype increases likelihood of premature events 5-fold**

Why Cholesterol Testing Matters:

Gidding, JAMA Cardiol. 2016;1(8):859-861

- **The age at onset of CHD in US men and women with FH is no different than it was more than 40 years ago when the first descriptions of FH natural history were published**.
- This puts the United States substantially behind European countries, making efforts to identify FH earlier in life crucial to improve outcomes.
  - for approximately every 30 mg/dL of lifelong genetically elevated LDL cholesterol, CVD risk is increased by 50%.

Barriers to Implementing Cholesterol Screening

- FH awareness
- Belief in preventing early CAD
- Time/comfort/reimbursement

Screening for FH

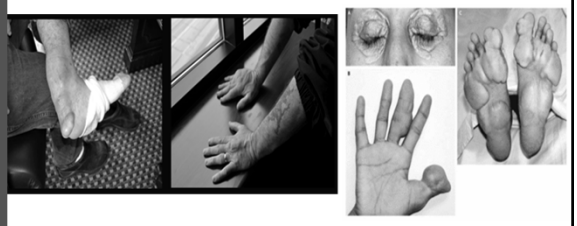
– LDL cholesterol can be used to discriminate those with FH and those without in childhood

- AAP/NHLBI Universal at age 9-11 years. Again at 17-21. Trigger reverse cascade
- Reverse Cascade
  - Identify children with FH
  - Identify first degree family members with high LDL cholesterol
  - Genotype the parents if possible

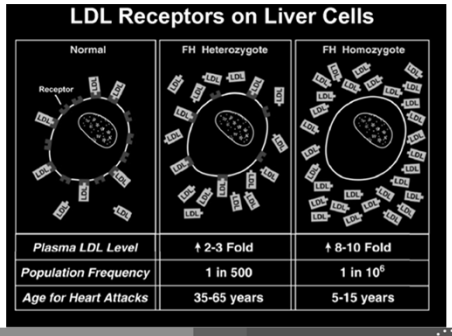
Economics of Detection and Treatment

- Health economic modeling shows considerable savings from treating FH in identified patients.
  - cost per life-year gained for DNA-based cascade testing of relatives of probands and intensive statin therapy averages $5000 to $6800
- Statin therapy would lead to 10% fewer CAD deaths per 1000 FH patients treated compared with no treatment
  - $8 million in saving from events avoided per 1000 relatives of index cases screened

Familial Hypercholesterolemia



Brown and Goldstein



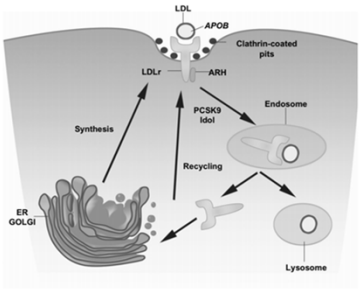
Homozygous FH

- Rare (1:1 million live births). (2 copies of defective gene)
  - High event rates, very early CAD and death
  - Start treatment immediately
    - Statins, Zetia, bile acid resins, apheresis
    - Echo, cath for supravalvar AS
    - Ross vs. valve vs. other
  - Role and timing of liver transplant?

HetFH

- Heterozygous
  - Common, 1:200. More in Netherlands, French Canadian, Amish, Hatian descent?
  - **Autosomal dominant** pattern of inheritance
- Most common is a monogenic form.
  - Defect encodes for
    - LDL receptor→reduced clearance
    - Apo B gene→impairs binding
    - Gain of gunction on PCSK9 gene→decreased clearance
  - Can be severe combined het

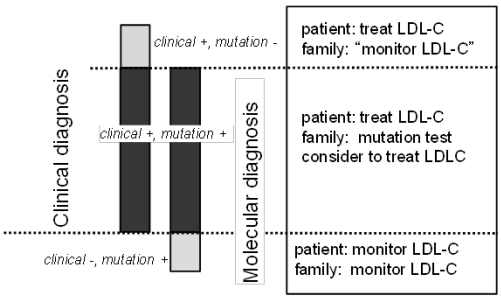
FH Genetics



Family History + Hypercholesterolemia = FH in Children*

- Cholesterol testing should be used to make a phenotypic diagnosis
  - > 190 mg/dl
  - > 160 mg/d and positive family hx
  - > 135 mg/dl and positive genetic diagnosis in the family
- Secondary causes ruled out (thyroid, liver, renal, medication)
- Genetic testing confirms the diagnosis (after parental testing)

FH; "one disease?"



