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Pediatric Lipid Management:

An Earlier Approach

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INTRODUCTION

Although adult cardiovascular disease (CVD) mortality has been curtailed primarily from improvements in atherosclerotic risk factor treatment, an alarming countervailing trend dominates the present and future of CVD: obesity, obesity-related dyslipidemia, and type 2 diabetes.^{1–6} Children offer a prime opportunity to continue CVD risk factor reduction and address emerging trends, especially dyslipidemia.

There are 4 general classes of pediatric dyslipidemias:

- Medication-related dyslipidemia
- Dyslipidemia related to lifestyle factors
- Genetic dyslipidemia
- Dyslipidemia secondary to a medical condition.

There are 3 chief genetic dyslipidemias (Table 1).

- Familial hypercholesterolemia (FH). FH is an autosomal dominant disorder that interferes with either apolipoprotein B (ApoB) assembly or the receptor-mediated clearance of low-density lipoprotein cholesterol (LDL-C) in roughly 1 in 500 persons with heterozygosity or 1 in a million homozygotes.^{7–10} However, homozygotes frequently develop xanthelasmas of the canthi, xanthomas on the

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ADDITIONAL RESOURCES

Centers for Disease Control resources on obesity. Available at: <http://www.cdc.gov/obesity/resources/index.html>.

2011 NHLBI integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Available at: <http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/index.htm>.

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extensor surfaces of limb joints, arcus senilis of the eye, and internal consequences, including myocardial infarction and ischemic cardiomyopathy, often in the first 2 decades of life. The heterozygous phenotype predisposes to early atherosclerosis and is more common than, and as treatable as, any disorder within national newborn screening programs.

- Familial combined hyperlipidemia. Familial combined hyperlipidemia is another genetic dyslipidemia with high LDL-C and triglycerides (TGs), but lacks the degree of TG increase necessary to trigger pancreatitis. It confers CVD risks nearly as high as FH and may be as prevalent as 1% of the population.^{11,12}
- Familial severe hypertriglyceridemia (HTG). Although 1 in 600 individuals have severe HTG (defined as TG>10 mmol/L or 885 mg/dL),¹³ much of this is caused by environment and lifestyle. Genetic or familial HTG has many implicated genes, but the most common is homozygous autosomal recessive loss of function mutations in lipoprotein lipase or apolipoprotein C2 and occurs in 1 in 1×10^5 individuals.^{13,14} Hindered degradation of TG leads to significantly increased serum TG.^{15,16} At levels of more than 1000 mg/dL, the risk of acutely life-threatening pancreatitis increases. However, risk stratification by TG level is inadequate because many lipid providers follow persons with TG greater than 2000 mg/dL who have never had pancreatitis. Despite this uncertainty, prompt treatment is recommended.¹⁷

Suggested responses to pediatric dyslipidemias include, but are not limited to, removing a causative agent, lifestyle modification, treating an underlying medical condition, and in severe cases pharmacotherapy. Each of these therapeutic maneuvers is intended to accomplish 2 important goals: preventing acute pancreatitis in individuals with very increased TGs levels and preventing atherosclerotic CVD later in life.

Childhood is also a key period for progress because children are susceptible to deleterious lifestyle influences; are directly affected by CVD risk factors; already accumulate atherosclerotic phenotypic changes; are more malleable to lifestyle habit alterations to avoid CVD risk factors; and, through internal motivation and/or support from guardians or peers, have the capacity to treat CVD risk factors through lifestyle modification alone. The clinical encounter offers an opportunity to leverage abnormal laboratory results into a multifaceted cardiometabolic remedy. In a recent study of medical providers caring for children, 74% thought that lipid screening and treatment would reduce future CVD outcomes. Despite this belief, only 16% universally screened their patients, 54% selectively screened, and 34% did not screen at all. These data underscore the need to engage providers.

The National Heart, Lung and Blood Institute (NHLBI) Expert Panel on Integrated Guidelines for Cardiovascular Disease Health and Risk Reduction in Children and Adolescents, released their guidelines in November 2011, unifying previously disjointed aspects of CVD prevention, including physical activity, nutrition, obesity, blood pressure, lipids, and tobacco use, under a singular aegis and updated these domains with a comprehensive review of relevant data.¹⁹ In compiling these revised recommendations, the

NHLBI guidelines lengthen the reach of CVD prevention to an earlier, more plastic stage of life.

