A Review of Guidelines for Dyslipidemia in Children and Adolescents

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ABSTRACT

The recent publication of new pediatric lipid screening guidelines represents a change in recommendations regarding lipid screening and management for pediatric patients that will affect all health care professionals who care for children and adolescents. The guidelines differ from the selective screening recommended by the 2007 US Preventive Services Task Force, instead recommending routine lipid screening for children and adolescents at ages 9-11 years and again at 17-21 years. Studies have shown that limiting lipid screening to patients with risk factors fails to identify many patients with genetic or acquired dyslipidemias. Without universal screening, many at-risk children will not be identified.

A CASE SCENARIO

An overweight 15-year-old male was referred to clinic after his father died suddenly at 33 years of age while working on an assembly line at a factory. Myocardial infarction was the confirmed cause of the father's death. The father's total cholesterol (TC) was greater than 300 mg/dL. A fasting lipid profile in the 15-year-old patient showed TC of 314 mg/dL, low-density lipoprotein (LDL) 254 mg/dL, high-density lipoprotein (HDL) 35 mg/dL, and triglycerides (TG) of 125 mg/dL, confirming a diagnosis of familial hypercholesterolemia (FH) along with features of familial combined hyperlipidemia (FCH).

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BACKGROUND

Significant lipid disorders in pediatrics commonly are missed.[1-4] Previous research on selected screening demonstrates that as many as half of children with genetic and acquired cholesterol disorders are missed without routine screening.[5,6] Publication of new pediatric lipid screening guidelines in the *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report*[7] in December 2011 representS a change in recommendations regarding lipid screening and management for pediatric patients that will affect all health care professionals who care for children and adolescents. The guidelines recommend universal lipid screening with a non-fasting TC, high-density lipoprotein (HDL), and non-HDL cholesterol at ages 9-11 years and again at 17-21 years in children and adolescents for routine screening. Children and adolescents with higher risk medical conditions or concerning family histories can be screened as young as 2 years old or at the time the medical condition or concerning family history is diagnosed. The screen should be considered every 5 years thereafter. These recommendations differ from the selective screening recommended by the 2007 US Preventive Services Task Force, which concluded that "the evidence was insufficient to recommend for or against routine screening for lipid disorders" in children and adolescents up to age 20.[8]

Overweight and obesity are well-established cardiovascular risk factors in adults, and pediatric obesity is linked to increased rates of dyslipidemia.[9] Unfortunately, the rising incidence of pediatric obesity in the United States is evident. Currently, approximately one-third of American children are overweight or obese.[10] Consequently, rates of pediatric dyslipidemia in the United States are rising.[11] Previously, pediatric cholesterol guidelines have focused on identifying children with elevated LDL or with FH. However, the most common pediatric dys-

lipidemia is now moderately to severely elevated TG, normal to mildly elevated LDL, and reduced HDL, most commonly seen in obese children and adolescents.

WHICH DYSLIPIDEMIAS ARE FREQUENTLY DIAGNOSED IN CHILDREN AND ADOLESCENTS?

Dyslipidemias are abnormal amounts of lipid (hydrophobic fat molecules such as cholesterol and fatty acids) and/or lipoprotein (aggregate molecules consisting of lipids and apolipoproteins that bind to lipids) in the blood. Levels of lipid and lipoprotein are a result of genetic and environmental contributions (diet, activity, etc). Normal ranges of lipids and lipoproteins have been established in the pediatric population. Dyslipidemias can be caused by primary genetic disorders or by secondary causes, the most common of which is obesity.

There are many described genetic dyslipidemia syndromes. The most common found in pediatric practice are FCH and FH.[12] Table 1 compares pediatric features of FCH and FH. FH occurs in 1 in 300-500 people in the US population and is inherited in an autosomal dominant pattern. FH patients present with severely elevated TC and LDL that is present from birth, and they typically have normal TG and HDL. Patients with FH develop premature cardiovascular disease, with 50% of men and 25% of women developing a cardiovascular event by 50 years old.[12]

FH is underdiagnosed and undertreated, particularly in the pediatric population. Some experts estimate that only 20% of patients with FH are diagnosed[1,2] and only a small percentage of those receive appropriate treatment.[2,13] FH guidelines do not require genetic testing to confirm the diagnosis, as it is unlikely to modify a patient's management approach at the current time.[14] FH should be suspected in a patient 20 years of age or younger if the untreated fasting LDL is ≥160 mg/dL or the non-HDL cholesterol is ≥190 mg/dL, values that are substantially above the 95th percentile.[3] The diagnosis is confirmed if the patient has a first-degree family member with premature atherosclerosis and an LDL > 200 mg/dL.

