**GUIDELINES FOR SCREENING, PREVENTION, DIAGNOSIS AND TREATMENT OF DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS**

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**ABSTRACT**

Clinical practice guidelines are developed to create a synthesis of evidence which, in turn, leads to recommendations that improve clinical decision-making. Guidelines are helpful for busy clinicians to improve outcomes and reduce unnecessary practice variation. Historically, guidelines were largely based on expert opinion. The modern approach to guideline development includes a complete review and grading of the available evidence. The evidence is then used to construct recommendations for clinical practice with grades based on the evidence. Pediatric lipid guidelines were first published in 1992. These guidelines included a screening approach based on family history and recommended a population approach to improve diet and physical activity in all children and adolescents, as well as a high-risk approach. This approach focused on treatment with lifestyle or with pharmacologic agents for those identified at high risk. The 2011 Integrated Guidelines provide the most comprehensive and up-to-date approach to pediatric dyslipidemia. In these guidelines, universal screening in 9-11 year-olds is recommended to identify children with genetic dyslipidemia or more lifestyle-related dyslipidemia. Pharmacologic treatment is recommended only for a small group of children and adolescents with marked elevation of LDL-C due to genetic dyslipidemias. For coverage of all related aeas of Endocrinology, please visit our on-line FREE web-text, WWW.ENDOTEXT.ORG..

**CLINICAL PRACTICE AND GUIDELINE DEVELOPMENT**

Clinical practice guidelines are becoming an increasingly important aspect of clinical care. Guidelines are designed to create a synthesis of evidence, including expert opinion where little evidence exists, to provide a straightforward approach to clinical decision making. Guideline development recognizes that the average practicing clinician has difficulty keeping abreast of developing medical science across a wide range of areas. This is especially true for generalists in primary care who must cover a wide range of medical issues with their patients. Guidelines are particularly helpful where there may be conflicting evidence or a range of levels of quality among studies included in the evidence base. In addition, when guidelines are widely utilized, they help to diminish unnecessary practice variation, improve outcomes and potentially can reduce costs by providing a more efficient pathway to appropriate diagnosis and treatment while eliminating unnecessary tests and procedures.

While the value of well-done clinical practice guidelines is now widely accepted, concerns have been expressed historically about their development (1). These concerns include the fact that there were no standards for the guideline development process or guideline committee composition. This sometimes resulted in concerns about the balance in expertise. In addition, relationships between committee members and pharmaceutical companies or other entities were often not disclosed, making potential conflicts of interest difficult to discern. There also have been no universal standards for the approach to reviewing and grading the evidence. This can lead to selective inclusion of research or to different approaches to weighting of the evidence. There has also been no standard approach to translating the evidence review into graded recommendations, which is the aspect of the process that is most useful and most used by clinicians. Often, clinical recommendations were presented as unanimous when, in fact, there was substantial discussion and even disagreement on the part of the committee members. This lack of a standard accepted process has sometimes led to clinical practice guidelines from different organizations that presented very different recommendations on the same topic, which potentially increases the confusion of clinicians even more.

As more experience has been gained with the process of guideline development, the process has improved over time. Presently, the government and health organizations which oversee guidelines construction now generally focus on more balanced committee membership and a more transparent approach to potential conflicts of interest. They require completion of a documented review of the evidence, increased transparency of committee discussion and improved identification of expert opinion in the guideline development process. However, key elements of the process still remain controversial. Good guidelines require the development of good key questions at the onset of the process. Constructing the best key questions still seems more of an art than a scientific endeavor. In addition, different organizations have different approaches to grading evidence and to constructing and grading recommendations from the evidence. For example, some organizations will essentially accept only evidence derived from randomized controlled clinical trials. While those trials do represent the strongest science, they are also the most difficult and expensive studies to perform. Clinical trials by their nature often address very narrow scientific and clinical questions. In addition, there are many areas that remain unaddressed by clinical trials for a variety of reasons, including areas where such trials are difficult to perform or even may be considered unethical, as well as areas where funding for such studies has not been available.

In the past, clinical practice guidelines have been viewed as static documents. This is really not appropriate as the science that informs clinical decision making is always evolving. Thus, guideline creation should be viewed as a continuous improvement process with new studies reviewed and graded as they become available. Newer electronic data bases and electronic health records make this approach to ongoing refinement of guidelines more feasible.

Unfortunately, guidelines are often not implemented in practice. Research has demonstrated that there is often a lag, which can be as long as a decade or more between development and routine implementation of guidelines (2). This is an area where more research is needed to determine best practices to encourage and enhance utilization of guidelines once they are developed.