THE GUIDELINES: FRAMEWORK AND SYNOPSIS

CVD risk factor modification can be subdivided into primary, secondary, and primordial prevention.²⁰ Primary prevention is the treatment of risk factors to avoid the first event, secondary prevention is the evasion of recurrent cardiovascular events in patients with a history of CVD, and primordial prevention is intervention to prevent CVD risk factors from arising at all.²¹ In order to inhibit the development of CVD risk factors, the NHLBI Integrated Guidelines make precise, developmentally appropriate suggestions interweaving CVD risk factor prevention within general pediatric practice. The screening and treatment sections focus on the premise that CVD risk factors must be centered on the child's aggregate combination of cardiac risks, rather than any particular risk factor.

It is well recognized that atherosclerotic abnormalities arise in childhood, that these changes are related to the presence of CVD risk factors, and that risk factors in adults are directly related to cardiac events in a continuous fashion.^{22–26} However, when the population is sick, as Geoffrey Rose²⁷ described, what is to be done? Nationally representative pediatric data show that overweight and obesity increase the relative risk of increased LDL cholesterol (LDL-C); however, approximately 45% of all adolescents with high LDL-C are of normal weight, suggesting that CVD risk factors are widespread. It is therefore essential that the proposed suggestions be scaled to the population level because fixating on excess weight misses almost half the problem.²⁸

It is also clear that population-wide interventions can be successful, as shown by tobacco use reduction. Tobacco use reduction has been achieved through mobilizing public sentiment; initiating economic disincentives; and placing restrictions on the procurement, advertisement, and use of tobacco products. Similar efforts to reduce the causes of hyperlipidemia, hypertension, or obesity meet entrenched resistance from the lack of data supporting secondhand harm from lifestyle behaviors and trepidation about the freedom of personal choice. Protecting children from circumstances that ultimately lead to CVD risk factors may be more readily accepted because their lifestyle choices are appropriately constrained by caregivers because they are less proficient in making their own healthy choices. Therefore the guidelines make primordial prevention recommendations for all children and primary prevention recommendations for affected children, including those with dyslipidemia.

Primordial Prevention Recommendations

1. The Integrated Guidelines seek to perform population-level prevention through each child. Nutrition recommendations include:
 - Breastfeeding for the first 12 months
 - Restricting calories derived from milk fat and fruit juice
 - After age 2 years, adherence to the Cardiovascular Health Integrated Lifestyle Diet (CHILD-1) diet¹⁹

2. Tobacco abolition is recommended from infancy and through childhood and adolescence
3. Universal recommendations with respect to activity and inactivity consist of:
 - Consistent active play in toddlerhood
 - One hour per day of moderate to vigorous exercise in older children and adolescents
 - Inactive screen time is fully discouraged before age 2 years
 - Screen time is restricted to less than 2 hours per day in older children

The guidelines advance, endorse, and stress this population-level approach to CVD risk factor mitigation as the new norm for US children. It is thought that this combination of interventions will simultaneously protect against incident dyslipidemia, diabetes, hypertension, and obesity.

Primary Prevention Recommendations

The Integrated Guidelines refine, extend, and combine previous guidelines from the American Academy of Pediatrics (AAP) 2008 guidelines on dyslipidemia detection.^{29,30} These prior efforts advocated for screening for lipid disorders in patients with high-risk medical conditions and/or abnormal family histories and pharmacologic management of severe pediatric lipid disorders. The 2011 NHLBI guidelines extend the AAP cholesterol guidelines by recommending universal screening to enhance the detection of young patients with FH who are subject to atherosclerotic events in early adulthood.