As with adults, FCH is the most common pediatric dyslipidemia seen in practice today, with some estimates of incidence as high as 1 in 100 children.[4] Pediatric patients have moderately to severely elevated TG, normal or mildly elevated LDL, and reduced HDL. It is most commonly associated with overweight or obesity, hypertension, and insulin resistance in the pediatric population.[4,15-19] Diagnostic criteria for FCH are less clear and the entity represents a much more heterogeneous population than does FH, making estimates of pediatric prevalence difficult.

Table 1. Features of Familial Combined Hyperlipidemia and Familial Hypercholesterolemia in the Pediatric Population

	Familial Combined Hyperlipidemia (FCH)	Familial Hypercholesterolemia (FH)
Incidence	~1:100	1:300-500
Inheritance Pattern	Polygenic	Monogenic (usually autosomal dominant)
Associated Conditions	Obesity, insulin resistance, hypertension	None
LDL Level	Normal	High
HDL Level	Low	Normal
TG Level	High	Normal

Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG; triglycerides.

Table 2. Risk Factors

High-Level Risk Factors

Hypertension requiring drug therapy (BP ≥ 99th percentile + 5 mmHg)
Current cigarette smoker
BMI ≥ 97th percentile
Presence of high-risk conditions
(Diabetes mellitus [DM] is also a high-level risk factor but it is classified here as a high-risk condition to correspond with Adult Treatment Panel III recommendations for adults that DM is considered a cardiovascular disease. equivalent.)

Moderate-Level Risk Factors

Hypertension not requiring drug therapy
BMI ≥ 95th percentile, < 97percentile
HDL-C < 40 mg/dL
Presence of moderate-risk conditions (Table 3)

Abbreviations: RF, risk factor; definitions for dyslipidemia algorithms (+) family history: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle, male <55 y, female < 65y

Adapted from: Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Report of the Expert Panel.[20]

Table 3. Special Risk Conditions

High Risk

Diabetes mellitus, type 1 and type 2
Chronic kidney disease/end-stage renal disease/post renal transplant
Post orthotopic heart transplant
Kawasaki disease with current aneurysms

Moderate Risk

Kawasaki disease with regressed coronary aneurysms
Chronic inflammatory disease (systemic lupus erythematosis, juvenile rheumatoid arthritis)
Human immunodeficiency virus infection
Nephrotic syndrome

Adapted from: Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Report of the Expert Panel.[20]

Table 4. Acceptable, Borderline-High, and High Plasma Lipid, Lipoprotein and Apolipoprotein Concentrations (mg/dL) For Children and Adolescents

Category	Acceptable	Borderline	High[a]
TC	< 170	170-199	≥ 200
LDL-C	< 110	110-129	≥ 130
Non-HDL-C	< 120	120-144	≥ 145
ApoB	< 90	90-109	≥ 110
TG			
0-9 years	< 75	75-99	≥ 100
10-19 years	< 90	90-129	≥ 130
Category	**Acceptable**	**Borderline**	**Low[b]**
HDL-C	>45	40-45	< 40
ApoA-I	>120	115-120	<115

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
[a] Values for plasma lipid and lipoprotein levels are from the National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels in Children. Non-HDL-C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL-C. Values for plasma apoB and apoA-I are from the National Health and Nutrition Examination Survey III.
[b]The cut points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively. Low cut points for HDL-C and apoA-I represent approximately the 10th percentile.

