Lipid Testing in Children

WHY?

Frances R Zappalla, D.O. FACC
Nemours Cardiac Center
Al du Pont Hospital for Children
Disclosures

“I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.”
Cardiovascular Disease

- Cardiovascular disease is the most common cause of death and morbidity in the United States

- Atherosclerosis is a chronic disease process with begins in childhood

- The progression of disease is determined by the presence of known cardiovascular risk factors
Early Atherosclerosis

The presence of atherosclerotic lesions in young adults were first documented during the Korean War with autopsy studies showing evidence of coronary atherosclerosis in 45% of soldiers with a mean age of 22

Enos WF et al. Coronary disease among US soldiers killed in action in Korea JAMA 1953

The Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY)

- Multicenter study looking at the relationship of cardiovascular risk factors measured post mortem and the presence of atherosclerosis in adolescents and young adults ages 15 through 34 years, who died accidentally
  - Smoking, obesity, hyperglycemia, and hypertension were positively associated with the presence of lesions even in the presence of a normal lipid profile.

Relationship of Atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. PDAY Research Group JAMA 1990
Bogalusa Heart Study

- Autopsy study of those who died accidentally or by suicide
- Fatty streaks were present in 50% of the children
- Fibrous streaks increased with age
  - 8% of children and 69% of adults
  - Extent of these lesions correlated with elevated total cholesterol, LDL cholesterol, triglycerides, blood pressure and BMI

Berenson GS et al. *Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (The Bogalusa Heart Study)*. AmJCard 1992
Berenson GS et al. *Association between multiple CV risk factors and atherosclerosis in children and young adults The Bogalusa Heart Study* NEJM 1998
Atherosclerosis: A Progressive Process

Normal → Fatty Streak → Fibrous Plaque → Occlusive Atherosclerotic Plaque → Plaque Rupture/ Fissure & Thrombosis

Endothelial dysfunction and plaque progression due to risk factors ... Smoking, high cholesterol, high blood pressure, diabetes, obesity

Clinically silent

10  20  30  40  50

Increasing age

Unstable Angina
MI
Coronary Death
Stroke
Critical Leg Ischemia
Why Screen Children?

- The primary reason to test children is to screen for high risk children with Familial Hyperlipidemia (FH)

- What is FH?
What is FH

- FH is one of the most commonly occurring genetic metabolic disorders
- Untreated, it leads to premature cardiovascular disease including
  - Heart attacks
  - Strokes
  - Aortic stenosis
- Lifestyle is NOT the cause and Lifestyle, although important as an adjunct treatment, will NOT lower the cholesterol levels in these individuals
- The genetic mutation makes the liver *incapable* of metabolizing excess LDL cholesterol
- It is also one of the most undiagnosed genetic diseases
FH – more common than once thought

- Heterozygous FH (HeFH).
  - Occurs in 1 in 250 people worldwide
  - Only about 10% with FH are diagnosed.
  - Untreated
    - Men have a **50% increased risk of MI by age 50**
    - Women have a **30% increased risk by age 60**
FH – more common than once thought

- **Homozygous FH (HoFH)**
  - It is very rare, occurring in about 1 in 160,000 to one million people worldwide.
  - Untreated, it can cause heart disease in childhood and early teens
  - LDL (low-density lipoprotein cholesterol) is can be >500 mg/dl

Nordestgaard B G et al. Eur Heart J: 2013, 34
Familial hypercholesterolemia (FH)

- Autosomal dominant mutations in genes controlling LDL levels
- Familial hypercholesterolemia (FH) defects in 2 other major genes, APOB and PCSK9,
- Inadequate LDL clearance leads to marked elevations of plasma LDL-C levels
- In HoFH, the LDLR pathway is either nonfunctional or markedly defective (2% to 30% activity)
  - Leading to plasma LDL-C levels 4 to 8 times above average (>500 mg/dl)
- In HeFH, the loss in receptor activity (up to 50%) leads to LDL-C levels 2 to 3 times above average
Familial Hyperlipidemia

- Children with FH start laying down cholesterol in their arteries (fatty streaks) as toddlers and by the time children reach the age of 12 many will already have measurable atherosclerosis.
- Treatment with cholesterol lowering medications can dramatically reduce the risk associated with FH.
- Observational studies from Europe have found that long-term cholesterol-lowering therapy with statins removes excess lifetime heart disease risk associated with FH.
The Faces of FH

First heart attack at 29
Xanthomas since age 10 – missed dx

Missed dx with He FH
Started meds age 5
First AVR age 28
First MI and Bypass age 35