Intervention is based on LDL-C, not on genetic result

Lipid Referrals

- 12 year old
- BMI 18
- LDL-155
- HDL-57
- TG-168

- 12 year old
- BMI 30
- LDL-119
- HDL-37
- TG-301

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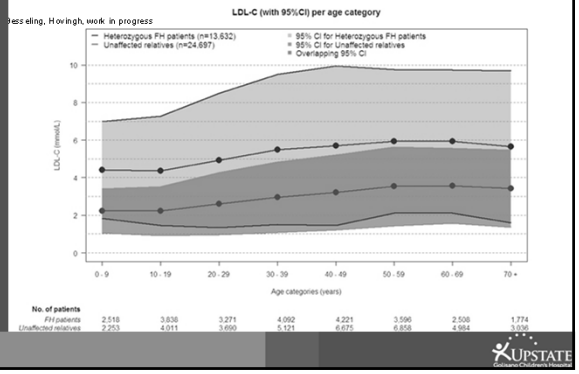
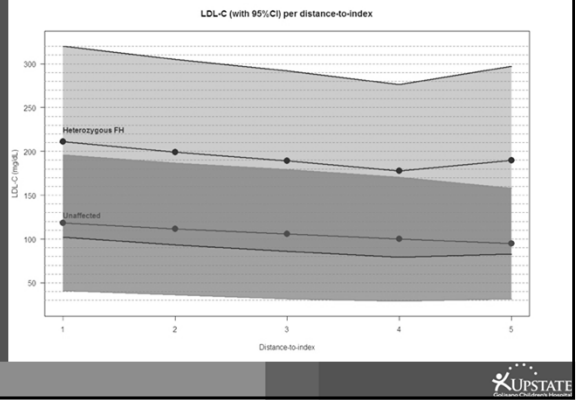
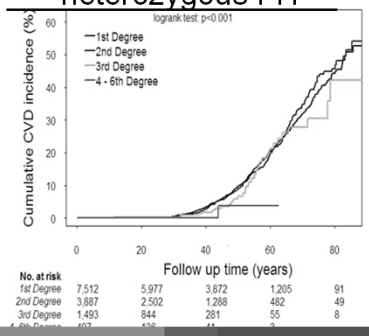
Range of LDL-C in heFH?

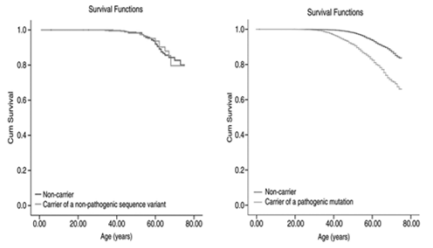




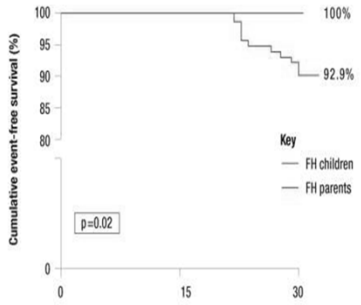
CVD incidence in heterozygous FH



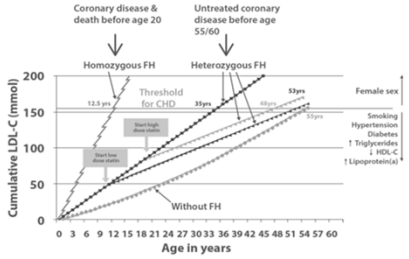
Does genetics matter?



Children Treated with Statins Have Lower Event Rates than Their Affected Parents



Impact of Early Treatment of FH on Lifelong LDL-C Exposure



Lipid Panel and Referal

- LDL (= TC-HDL-(TG/5))
  - Main Apo-B carrying component
  - Normal value for children in 110
  - >190 suggests Het FH and is threshold to treat
  - >300 suggests severe combined het
  - >500 suggests HoFH
  - Low in Hypobetalipoproteinemia
- HDL
  - Responsible for reverse cholesterol transport
  - Will be low in Met Synd, hypoalpha, others
- TG
  - Represents absorbed fats and metabolized sugars
  - Typically <150
  - Elevated in MetSynd, Familial Combined, Chylomicronemia, Familial Hypertrig, Type III
  - Can be a source of "Beta shift"
- Non-HDL
  - Total – HDL
  - Represents burden of Apo-B containing lipoproteins
  - Helpful to look at in HTG

Lipid Panel and Referral

- LDL >190 mg/dl refer to lipid clinic
- LDL >160-190 with a convincing family history
- LDL >130-160. Repeat after diet and exercise in 6-12 months. If still high, consider referral.
- LDL < 40 consider referral to lipid clinic