Adapted from: Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Report of the Expert Panel.[20]

Table 5. Recommended Cut Points for Lipid and Lipoprotein Levels (mg/dL) in Young Adults[a]

Category	Acceptable	Borderline High	High
TC	< 190	190-224	≥ 225
LDL-C	< 120	120-159	≥ 160
Non-HDL-C	< 150	150-189	≥ 190
TG	< 115	115-149	≥ 150
Category	**Acceptable**	**Borderline Low**	**Low**
HDL-C	>45	40-44	< 40

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.
[a]Values provided are from the Lipid Research Clinics Prevalence Study. The cut points for TC, LDL-C, and non-HDL-C represent the 95th percentile for 20- to 24 year old subjects and are not identical with the cut points used in the most recent NHLBI adult guidelines, ATP III, which are derived from combined data on adults of all ages. The age-specific cut points given here are provided for pediatric care providers to use in managing this young adult age group.
For TC, LDL-C, and non-HDL-C, borderline high values are between the 75th and 94th percentile, while acceptable are < 75th percentile. The high TG cut point represents approximately the 90th percentile with borderline high between the 75th and 89th percentile and acceptable <75th percentile. The low HDL-C cut point represents roughly the 25th percentile, with borderline low between the 26th and 50th percentile and acceptable > the 50th percentile.

Adapted from: Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Report of the Expert Panel.[20]

WHAT DO THE GUIDELINES RECOMMEND?

Cardiovascular Risk Factors

Guideline recommendations regarding frequency and type of lipid screening vary based on the presence of cardiovascular risk factors. Common risk factors encountered in pediatric practice include overweight and obesity, hypertension, and diabetes. A detailed listing of high-level and moderate-level risk factors is summarized in Tables 2 and 3.[20]

Children with no cardiovascular risk factors

Recent guidelines published by the National Cholesterol Education Program Expert Panel have endorsed universal screening of all children from 9 to 11 years old and again at 17 to 21 years old with a non-fasting lipid screen in order to identify children with dyslipidemias at a young age.[7] This recommendation is different from the 2007 US Preventive Services Task Force (USPSTF) recommendations regarding screening of children and adolescents for dyslipidemias. The USPSTF concluded "the evidence is insufficient to recommend for or against routine screening" in children and adolescents up to age 20 and instead endorsed selective screening of children and adolescents at increased risk for early cardiovascular disease[8]. Both sets of guidelines offered their recommendations as a level of evidence "C," reflecting expert consensus in the absence of data from large randomized controlled trials in children.

According to the NCEP Expert Panel, the initial screening test can be a non-fasting total and HDL cholesterol, which are accurate in the non-fasting state. The non-HDL cholesterol can then be calculated using the formula non-HDL=TC – HDL. Evidence supports that lipid levels drawn before puberty have a high correlation with adult levels and are stable, unlike levels drawn during puberty. During puberty, hormonal changes have been associated with a decrease in LDL levels, with fluctuations in HDL and TG. The Dietary Intervention Study in Children (DISC) showed an average decrease in LDL of 23.3 mg/dL in boys and 10.6 mg/dL in girls in Tanner stage 4 or 5 compared to their LDL level at Tanner stage 1.[21] As a result of these normal decreases in LDL during puberty, the sensitivity and specificity of predicting adult LDL levels based on levels obtained during puberty is compromised and indiscriminate testing leads to a high false negative rate of detection. For this reason, universal screening is not recommended during adolescence. Despite decreases in LDL levels during puberty, guidelines use the same reference ranges for lipid profiles in adolescents as they do in children. This is because the recommended thresholds to initiate lifestyle or medical therapy are the same for children and adolescents, regardless of pubertal status.

Universal screening is not recommended prior to age 9 due

Figure 1. Dyslipidemia Algorythm: TARGET LDL-C (Low-Density Lipoprotein Cholesterol)

