

Evaluation and Management of Hyperlipidemia in Children

Douglas Rogers, MD
Center for Pediatric and Adolescent Endocrinology
Department of Preventive Cardiology

Cleveland Clinic Children's

Unfortunately neither I nor any immediate family members have any financial interests that may be construed as a conflict of interest with this presentation.

Thank You:

Michael Davidson, DO
Byron Hoogwerf, MD
Nadia Khoury, MS-III
Richard Lorber, MD
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Michael Macknin, MD

Objectives

- Determine when and what cholesterol and related testing is indicated in children
- Assess practical dietary management
- Determine when pharmacological treatment is warranted.

“The more I learn, the less I understand.”

Don Henley



2 10/12 y.o. girl presents with cholesterol 322, LDL 259. Her father had an MI at age 29. Family already follows a Mediterranean Diet.

QUESTIONS

1. What is the cause of this patient's hypercholesterolemia?
2. What can be done at this age to lower the LDL further?
3. Are any medications indicated now?
4. Will any medications be indicated in the future?
5. If so, what and at what age?

Risk Factors for Early Coronary Heart Disease

- Non-modifiable
 - Male
 - Family history of early CHD
 - Elevated Lipoprotein “little a” [Lp(a)]
 - Chronic renal failure
 - Post-transplant
 - Lupus
 - Elevated highly sensitive CRP

Risk Factors for Early Coronary Heart Disease

- Potentially modifiable or preventable
 - High LDL cholesterol
 - Low HDL cholesterol
 - Hypertension
 - Obesity
 - Metabolic syndrome
 - Tobacco use
 - Sedentary lifestyle
 - Stress
 - ? Diabetes, types 1 & 2

Previous Indications for Cholesterol Screening in Children

- Child older than age 2 years
- Family history of premature CHD
 - Males before age 55
 - Females before age 65
- Family history of dyslipidemia
- Parent with hypercholesterolemia (>240)
- Medical conditions that cause dyslipidemia or predispose to early CHD

<http://pediatrics.aappublications.org/cgi/content/full/122/1/198>

Medical Conditions that Cause Dyslipidemia or Predispose to Early CHD

- Diabetes, type 1 and type 2
- Hypertension
- Chronic liver disease (cholestasis)
- Chronic kidney disease (nephrotic synd)
- Chronic treatment with
 - glucocorticoids, sirolimus
- Post transplant
- Systemic lupus erythematosus

Screening for Hyperlipidemia in Children

- Total cholesterol
 - Does not need to be fasting
 - If >170, proceed to fasting lipid panel
- Total cholesterol – HDL= Non-HDL cholesterol
 - Does not need to be fasting
 - If non-HDL cholesterol >160, proceed to fasting lipid panel
- Fasting lipid panel
 - Do this initially in children with a medical condition that predisposes to CHD

Why not Screen All Children for Hyperlipidemia?

- Factors for universal screening:
 - Most parents don't know what their cholesterol level is.
 - Targeted screening only identifies about 50% of children with hypercholesterolemia.
- Factors against universal screening:
 - All families should be encouraged to follow the American Heart Association step 1 diet:
 - limit fat calories to 30% of total calories
 - limit saturated fat to 30% of total fat.
 - Further treatment would not be indicated unless there were other CHD risk factors.

Most Recent Recommendations

- Universal screening of all children between the ages 9 –11 years
 - Non-fasting lipid panel
 - Non-HDL cholesterol
- Targeted screening of children between ages 2 – 8 years
 - For children with 2 or more risk factors
 - Fasting lipid panel

National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Washington, DC: US Dept of Health and Human Services; 2012. NIH publication 12-7486A. http://www.nhlbi.nih.gov/guidelines/cvd_ped/

Xanthomas usually occur over the elbows and knees.