1. Universal screening can be initiated with either:
 - a. A calculated nonfasting non-high-density lipoprotein cholesterol (HDL-C) level, and HDL-C level, or
 - b. A fasting lipid panel
2. Abnormal levels should be confirmed with a repeated fasting test, especially for TG irregularities
3. Targeted lipid screening can occur
 - a. At any time after age 2 years for children at high atherosclerotic risk (Box 1)¹⁹
 - b. At the provider's preference, or
 - c. At the family's discretion
4. Very high levels of TG or LDL-C (500 mg/dL and 250mg/dL, respectively) trigger a referral to a lipid specialist in order to manage genetic dyslipidemias

The NHLBI guidelines are designed to set thresholds to reflect the well-documented age-specific distribution of lipid levels in the hope of increasing the number of children eligible for attention but constraining the number eligible for medication. They also mirror the 3

category groupings of the Adult Treatment Panel III/National Cholesterol Education Program in defining acceptable lipid values (Table 2).

Treatment of CVD risk factors is an essential part of the NHLBI guidelines. It is also clear that CVD risk factors are modifiable. Adult cohort studies show that 90% of CHD and incident stroke and were attributable to modifiable risk factors.^{31–34} Temporal trends show that smoking rates have decreased in adults, and, in American children, cholesterol levels seem to be declining as well.^{35,36} According to recent randomized controlled trials in adults with type 2 diabetes, coronary disease with systolic heart failure, and chronic stable angina, aggressive CVD risk factor modification was as effective as invasive revascularization in averting CVD events.^{37–39} In contrast, 30-year global trends show that obesity prevalence is increasing and cholesterol levels are worsening.^{40,41} Therefore, clinicians can be confident that CVD risk factors are modifiable in both the positive and negative directions. Therapy in children is justified by direct links between risk factors in adolescence and atherosclerotic disorders, CVD risk factor stability from childhood to adulthood, and the ability of pediatric risk factors to predict adverse vascular changes and CVD events, even after adult CVD risk factor level adjustment.^{24,25,42–46}

The Expert Panel recommends that children with lipid disorders partake of dyslipidemia-determined special diets for at least 6 months and diminish obesity if appropriate. After 6 months of lifestyle modification, persistent LDL-C increase triggers referral to lipid specialists to consider statin initiation. The presence of multiple risks or higher intensity risks progressively decreases the LDL-C threshold to initiate statin pharmacotherapy, and decreases the goal LDL-C concentration on treatment.^{47–51} The key components of TG treatment center on simple carbohydrate intake reduction, increased omega-3 intake through fish consumption or omega-3 supplements, or severe reduction in fat intake as appropriate. If these maneuvers are ineffective in reducing TG levels sufficiently to mitigate the risk of pancreatitis, referral to a lipid specialist for non-HDL reduction through lipid pharmacotherapy is advised.

CHALLENGES TO THE LIPID MANAGEMENT GUIDELINES

Universal Screening

The most controversial topic raised by the integrated panel has been a call for universal lipid screening, which is intended to improve identification of genetic dyslipidemias like heterozygous FH. FH seems to fulfill 1968 World Health Organization criteria: it occurs in 1 in 500 births, silently leads to highly increased LDL-C over a person's life, manifests as CVD mortality events in young adulthood, and the combination of lipid-lowering drugs and lifestyle modification seems to attenuate the excess risk.⁵² Approximately 20% of girls and 50% of boys with FH heterozygosity will have a coronary event before age 50 years.^{7,8,53} Although previous guidelines restricted screening to only those children with an increased risk of dyslipidemia based on personal health features or family history, studies show that reliance on family history of CVD events or high lipid levels may miss 30% to 60% of afflicted children because of a lack of knowledge about family history, lack of understanding about lipid levels, the ability of medications presently available to profoundly reduce or prevent CVD events in affected adults, or a parent's refusal to be tested for

cholesterol level.^{9,54–57} Focusing on children treats them as individuals worthy of care independent of the dependability of their parents and, in a reverse cascade, may boost identification of family members with FH who might not have been detected otherwise.

The disadvantages of universal screening should not be glossed over.^{58–60} Children could be incorrectly labeled as abnormal from a nonfasting lipid screening, because CVD risk factors fluctuate throughout childhood and adulthood. However, also similar to adults, isolated lipid measurements in childhood predict atherosclerosis in adulthood.^{24,25,42} The guidelines recommend using high thresholds to designate abnormal levels in conjunction with taking the average of multiple lipid values to help avoid misclassification and errors from regression to the mean. It is highly likely that a small number will be inappropriately labeled as FH despite following the guidelines in obtaining 2 more fasting lipid panels. More data must be gathered to assess the negative and positive biological, social, and psychological effects of this screening approach.