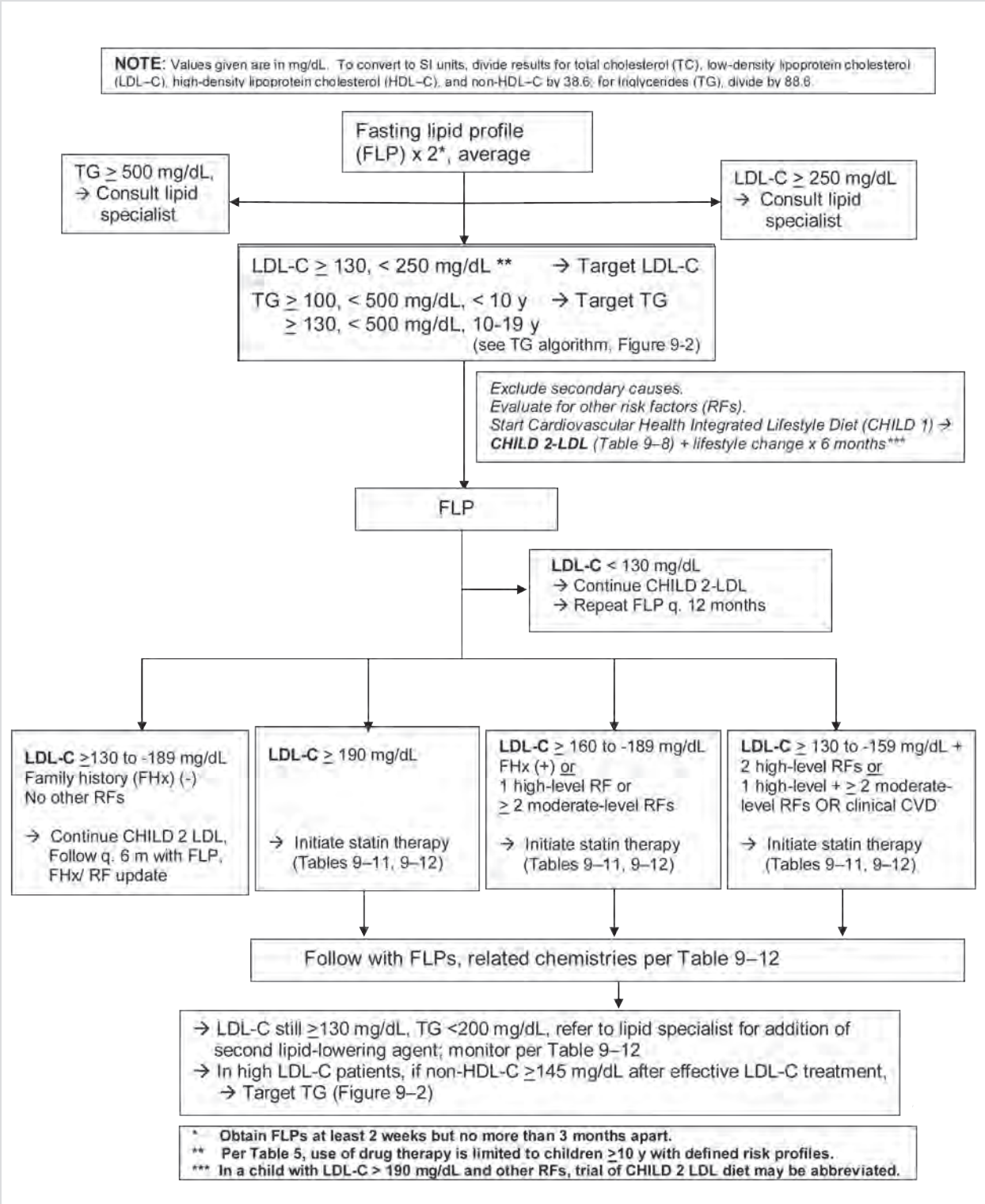

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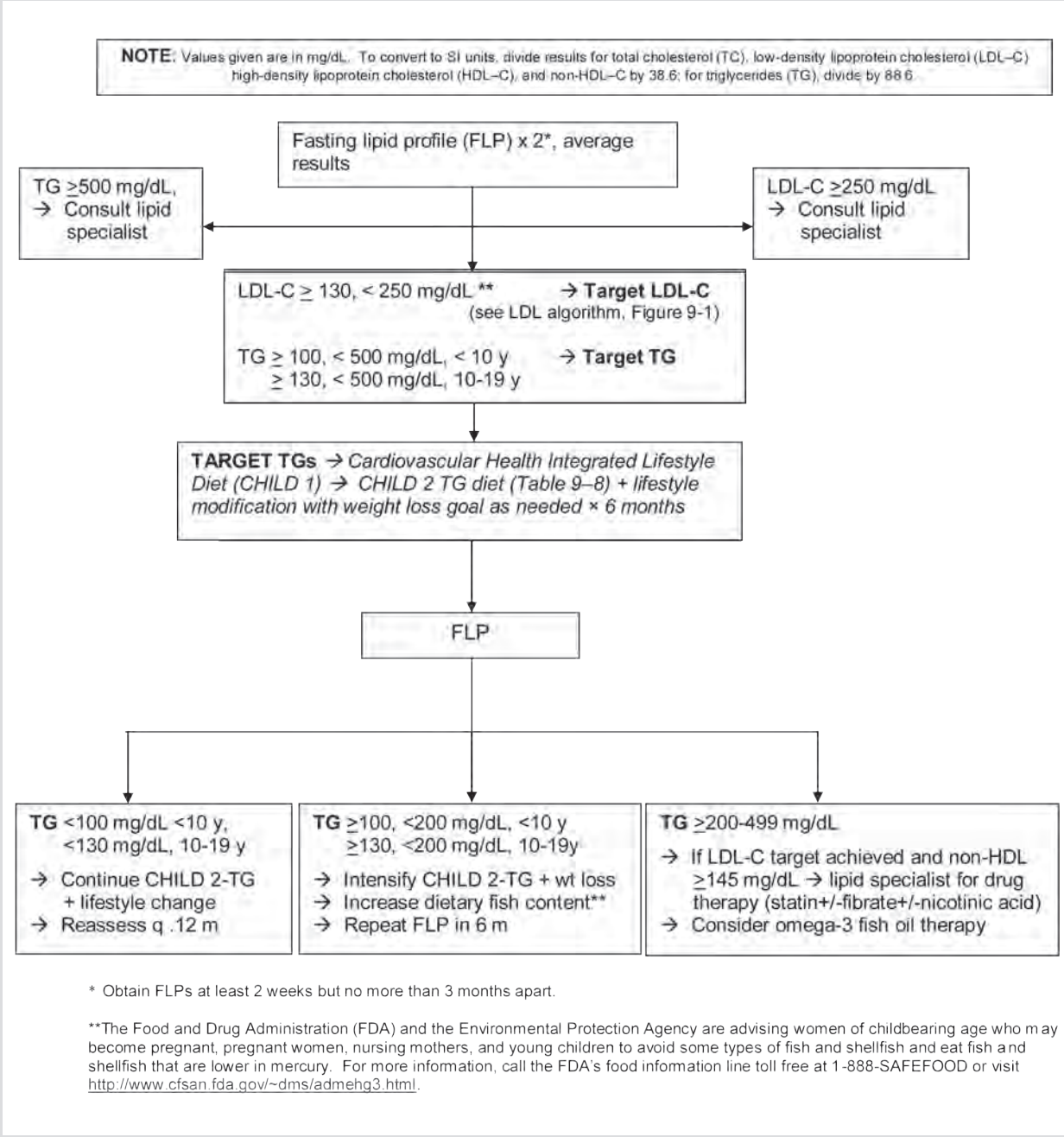
Figure 2. Dyslipidemia Algorythm: TARGET TG (Triglycerides)



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to the minimal data regarding medication use in children less than 8 years old. However, if new risk factors are identified between 10 and 17 years of age, then targeted screening with a fasting lipid profile may be appropriate.

Acceptable ranges for fasting and non-fasting lipid profiles for children, adolescents, and young adults are shown in Tables 4 and 5. If a non-fasting lipid screen is abnormal, 2 fasting lipid profiles (TC, LDL, HDL, and TG measured) should be performed, with the average result taken.[7]

Children with cardiovascular risk factors

Children with a family history of premature cardiovascular disease may be screened with a fasting lipid profile at an earlier age, as young as 2 years old if this would result in a change in management of the child and family. Deciding if a child has a

"strong" family history of "early" cardiovascular disease can be subjective, and so a definition for a positive family history of premature cardiovascular disease is given in Table 2. Children with conditions that predispose to dyslipidemia should be screened with a fasting lipid profile when the condition is diagnosed and every 5 years thereafter. Common medical conditions that predispose children to dyslipidemia are listed in Tables 2 and 3.

Treatment of dyslipidemias

Treatment of identified dyslipidemias is indicated for those children who are at higher risk for accelerated atherosclerosis. This is intended to prevent premature atherosclerosis in those at highest risk, and establish lifelong healthy practices. Suggested treatment algorithms for elevated LDL and elevated TG are shown in Figures 1 and 2, respectively. Lifestyle modification is first-line treatment for nearly all patients. This includes regular physical activity and limited "screen time" as well as a diet low in fat, saturated fat, and cholesterol. Controlling intake of refined carbohydrates is useful, particularly in the setting of hypertriglyceridemia. Appropriate caloric intake is also important, particularly if the child is overweight or obese. Referral to a dietician experienced in treating children and families for medical nutrition therapy can be very helpful. Regular follow-up is important, and if dyslipidemias persist, then pharmacologic treatment may be recommended after careful consideration of a child's family history and cardiovascular risk factors.