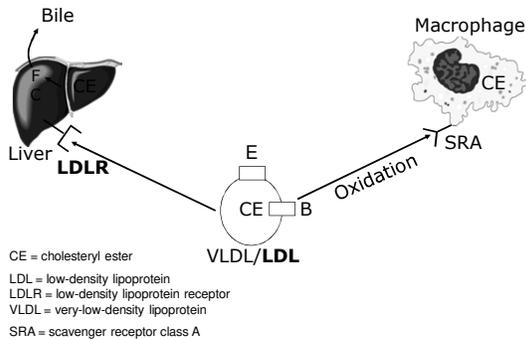
Abnormal Lipid Panel Patterns

Abnormality	Cholesterol	Triglyceride	HDL	LDL
Hypercholesterolemia	High	Normal	Low	High
Homozygous Hypercholesterolemia	Very high	Normal	Low / Normal	Very High
Hypertriglyceridemia	Normal / High	Very high	Low	Normal
Mixed Hyperlipidemia	High	High	Low	High

1. High Cholesterol and LDL

- Often familial
 - occurs in 1 per 250 children
 - mutation of one LDL receptor allele
 - mutation of Apo lipoprotein E or B
- Associated with early CHD
- Treat with
 - diet
 - low saturated fat
 - use foods with added vegetable stanols and sterols
 - if LDL remains > 160,
 - HMG-CoA reductase inhibitor
 - may add ezetimibe

Role of LDL Receptor in LDL Metabolism



HMG-CoA Reductase Inhibitors

HMG = 3-OH-3-methylglutaryl

- Decrease synthesis of cholesterol
- Increase LDL receptors
- Generally not approved below age 10
- Contraindicated in pregnancy, or nursing
 - potentially fertile women should use contraception
- Start with lowest dose
- May be associated with myalgia,
 - Supplements with co-Q-10 may alleviate myalgia
- Rarely cause myositis
 - check CPK
- Anti-inflammatory effect may help stabilize atherosclerotic lesions

HMG-CoA Reductase Inhibitors

<u>Brand Name</u>	<u>Generic Name</u>	<u>Available Doses</u>	<u>Properties</u>
Altoprev	Lovastatin	10, 20, 40, 60	Avoid CYP3A4 inhibitors
Crestor	Rosuvastatin	5, 10, 20, 40	May raise HDL, long half-life
Lescol	Fluvastatin	20, 40, 80	Avoid CYP2C9 inhibitors
Lipitor	Atorvastatin	10, 20, 40, 80	Avoid CYP3A4 inhibitors
Mevacor	Lovastatin	20, 40	Avoid CYP3A4 inhibitors
Pravachol	Pravastatin	10, 20, 40, 80	Approved down to age 8
Zocor	Simvastatin	5, 10, 20, 40,	Avoid CYP3A4 inhibitors
Red yeast rice			OTC, same side effects as other Statins.

CYP3A4 Inhibitors

- Macrolide antibiotics
- Azole antifungals
- Non-dihydropyridine calcium channel blockers
- Protease inhibitors
- Cyclosporine
- Amiodarone
- Large quantities of grapefruit juice

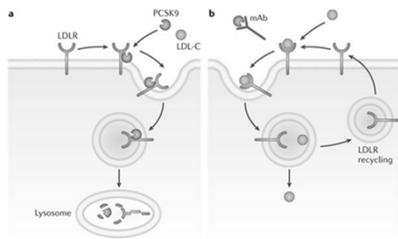
Ezetimibe

- Inhibits intestinal absorption of cholesterol
- Not approved below age 10
- Not very effective as monotherapy
- Available alone or in combination with Simvastatin

Alirocumab

- Humanized monoclonal anti-PCSK9 antibody
 - Given s.c. every 2 weeks
- PCSK9 is a serine protease in plasma that binds to the LDL receptor and targets it for lysosomal degradation.

Injected antibodies to PCSK9 decrease the degradation of the LDL receptor and allow more receptors to recirculate back to the liver cell surface.