Lifestyle Dyslipidemias

The panel acknowledges the probability of discovering lifestyle-driven dyslipidemias and advocates that such children should receive medical attention. Critics note that lipid values fluctuate during childhood and that obesity increases an individual's risk for having abnormal lipid values. With this information they object to classifying a multitude of children, who are already psychologically vulnerable from an abnormal weight label, with an abnormal cholesterol label. If the goal is to lose weight, failure is common and makes the child feel even worse.^{58–60}

Although obesity increases the risk of accruing lifestyle-induced dyslipidemias, note that a large proportion of dyslipidemic children are of normal weight, and the most patients who are of abnormal weight are not dyslipidemic.²⁸ In a related analysis that may parallel efforts in lipid management, detecting and treating abnormal weight with the goal of modifying blood pressure–related CVD did not seem to be a cost-effective way to prevent CVD outcomes.⁶¹ Although the origins of both derive from suboptimal diets and activity levels, dyslipidemia and excess weight are not synonymous. Specific lifestyle modification can modify dyslipidemia without affecting weight immediately.^{62–65} As described in the guidelines, for example, the avoidance of simple carbohydrates is not expected to significantly alter LDL-C, but may be useful in hindering insulin resistance mediated by high TG. These dyslipidemia-specific dietary instructions are effective but onerous for families and so should not be applied to the entire population. On the contrary, recent adult meta-analytical data on the effects of dietary saturated fat on CVD and CHD risk outcomes in prospective adult cohort studies suggested that dietary saturated fat was not associated with increased CVD or CHD risk.¹¹ However, a broad-based adult cohort is not equivalent to a population presenting early in life with markedly abnormal lipid values, and thus the data cannot be generalized to pediatric dyslipidemia. In addition, the CHILD-1 diet recommended for all children without dyslipidemias safely encourages moderation in simple carbohydrates, processed foods, and saturated fat, as well as encouraging consumption of vegetables and lean proteins, which is widely accepted as a sensible approach.¹⁹ In addition, when motivated to avoid medication, youth and families may become more engaged.

By extension, critics are concerned about lifestyle dyslipidemic patients being loosely prescribed statins. The NHLBI panel instead mandates lifestyle alterations as the primary response. Only after this has been assiduously exhausted and additional CVD risks are also present can pharmacotherapy be considered, preferably under a lipid specialist's guidance. This advice is distinctly at odds with treatment patterns among adult providers. The most recent evidence on lipid-lowering therapy indicates that the number of children being treated is grossly inadequate.^{66,67} Contrary to popular fears, the guidelines advocate against the indiscriminate distribution of statin drugs to obese children.

Lipid-lowering Treatment

The main criticisms of pediatric lipid pharmacotherapy in general are:

- Invocation of 10-year CVD risk calculators to show that children are inherently low risk
- Lack of data on the benefits of childhood treatment
- Lack of long-term safety data

It is important to recall that the primary intended pediatric recipients of lipid-lowering medications are those with FH. It is improper to use the Framingham 10-year risk calculator on those with genetic dyslipidemia. The Framingham calculator is intended for and derived from a general population cohort, not a high-risk diagnosis such as FH. For example, inputting a cholesterol value of more than 320 mg/dL into the online calculator results in an error message requesting a smaller value. A more suitable risk assessment is family history data in patients with FH showing 50% and 20% risk of coronary events in men and women less than 50 years of age, respectively.^{7,8,68}

The criticism regarding lack of long-term data is well taken. The guidelines outline existing data regarding the efficacy and tolerability of statins in reducing LDL-C. However, there are neither studies on the ability of statin therapy started in youth to reduce CVD events nor long-term safety studies, because the logistical complexity and cost of clinical trials following large numbers of patients over several decades are impractical. A recent meta-analysis of placebo adult randomized controlled trials compared the effect of short-term lipid-lowering agents versus naturally occurring LDL-C-lowering genetic mutations on CVD events.⁵¹ This elegant study revealed that CVD prevention per unit LDL-C decrease was several times more effective by genetic polymorphism than by pharmacologic intervention, implying that the amount of time spent at a reduced LDL-C concentration was the leading feature of additional CVD protection. Furthermore, sequence variations in the *PCSK9* gene, which is known to reduce LDL-C, caused 88% and 47% reductions in cardiac disease in African American and white populations.¹⁸ These findings are also in accord with anthropologic epidemiology, which shows lower rates of CVD in cultures with habitually low LDL-C on a population basis.^{69,70}