**GUIDELINES FOR PEDIATRIC DYSLIPIDEMIA**

The first guidelines on pediatric lipid management were developed by the National Cholesterol Education Program (NCEP) of the National Heart Lung and Blood Institute (NHLBI) and were published in 1992 (3). The guidelines were developed by a pediatric committee that worked in parallel with the NCEP adult panel of experts. The guideline construction did not involve a complete, formal evidence review with grading of the evidence. Much of the report was based on expert opinion and extrapolation of data collected in adults to create an approach to pediatric patients. The report presented two approaches to pediatric dyslipidemia. The first was a population-based approach, which focused on diet and lifestyle issues for the entire population. The second was focused on identification and treatment of higher risk children and adolescents.

The goal of the population approach was to prevent dyslipidemia from developing in the first place. This has come to be called primordial prevention. The population approach encourages healthy diet and physical activity for all children and adolescents. This approach includes all family members, as well.

The individualized approach aimed to identify and treat children and adolescents who are at greatest risk for having high blood cholesterol as adults and who had an increased lifetime risk of atherosclerotic cardiovascular disease. In the individual approach, the committee recommended selective screening of children who have a family history of premature cardiovascular disease or at least one parent with elevated serum cholesterol. This approach assumed that all adults would have their lipid levels tested as part of routine care. The committee considered universal screening, but decided that the selective screening approach would recognize the influence of genes and environment and would be more efficient. This selective screening approach, sometimes referred to as cascade screening, is used in many European countries to identify children and adolescents with familial hypercholesterolemia (FH).

The committee also presented cut points for acceptable, borderline and high elevated LDL-C based on percentiles from the Lipid Research Clinical Prevalence Study (4). The panel then used these cut points to establish an approach to initiation of and goals for diet therapy. The panel developed separate cut points derived from studies of adults for initiation of drug therapy. They developed a two-step approach to diet therapy with Step 2 having greater restriction of saturated fat and cholesterol in the diet. For drug therapy, the panel recommended the use of bile acid sequestering agents for routine use. This report did not provide a focus on triglycerides or HDL-C and did not recommend the use of HMG CoA reductase inhibitors for pharmacologic therapy.

These 1992 Guidelines served as the approach to screening, diagnosis and treatment for many years. They also served as the basis for research with investigators studying the effectiveness of a selective approach to screening and other aspects of the guidelines (5). In addition, clinical trials were launched to study the effect of dietary and pharmacologic intervention in children and adolescents with dyslipidemia (6,7).

As new evidence became available, some of which supported the 1992 Guidelines and others which suggested alternative approaches, organizations such as the American Academy of Pediatrics (8,9) and the American Heart Association (10,11) empaneled committees to produce guidelines and recommendations, which were refinements of the original 1992 guidelines. None of these efforts included a formal, complete review and grading of the evidence or grading of the recommendations.

In a parallel process, the United States Preventive Services Task Force (USPSTF) initiated a review of the evidence regarding cholesterol screening in children and adolescents (12). This review is due to be updated in 2016. The USPSTF uses a formal evidence review and grading based on a series of key questions. The USPSTF has reported an “I” recommendation on lipid screening. This means that they found insufficient evidence for or against lipid screening in children and adolescents.

There are several reasons why an “I” recommendation resulted from the USPSTF review of the evidence. The first has to do with the key questions asked as the framework for the review. A close inspection of the key questions demonstrates that 3 of the 7 questions are probably not answerable because the types of studies needed to answer the questions cannot reasonably be done. These unanswerable key questions are presented in Table 1. A second reason is that the review specifically excluded individuals with genetic dyslipidemias, such as heterozygous familial hypercholesterolemia (FH). One could argue that these are the individuals most important to detect in any screening program as there is a prevalence of 1:250 individuals with FH and a clear increased lifetime risk of atherosclerotic cardiovascular disease (CVD). These patients are the most likely to benefit from early identification and more aggressive interventions. Because they are completely asymptomatic, these individuals are likely only to be identified via a screening program. Third, the USPSTF requires a very high standard for research, including randomized clinical trials of screening, which are much less likely to be done in children than in adults.

**TABLE 1: KEY QUESTIONS IN THE USPSTF REVIEW OF LIPID SCREENING IN CHILDREN AND ADOLESCENTS**

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| 1. **Does screening for dyslipidemia in children and adolescents reduce or delay myocardial infarction and stroke events in adulthood?** |
| 1. What is the diagnostic yield and positive predictive value of screening children and adolescents for dyslipidemia? |
| 1. What are the harms of screening for dyslipidemia in children and adolescents? |
| 1. Does treatment of dyslipidemia in children and adolescents reduce intermediate outcomes in childhood and adolescence? 2. Drug treatments 3. Nondrug treatments |
| 1. What are the harms of drug treatment of dyslipidemia in children and adolescents? |
| 1. **What is the association between intermediate outcomes in children and adolescents and myocardial infarction and stroke event in adulthood?** |
| 1. **Does treatment of dyslipidemia in children and adolescents reduce or delay myocardial infarction and stroke events in adulthood?** 2. **Drug treatments** 3. **Non-drug treatments** |