Nature Reviews | Drug Discovery

Stanols and Sterols

- Compete with cholesterol for intestinal absorption
- Available over the counter
 - Cholestoff
- Added to some foods
 - Benecol, Take Control, Smart Balance Omega Plus
 - Minute Maid Heart Wise

American Academy of Pediatrics
Recommended LDL Concentrations for Pharmacologic
Treatment of Children and Adolescents 10 Years and Older

<u>Patient Characteristics</u>	<u>Recommended Cut Points</u>
1. No other risk factors for CVD	1. LDL > 190 despite diet
2. Other risk factors present:	2. LDL > 160 despite diet
3. Children with Diabetes	3. LDL > 130

<http://pediatrics.aappublications.org/cgi/content/full/122/1/198>

When to Medically Treat
Hypercholesterolemia in Children

- Child is over 10 years old.
- Family has made as many lifestyle changes as they can.
 - limiting saturated fat
 - restricting red meat and dairy fat
- Child is using OTC stanols/sterols.
- LDL is still elevated per AAP criteria

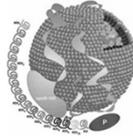
Decision Guide for Adults

<https://statindecisionaid.mayoclinic.org/>

Treatment for elevated Lp(a) is 2 baby aspirin daily.

Lipoprotein(a) or Lp(a)

- Lp(a) - LDL like particle with a molecule of Apolipoprotein B-100 linked by a disulphide bridge to Apolipoprotein (a).
- The apo(a) component is similar to plasminogen in terms of structure and competes with plasminogen for binding sites resulting in reduced fibrinolysis and the formation of blood clots.
- Lp(a) is also thought to speed up the process of atherosclerosis by binding LDL, calcium and other components into an atherosclerotic plaque on the blood vessel wall.
- This dual action of Lp(a) explains its role in the promotion of cardiovascular disease.



2. Extremely High Cholesterol and LDL

- Due to mutation of both LDL receptor alleles
- Always familial, both parents heterozygous
- Associated with very early CHD and death
 - Probably occurs 1 in 500,000
- Total cholesterol may be over 800mg/dl
- Treat with
 - Diet
 - HMG-CoA reductase inhibitor and ezetimibe
 - PCSK9 antibodies
 - Plasmapheresis

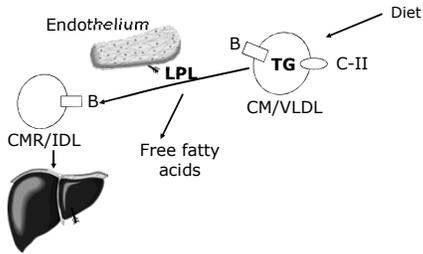
2. Extremely High Cholesterol and LDL

- Lomitapide
 - Inhibits microsomal triglyceride transfer protein required for VLDL formation
 - Liver toxicity
- Mipomersen
 - antisense oligonucleotide targets mRNA for apolipoprotein B, administered as a weekly injection
 - Liver toxicity
- Plasmapheresis (LDL >300)
- Liver transplant

3. Very High Triglyceride, Normal-High Cholesterol

- Often familial
 - endothelial lipoprotein lipase deficiency
 - Apo lipoprotein C-II deficiency
- Triglyceride levels may exceed 1,000mg/dl
- May cause pancreatitis
- Treat with
 - Diet
 - Fish oil, 1,000mg q.i.d.
 - Lovaza 840mg Omega-3 oils per capsule
 - Fenofibrate

Role of Endothelial Lipoprotein Lipase in Triglyceride Metabolism



CM = chylomicron; CMR = chylomicron remnant; IDL = intermediate-density lipoprotein; LPL = lipoprotein lipase; TG = triglyceride

Fenofibrate

- Activates peroxisome proliferator activated receptor α (PPAR α)
 - down regulates transcription of the gene for Apo lipoprotein C-III
 - Apo lipoprotein C-III inhibits endothelial lipoprotein lipase
 - LDL molecules become larger and less atherogenic
- Decreases metabolism of HMG-CoA reductase inhibitors