Critics of the guidelines cite unforeseen side effects from other medicines in the past as a reason to avoid a hypothetical pediatric-specific adverse event for lipid-lowering medicine. In contrast, the volume of patient data from statin therapy in adults and children is overwhelming and argues against additional adverse events beyond the well-described

myotoxicity, emerging risks regarding incident diabetes mellitus, and possible risk of hepatotoxicity.^{47–49,71} When family history involves early and severe CVD in a parent, the discussion about treatment takes on a greater sense of urgency. Although the described risks are important to consider, the preponderance of data support the use of lipid-lowering medication in children affected by FH. However, the decision to treat an affected child is always a collaborative one between provider, parent, and child.

SUMMARY

The NHLBI Expert Panel Integrated Guidelines promote the prevention of CVD events by encouraging healthy behaviors in all children, screening and treatment of children with genetic dyslipidemias, usage of specific lifestyle modifications, and limited administration of lipid pharmacotherapy in children with the highest CVD risk. These recommendations place children in the center of the fight against future CVD. Pediatric providers may be in a position to shift the focus of CVD prevention from trimming multiple risk factors to cutting out the causes CVD.

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KEY POINTS

- Numerous long-term observational cohort studies show that subclinical atherosclerosis is a progressive disease that arises in childhood and continues through the adult years.
- Deficiencies in targeted lipid screening to identify high-risk individuals led the 2011 National Heart, Lung and Blood Institute Expert Panel for Pediatric Cardiovascular Disease (CVD) Risk Reduction to recommend universal screening.
- Amid concerns that extended screening may induce inappropriate treatment, pharmacotherapy is restricted to patients with genetic dyslipidemias and multiple high-risk CVD factors.
- This article presents a synopsis, and discusses challenges to the guidelines and our own criticisms and suggested future directions.

Box 1**Risk factor definitions for dyslipidemia algorithms****Family history**

In parent, grandparent, aunt, or uncle a history of myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, or sudden cardiac death before age 55 years in men or 65 years in women

High-level risk factors

Hypertension requiring therapy (>99% + 5 mm Hg)

Current cigarette smoker

Body mass index (BMI) greater than 97%

High-risk conditions

Diabetes mellitus, type 1 or 2

After heart transplant

Chronic kidney disease

End-stage renal disease

After renal transplant

Kawasaki disease with coronary aneurysms

Moderate-level risk factors

Hypertension not requiring medication

BMI greater than 95% but less than or equal to 97%

HDL-C less than 40 mg/dL

Moderate-risk condition

Chronic inflammatory disease

Human immunodeficiency virus infection

Nephrotic syndrome

Kawasaki disease without coronary aneurysm

Adapted from Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213–56; with permission.

Table 1

Prominent genetic dyslipidemias in children

Dyslipidemia	Abnormal Lipid Fraction	Prevalence Estimate	Predominant Mechanism/Mechanism Defect
Familial hypercholesterolemia	High LDL-C	Heterozygotes, 1 in 500 Homozygotes, 1 in million	Decreased LDL-C clearance
Familial combined hypercholesterolemia	High LDL-C and high triglycerides/VLDL	1 in 100 ¹¹	Increased ApoB production
Familial severe hypertriglyceridemia	High triglycerides/VLDL	1 in 100,000 ¹³	Decreased triglyceride/VLDL degradation

Abbreviations: ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein.

Table 2

Lipid parameter classification

Category	Acceptable	Borderline	High
Total cholesterol	<170	170–199	200
LDL-C	<110	110–129	130
TG			
0–9 y	<75	75–99	100
10–19 y	<90	90–129	130
Non-HDL-C	<120	120–144	145
ApoB	<90	90–109	110
Category	Acceptable	Borderline	Low
HDL-C	>45	40–45	<40
ApoA-I	>120	115–120	<115

Abbreviation: ApoA–I, apolipoprotein A–I.

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