**Unanswerable questions are in bold.**

In 2011, the results of an NHLBI panel, which performed a complete review and grading of the evidence, were published as part of an integrated approach to CVD risk factor evaluation and management in children and adolescents (13-14). These Integrated Guidelines represent the most up-to-date approach to lipid screening, diagnosis and treatment and are a departure from previous guidelines. First, the guidelines recommended universal screening for lipid disorders. This means that all children age 9-11 should have their lipids tested one time. This can be performed with either a fasting lipid profile or a non-fasting test to evaluate non-HDL-C. This universal approach was recommended because studies showed that using only a selective screening approach would potentially miss 30-60% of children and adolescents with substantial elevations of cholesterol (5). The universal screening approach is largely designed to identify children with genetic dyslipidemia, such as familial hypercholesterolemia. However, it will also identify children with dyslipidemia, largely elevated triglycerides and low HDL-C, due to lifestyle factors and obesity.

The Integrated Guidelines continued to support both a population and a high risk approach to dyslipidemia. The recommendation for diet for the general population is the Cardiovascular Health Integrated Lifestyle Diet (CHILD) 1. For higher-risk patients identified through screening, the CHILD 2-LDL diet was recommended if the LDL-C was elevated. This diet further restricts intake of saturated fat and cholesterol in the diet. For those with elevated triglycerides and low HDL-C, the CHILD 2-TG diet was recommended. This diet includes reduced intake of simple sugars in addition to reduction in saturated fat.

The Integrated Guidelines now present statin agents as first-line pharmacologic treatment for substantial elevation of LDL-C (190mg/dL) with no other risk factors, or 160mg/dL with 1 high level or ≥ 2 moderate-level risk factors in children and adolescents age 10 years and older.

The Integrated Guidelines have not been without controversy (15-17). In addition, uptake of the Integrated Guidelines has been less than optimum (18). One potential reason for confusion regarding the guidelines is the potential concern about the impact of obesity on dyslipidemia. This result, in part, derives from a misunderstanding of the difference between the issues related to genetic forms of dyslipidemia, such as FH, and those that are largely due to lifestyle. It needs to be clarified that most individuals who have an LDL-C level in the range where medication would be recommended have a genetic from of dyslipidemia, usually heterozygous FH. Individuals with lifestyle-based dyslipidemia rarely have LDL-C levels that would trigger the recommendation for pharmacologic treatment. Obesity results in elevated triglycerides and low HDL-C with only a modest increase in LDL-C. Estimates are that fewer than 1% of children and adolescents would qualify for statin treatment (19).

This potential confusion over different aspects of dyslipidemia and their consequences have led to American Heart Association (AHA) and the National Lipid Association (NLA) to sharpen the focus on familial hypercholesterolemia (19-21). While these scientific statements did not include a formal review and grading of the evidence, they provided a new focus for clinicians and may simplify the clinical approach to pediatric dyslipidemia. Clinicians should probably focus first on identification and treatment of individuals with the array of genetic defects that underlie FH and their family members who also have this genetic abnormality. Because this genetic defect occurs in 1:250 individuals, it is one of the most prevalent genetic diseases. Individuals with heterozygous FH have substantial and often marked elevation of LDL-C. These individuals have been shown to be at increased lifetime risk of atherosclerotic CVD and are at risk for adverse outcomes in their 30’s, 40’s, 50’s and 60’s. Unfortunately, the first clinical sign of the disease for these patients may be a myocardial infarction or sudden cardiac death. Because this is often an asymptomatic condition, particularly in childhood, lipid testing is essentially the only way to identify affected individuals. Treatment with statins and other pharmacologic agents can be quite effective at lowering LDL-C levels and decreasing the risk for adverse cardiovascular outcomes.

In conclusion, the evidence related to risk, identification and effective treatment of dyslipidemia has continued to expand. This has allowed development of guidelines for management of pediatric patients with dyslipidemia. Unfortunately, uptake of these guidelines by primary care clinicians has been slow. There is a need for ongoing high-quality studies in this area so that new study results can be included in subsequent evidence reviews and clinical practice guidelines can be improved.  
A major limiting factor in the development of Guidelines regarding the screening, identification and treatment of dyslipidemia in children and adolescents is the lack of studies which produce the evidence to support such guidelines. There are examples of guidelines in pediatric healthcare that have been well accepted based on evidence. These include US Preventive Services Task Force recommendations for screening for obesity using Body Mass Index (22), guidelines for the diagnosis and management of asthma from the National Heart, Lung and Blood Institute (23) and for the diagnosis and management of an initial urinary tract infection in febrile infants from the American Academy of Pediatrics (24). These guidelines have generally been accepted in pediatric practice, although not always without controversy (25). As we seek to improve outcomes through better standardization of delivery of healthcare, improved evidence-based guidelines will be increasingly important.

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