When to Medically Treat Hypertriglyceridemia in Children

- Child is over 10 years old.
- Family has made as many lifestyle changes as they can.
 - eliminating beverages with sugar
 - limiting fats and oils in diet
- Child is using OTC fish oil.
 - Lovaza, available by prescription
- Fasting triglyceride level is still > 400 mg/dl

4. Mixed Hyperlipidemia High LDL and High Triglycerides

- May be familial
- Usually due to lifestyle
 - obesity
 - lack of exercise
 - unhealthy diet
- May be associated with other conditions
 - metabolic syndrome
 - polycystic ovaries
 - type 2 diabetes

Treatment of Mixed Hyperlipidemia

- Lifestyle changes
 - diet
 - eliminate beverages with sugar
 - increase amount of fiber
 - restrict saturated fat
 - limit red meat
 - use fat free milk
 - avoid fast food and buffet restaurants
 - choose snacks carefully
 - activity

Treatment of Mixed Hyperlipidemia

- OTC medical treatment
 - fish oil
 - stanols and sterols
 - niacin
 - may worsen glucose intolerance
 - flushing
- Medical treatment
 - HMG-CoA reductase inhibitors

When to Medically Treat Mixed Hyperlipidemia in Children

- Child is over 10 years old.
- Child has 2 or more risk factors for CHD
- Family has made as many lifestyle changes as they can.
 - eliminating beverages with sugar
 - limiting fats and oils in diet
 - increasing activity
- Child is using fish oil and stanols
- LDL is still > 160 mg/dl

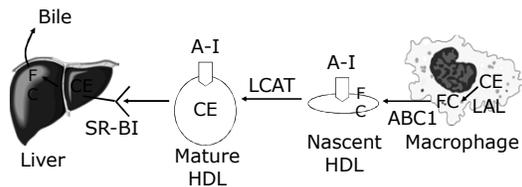
Review of Medical Treatment for Hyperlipidemia

<u>LIPID ABN</u>	<u>UNDER AGE 10</u>	<u>OVER AGE 10</u>
High cholesterol	Stanols/sterols	Statins, ezetimibe Anti-PCSK9 Ab
High triglycerides	Fish oil	Fenofibrate
Mixed hyperlipidemia	Stanols/sterols & fish oil	HMG-CoA reductase inhibitors
Extremely high cholesterol	Plasmapheresis Liver transplant Anti-PCSK9 Ab	Plasmapheresis Liver transplant Anti-PCSK9 Ab

Future Considerations

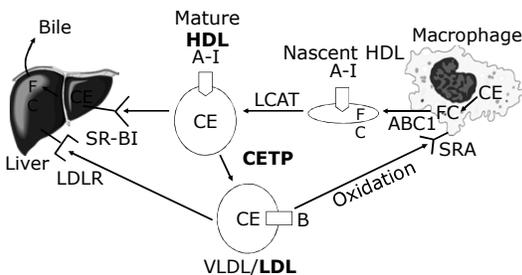
- Medications are being developed to raise HDL levels
 - Cholesteryl ester transfer protein inhibitors
- Enzyme replacement treatment for Lysosomal Acid Lyphase deficiency, now available.
- Drugs that target the thyroid hormone receptor in the liver

HDL Metabolism and Reverse Cholesterol Transport



LAL = lysosomal acid lipase; (Deficiency causes Wolman or CESD disease)
 ABC1 = ATP-binding cassette protein 1; (Deficiency causes Tangier disease)
 A-I = Apo lipoprotein A-I;
 CE = cholesteryl ester; FC = free cholesterol;
 LCAT = lecithin:cholesterol acyltransferase;
 SR-BI = scavenger receptor class BI

Role of CETP in HDL Metabolism



CETP = cholesteryl ester transfer protein
 LDL = low-density lipoprotein
 LDLR = low-density lipoprotein receptor
 VLDL = very-low-density lipoprotein

What Is a Provider To Do?