TC=371 LDL=245 at age 29
LDL cholesterol >800

Apheresis results in 60% to 70% reduction in LDL-C and Lp(a) immediately following the procedure, but levels usually return to baseline in 2 weeks.
Sudden Death in Competitive Athletes

- 26-year-old Norwegian swimmer Alexander Dale-Owen – heart attack (Familial hypercholesterolemia)
- 32-year-old Claire Squires collapsed in sudden cardiac arrest during the London Marathon
- Italian volleyball Olympian Vigor Bovolenta died after suffering a heart attack during a professional match. He was 37.
- Piermario Morosini, a 25-year-old midfielder, collapsed while playing soccer for Livorno. The team was playing against Pescara. Though he was rushed to the hospital, nothing could be done and he died shortly after. He had suffered from a heart attack
- 24-year-old Serbian rower Nemanja Nesic. Nesic had regular medical checkups - the most recent five weeks before his death. There was no indication that anything was wrong with his health.
High Risk Populations

- French Canadians
- Ashkenazi Jews
- Lebanese
- South African Afrikaners.

- In these populations FH frequency can be as high as 1 in every 67 people
Familial combined hyperlipidemia (FCHL)

- Another common causes of genetic hyperlipidemia
- FCHL has been shown to be 3 times more prevalent than familial hypercholesterolemia
- The primary abnormality in FCHL is an overproduction of VLDL and apoB-100 by the liver, a reduction of fatty acid uptake by adipose tissue, and a decrease in clearance of chylomicron remnants.
- The resulting lipid pattern is variable
- Typically, FCHL presents in adulthood but can be seen in adolescents as it is unmasked by weight gain.

- *Children with normal lipid values but a family known to have FCHL should be retested later in adolescents*
Risk Factors

- Epidemiologic studies have shown that a family history of premature heart disease in a first-degree relative is an important independent risk factor for future CVD.

- Heart disease includes:
  - Heart attack
  - treated angina
  - percutaneous coronary catheter interventional procedure
  - coronary artery bypass surgery
  - Stroke
  - sudden cardiac death

- Premature heart disease is
  » in a male before the age of 55 years or
  » a female before the age of 65 years
Why Universal Screening

- Significant evidence exists that only using a family history of premature CVD or hyperlipidemia as the primary factor to screen children misses 30% to 60% of children with dyslipidemias.

  - Pediatrics 2010:126;260-265
Implementation of Lipid Screening Guidelines in Children by Primary Pediatric Providers

- 74% of providers reportedly believed that lipid screening and treatment would reduce future cardiovascular risk

- However….
  - 34% performed no screening,
  - 50% screened selectively
  - Only 16% performed universal screening.

- Pediatricians were more likely to screen with 30% performing universal screening and 41% performing selective screening.  
  
  *J Pediatr* 2014;164:572-6
Implementation of Lipid Screening Guidelines in Children by Primary Pediatric Providers

- Barriers to screening
  - Providers uneasiness addressing lipid disorders (43%)
  - Unfamiliarity with screening guidelines (31%).
- 83% were uncomfortable managing lipid disorders.
- 57% were opposed to the use of lipid-lowering medications in children.

J Pediatr 2014;164:572-6
# Lipid Values for Children

**National Cholesterol Education Program Expert Panel**

Values in mg/ DL

<table>
<thead>
<tr>
<th>Category</th>
<th>Acceptable</th>
<th>Borderline</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>TC</td>
<td>&lt; 170</td>
<td>170-199</td>
<td>≥ 200</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt; 110</td>
<td>110-129</td>
<td>≥ 130</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>&lt; 120</td>
<td>120-144</td>
<td>≥ 145</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>TG</th>
<th>0-9 years</th>
<th>75-99</th>
<th>≥ 100</th>
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<tbody>
<tr>
<td></td>
<td>10-19 years</td>
<td>90-129</td>
<td>≥ 130</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Acceptable</th>
<th>Borderline</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>&gt; 45</td>
<td>40-45</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>
Lipid levels in Children and teens

- The lowest mean childhood LDL cholesterol and total cholesterol levels occurred consistently at 14 to 16 years of age, regardless of adult lipid status.
  - levels fall as much as 10-20%
- The complete phenotypic expression of some inherited disorders like Familial Combined Hyperlipidemia may be delayed until adulthood.
  - only 10 to 20% of patients diagnosed in childhood
  - 10% of premature coronary artery disease is caused by FCHL
- Therefore…. highest sensitivity for lipid testing is between 5-10 and 17–19 yrs.