Lipid Panel and Referral

- TG >300. Refer to lipid clinic.
- TG >150
  - Repeat in 6 months after Diet and Exercise. If still high, consider referral.
- Consider secondary evaluation
  - TSH, CMP, UA, +/- A1c

Lipid Panel and Referral

- Concern for adverse reaction on statin
- Concern for need for statin while on nephro/hepatotoxic medications
- Unclear lipid results in the setting of complex medical conditions

FH Treatment

- Low fat diet, exercise, weight loss
  - (30% total calories, sat fat 7-10%, total chol 300mg per day)
  - Will typically have a greater response to this than non-FH controls
- Statins are first line
- Addition of plant sterols/stanols is beneficial (WelChol)

FH Pharmacologic Treatment

- For children aged 8-10 years
  - LDL-C is ideally reduced by 50%
- For children aged ≥ 10 years
  - if there are additional cardiovascular risk factors, including elevated Lp(a), target LDL-C should be < 130 mg/dL
- Benefits of LDL-C reduction should be balanced against the long-term risk of treatment side effects.
  - Numerous studies in children with FH have demonstrated short term safety
    - 2 year study length is a limitation

FH Pharmacologic Treatment

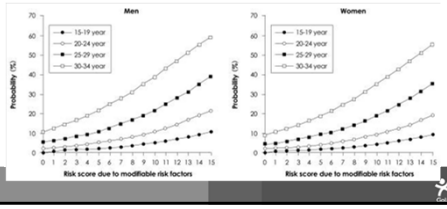
- Statin myopathy/myalgias
  - ~1-5% of adults in studies will have muscle related effects
  - 10-40% of adults in clinical practice will complain of myalgias at some point
  - Myopathy and rhabdo are very rare <<<1%
- Uncommon in children
  - Unpublished EMR data review
    - 300+ patients prescribed statins for a variety of indications
    - Follow up length varied but averaged >2 years
    - No adverse events, no significant change in lab values
- No routine lab monitoring recommended
  - CPK/LFTs

FH Pharmacologic Treatment

- Cholesterol absorption inhibitors – Zetia
- Bile acid sequestrants
- PCSK9 inhibitors – $16K year
- Mipomersen – antisense RNA inhibitor to apo B. $176000 per year
- Lomitapide – microsomal triglyceride transfer protein inhibitor $250000 per year
- LDL apheresis

Ongoing Research

- Is there a Framingham Risk Score for Children
  - Patholobiological Determinants of Atherosclerosis in Youth (PDAY) Score
    - Predicts Coronary Calcium Score. Performs best in young age groups..



Ongoing Research

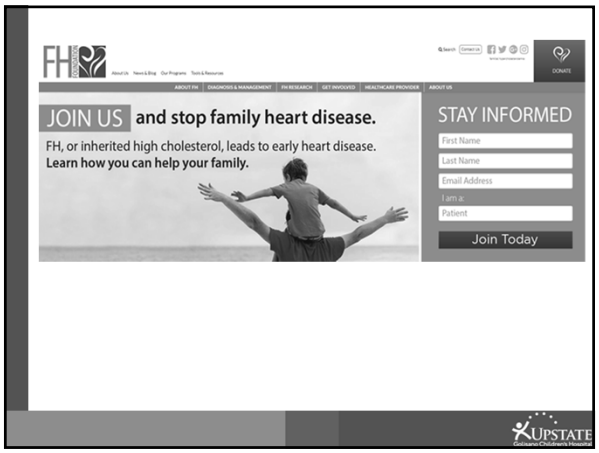
- How do risk stratify children with FH at an early age?
  - Lp(a), lipid function testing
- Assessment of subclinical atherosclerosis in adults and children.
  - CT and other non-invasive methods
- Use of PCSK9 inhibitors in children

Ongoing Research

- Cost-effectiveness studies that include universal and or cascade screening methods
  - Big data/EMR based screening/risk models

Summary

- Atherosclerosis begins in childhood
- Familial hypercholesterolemia can be identified and intervened on in childhood
- LDL >190 virtually confirms the diagnosis
- Statins alter lifetime risk in those with FH
- Lipid Clinic


FH
DONATE
ABOUT FH
DIAGNOSIS & MANAGEMENT
FH RESEARCH
GET INVOLVED
HEALTHCARE PROVIDER
ABOUT US
JOIN US and stop family heart disease.
FH, or inherited high cholesterol, leads to early heart disease.
Learn how you can help your family.
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Last Name
Email Address
I am a:
Patient
Join Today
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