- For children age 2 - 8:
 - Determine if any parent, grandparent, aunt or uncle has had a heart attack or stroke before age 55.
 - Determine if either parent has had a cholesterol level above 240mg/dl.
- If yes to either of the above:
 - check a random cholesterol and HDL
- For children over age 9:
 - Check a random lipid panel
 - OR
 - Check cholesterol and HDL to determine the non-HDL cholesterol

What Is a Provider To Do?

- If non-HDL cholesterol is above 160:
 - obtain fasting lipid panel, TSH
- If the LDL is above 160:
 - start diet changes
 - use spreads made with stanols and sterols
 - try to eat fish twice weekly
 - use only olive oil or canola oil when necessary
 - eliminate red meat and dairy fat
 - limit saturated fat to 1/3 of total fat

Rule of Threes

3:1 = Total calories : fat calories
then
3:1 = Total fat grams : saturated fat grams

What Is a Provider To Do?

- If LDL remains above 160, patient over age 10, and there are at least 2 risk factors for CHD:
 - start low dose of HMG-CoA reductase inhibitor
 - refer to pediatric dyslipidemia clinic
 - 216-444-9353

What Is a Provider To Do?

- If triglycerides are greater than 400:
 - Check TSH
 - Encourage lifestyle changes:
 - eliminate beverages with sugar from household
 - increase the amount of fiber in the diet
 - restrict saturated fat to 1/3 of total fat
 - limit red meat
 - use fat free milk
 - avoid fast food and buffet restaurants
 - choose snacks carefully
 - increase activity

What Is a Provider To Do?

- If triglycerides remain above 400:
 - Start fish oil, 1000mg p.o. q.i.d.
 - Refer to a pediatric dyslipidemia clinic
 - 216-444-9353



2 10/12 y.o. girl presents with cholesterol 322, LDL 259. Her father had an MI at age 29. Family already follows a Mediterranean Diet.

QUESTIONS

1. What is the cause of this patient's hypercholesterolemia?
2. What can be done at this age to lower the LDL further?
3. Are any medications indicated now?
4. Will any medications be indicated in the future?
5. If so, what and at what age?



2 10/12 y.o. girl presents with cholesterol 322, LDL 259. Her father had an MI at age 29. Family already follows a Mediterranean Diet. Her younger sister also has hypercholesterolemia.

QUESTIONS

1. What is the cause of this patient's hypercholesterolemia?
FAMILIAL HYPERCHOLESTEROLEMIA
2. What can be done at this age to lower the LDL further? DIET and STANOLS / STEROLS
3. Are any medications indicated now? NO
4. Will any medications be indicated in the future? YES
5. If so, what and at what age?
Atorvastatin started at age 10
Last LDL 126

Things I Didn't Talk About.

- Bile acid binding resins
 - very poorly tolerated.
 - although still considered a first line medical therapy in children, compliance is so poor, probably not worth trying.

Things I Didn't Talk About.

Historical classification system for lipid disorders that I do not find helpful.

Fredrickson Classification of Lipid Disorders [†]		
Frederickson phenotype	Lipoprotein abnormality	Typical lipid levels
I	Chylomicrons	Triglycerides (TG) >99th percentile
IIa	LDL	Total cholesterol (TC) >90th percentile; depending upon type, may also see TG and/or apolipoprotein B ≥90th percentile
IIb	LDL and VLDL	Depending upon type, TC and/or TG ≥90th percentile and apolipoprotein B ≥90th percentile
III	Remnants of VLDL and chylomicrons	TC and TG >90th percentile
IV	VLDL	TC >90th percentile; depending upon type, may also see TG >90th percentile or low HDL
V	Chylomicrons and VLDL	TG >99th percentile

[†]Adapted from Fredrickson, DS, Ann Intern Med 1971; 75:471.

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