In general, children 9 years of age and younger should be offered only pharmacologic treatment under high-risk circumstances. Severe dyslipidemia, a high-risk medical condition, or evident cardiovascular disease may warrant medication, but this should be done under the care of a physician with significant experience in lipid disorders and treatment. For children and adolescents 10 years and older, consultation with a lipid specialist is recommended if the average LDL ≥ 250 mg/dL or if the average TG ≥ 500 mg/dL. Lipid profiles this markedly abnormal generally indicate a primary dyslipidemia. While lifestyle modification is important in the management of any dyslipidemia, these conditions invariably require treatment with one, if not several, medications.

For less severe dyslipidemias, lifestyle modifications and close monitoring are usually appropriate initial steps, but appropriate treatment of pediatric patients with persistently abnormal lipid profiles and/or cardiovascular risk factors may include medication. Consultation with the patient and family is important prior to the initiation of any medication.

DOES SCREENING MAKE A DIFFERENCE?

It is well-established that atherosclerosis begins in childhood.[22-24] The presence of fatty streaks in the arterial intima during childhood and the reversibility of these early atherosclerotic lesions lend support to the concept of early treatment, including lifestyle modification and medications.[25,26]

Screening and treating children for lipid disorders remains controversial because there are no studies demonstrating that treatment of dyslipidemias in childhood will prevent cardiovascular events later in life. While ideal, randomized controlled trials of screening and treating pediatric patients are not practical due to limitations of cost, study size, and length of follow-up required.[27] However, there is evidence that modifying established cardiovascular risk factors will delay the development and progression of atherosclerotic lesions in children.[28-32] The presence of atherosclerotic lesions, even in young adults, has been linked to a shorter life expectancy and an increase in cardiovascular events.

The presence or absence of cardiovascular risk factors alters a person's atherosclerotic burden, even in childhood. Young adults with no or minimal cardiovascular risk factors have less atherosclerosis, live longer, have fewer cardiovascular events, and have a better quality of life.[28,29] One trial showed that when healthy boys were fed a low saturated fat, low cholesterol diet from 7 months of age through 11 years, they were shown to have lower TC and LDL throughout childhood, and had better vascular endothelial function compared to controls. Girls following this diet had less obesity. Importantly, despite a low-fat diet starting at 7 months of age, cognitive, neurologic, and pubertal development were similar between the two groups.[30]

It has also been established that modification of preexisting cardiovascular risk factors can decrease a child's atherosclerotic burden. Children with very high LDL that are treated have less carotid atherosclerosis than those that are untreated. In those patients, if appropriate medical and lifestyle interventions are started at younger ages, the decrease in atherosclerosis is even greater.[31]

Why the argument for universal screening?

In response to concerns regarding pediatric obesity and associated pediatric dyslipidemia, in 2008 the American Academy of Pediatrics (AAP) revised its guidelines and recommended screening with a fasting lipid profile for all children between 2 and 10 years old with identified family history or patient risk factors. Recommendations indicated that a patient's family history should prompt screening if a parent, grandparent, aunt, or uncle had high cholesterol or cardiovascular disease, or if family history was unknown. Any patient with overweight or obesity, hypertension, tobacco use, or diabetes also met criteria for screening.[32]

However, in order for this type of selective screening program to work, the patients that meet screening criteria need to be properly identified. There are no clear standards for accurate

family histories, and accurate measurement and interpretation of blood pressure in children and adolescents can be challenging. In order to identify patients with cardiovascular risk factors, the risk factors themselves need to be identified.

In order for any selective screening program to work, the screening criteria need to be sensitive enough to detect affected patients. Unfortunately, this is not the case with pediatric dyslipidemias.[5,6,33-37] One study screened LDL in over 20,000 fifth graders. In that particular study, 71% of children met 2008 AAP screening criteria. Of those children, 8.3% had an abnormally elevated LDL, and 14% of children with an abnormal LDL required pharmacologic treatment. Of the 29% that did not meet screening criteria, 9.5% had an abnormal LDL, and 18% of those children with an abnormal LDL required pharmacologic treatment. Dyslipidemia requiring pharmacologic treatment was more common among children who did not meet screening criteria than among those who did.[5] Another study of 678 children found the 2008 AAP screening criteria were only 54%-66% sensitive in identifying children with a dyslipidemia.[6]

CONCLUSION

Dyslipidemias are common in pediatrics. They are increasing in incidence and frequently are missed with selective screening. It is important to identify common genetic risk factors. Identifying cardiovascular risk factors in children can be challenging, and risk factors often are missed. Even if risk factors are properly identified, studies have shown that limiting lipid screening to those patients with risk factors fails to identify many patients with genetic or acquired dyslipidemias. Without universal screening, many at-risk children will not be identified.