- PEDIATRICS Volume 118, Number 1, July 2006
Non-HDL Cholesterol

- LDL is calculated by the Friedewald equation, LDL = [Total C] - [HDL-C] - [TG/5].

- **Non-HDL = Total cholesterol – HDL**
  - Significant predictor of the presence of atherosclerosis
  - A better marker of persistent dyslipidemia and atherosclerosis risk than TC, LDL-C or HDL-C alone.

- Non-HDL-C can be accurately calculated in a non-fasting state however…….
Indication for Statin Therapy in Children

- High risk children defined as those having an LDL > 190 mg/dL despite dietary therapy
- LDL > 160 mg/dL with one risk factors
- LDL > 130 mg/dL with diabetes or multiple risk factors
High Risk Groups Requiring Early Treatment

- **High Risk:**
  - Diabetes mellitus, type 1 and type 2
  - Chronic kidney disease/end-stage renal disease/post renal transplant
  - Postorthotopic heart transplant
  - Kawasaki disease with current aneurysms

- **Moderate Risk:**
  - Kawasaki disease with regressed coronary aneurysms
  - Chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis)
  - Human immunodeficiency virus infection
  - Nephrotic syndrome
Current Recommendations from the NLA and AAP

- Ho FH need to be referred to a lipidologist ASAP

How to find help

- FH Foundation
  - www.fhfoundation.org

- National Lipid Association
  - www.NLA.org
Current Recommendations from the NLA and AAP

- Initiate cholesterol lowering medications at around the age of 8 for children with FH.
- Statins are the drugs of first choice.
- Six statins are FDA approved for children ages 10 and older:
  - rosvastatin (Crestor®),
  - atorvastatin (Lipitor®)
  - simvastatin (Zocor®)
  - pravastatin (Pravachol®)
  - lovastatin (Mevacor®)
  - fluvastatin (Lescol®)
  - pravastatin (Pravachol®)
- pravastatin (Pravachol®) for ages ≤ 8 years
Treatment Goal in Children

- For children aged 8-10 years
  - LDL-C is ideally reduced by 50% from pre-treatment levels

- For children aged ≥ 10 years, especially if there are additional risk factors i.e.;
  - Elevated Lp(a)
  - Diabetes
  - Hypertension

- Target LDL-C should be < 130 mg/dL
Additional medication

- ezetimibe (Zetia®) inhibits the absorption of cholesterol from the intestines.
- It can lower the LDL by about 20%.
- It has been studied in children and found to be well tolerated.
- Now approved by the FDA for use in children over the age of 10.
Initiation of high-dose statin monotherapy is standard of care

- Ezetimibe is added when patient is not at goal

- Bile acid sequestrants, nicotinic acid and fibrates are added alone or in combination for those not at goal

- Apheresis for patients on maximally tolerated therapy and 1-LDL-C >300 mg/dl or 2-CAD and LDL>200 mg/dl. Mipomersen and lomitapide are first-line therapy in HoFH

- Potential future therapy

FH Patients

STATIN

Not at goal/Intolerant

Cholesterol absorption inhibitors

Bile acid sequestrants

Nicotinic acid

Fibrates

Not at goal/Intolerant

Apheresis

Mipomersen

Lomitapide

PCSK9 inhibitors

Allan D. Sniderman et al. JACC 2014;63:1935-1947
PCKS9 Inhibitors

- PCKS9 (proprotein convertase subtilisin/kexin type 9) lowers the amount of LDL the liver can remove from blood by blocking or preventing recycling of the LDL receptor so serum LDL increases.

- If PCSK9 inhibitors bind to PSCK9 and allow the LDL receptors to recycle and eliminate LDL from blood.

- PCKS9 monoclonal antibodies are administered by subcutaneous injection

- PCSK9 inhibitors used in He FH patients who are intolerant to statins or have an elevated LDL-C level despite being on maximally tolerated statin therapy.
Currently only FH patient registry in the United States

Hybrid model with patient- and clinician-entered data

Patients enroll via FH Foundation website
  – Mobile friendly
  – Easy to navigate
  – Give back education to patients i.e. MeTree function
FAMILIAL HYPERLIPIDEMIA (FH)

- FH is a treatable disease
- The risk of premature coronary heart disease (CHD) is elevated about 20-fold in untreated FH patients.
- Long-term drug therapy significantly reduces or removes the excess lifetime risk of CHD
Familial Hypercholesterolemia Foundation
2017 Global Summit
Sept 24, 2017 – National Day FH Awareness Day

FH is DIFFERENT
FH is LIFE-THREATENING
FH is MANAGEABLE
FH is UNDIAGNOSED