Atherosclerosis starts in the very young, and in rare cases of severe dyslipidemia where medical management is indicated, early intervention has been shown to improve vascular function and reduce risk for future disease. Initiation of medication is not and cannot be the first-line treatment: for all patients with dyslipidemia, lifestyle intervention is vital in the management of a disease process that eventually carries high morbidity and mortality. Ignoring genetic disease in children that predisposes them to early morbidity and mortality because 30-year results of randomized controlled trials are not available is unacceptable.

Development of medical guidelines is complex but serves an essential purpose: to provide recommendations for treatment based on evidence. Large, long-term trials in pediatric medicine are virtually nonexistent. With the creation of any guideline, evidence ratings are provided and potential conflicts of interest are disclosed to help clinicians make informed decisions regarding management of their individual patients. Controversies can and do arise when guidelines disagree; it is part of the art and science of medicine.

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CME

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Quiz: A Review of Guidelines for Dyslipidemia in Children and Adolescents

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Understand the broad outlines of the current recommendations for screening for dyslipidemia in children and adolescents.
2. Recognize the levels of lipids that would trigger more aggressive treatment of dyslipidemia in children and adolescents.
3. Understand the diagnostic features of the two most common inherited forms of dyslipidemia in children and adolescents: Familial Combined Hyperlipidemia (FCH) and Familial Hypercholesterolemia (FH).

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QUESTIONS

1. Which of the following statements are true?
   A. Approximately 20% of American children are overweight or obese.
   B. As many as half of children with genetic and acquired cholesterol disorders are missed without routine screening.
   C. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents published by the National Heart, Lung and Blood Institute in December 2011 recommend universal lipid screening for all children ages 9 to 11 years and again at 17 to 21 years of age.
   D. Children or adolescents with a LDL ≥ 250 mg/dL or triglycerides ≥ 500 mg/dL almost certainly have a primary dyslipidemia and should be considered for referral to a specialist with experience in treating pediatric lipid disorders.
   - ❑ All of the above
   - ❑ A and B only
   - ❑ C and D only
   - ❑ B, C, and D only
   - ❑ A, B, and C only

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2. Which of the following statements concerning FH and Familial Combined Hyperlipidemia FCH are false?
   A. The most common pediatric dyslipidemia seen practice today is FCH.
   B. FCH is characterized by an elevated triglyceride level, a reduced HDL level, and a normal or mildly elevated LDL level.
   C. The incidence of FCH is about 1 in 100, whereas the incidence of FH is about 1 in 300-500.
   D. FC is under underdiagnosed and undertreated, particularly in the pediatric population.
   E. FH should be suspected in a patient 20 years of age or younger if the untreated fasting LDL is greater than 160 mg/dL or the non-HDL cholesterol is greater than 190 mg/dL.
   - ❑ A
   - ❑ B
   - ❑ C
   - ❑ D
   - ❑ E
   - ❑ All statements are correct

3. Which of the following statements are true?
   A. The screening test recommended for children and adolescents with no cardiovascular risk factors should be a total cholesterol, HDL, and non-HDL cholesterol.
   B. If a nonfasting lipid screen is abnormal, 2 fasting lipid profiles should be performed, with the average result taken. Subsequent treatment decisions should be based on these values.
   C. Lipid levels may be drawn during puberty since they are highly correlated with adult lipid levels.
   D. Children with conditions that predispose them to dyslipidemia should be screened with a fasting lipid profile when the condition is diagnosed and every 5 years thereafter.
   E. Children and adolescents with family histories strongly positive for cardiovascular disease can be screened as young as 2 years of age.
   - ❑ All of the above
   - ❑ None of the above
   - ❑ A, B, and C only
   - ❑ A, B, D, and E only
   - ❑ D and E only

4. Patients with FH develop premature cardiovascular disease with 50% of men and women developing a cardiovascular event by 50 years of age.
   - ❑ True
   - ❑ False

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