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

Stephen R. Daniels, MD, PhD. Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO. Stephen.daniels@childrenscolorado.org

Updated January 8, 2023

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 level of evidence to support them. 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. New guidelines from the American Heart Association/American College of Cardiology largely support the Integrated Guidelines.

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 guideline 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 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 not appropriate as the science that informs clinical decision making is always evolving. In the case where the science is rapidly evolving, a guideline may be out of date shortly after it is published. Thus, guideline creation should best 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 suggests that clinicians may be implementing treatment that is not supported by the best evidence. 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

NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) 1992

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.

United States Preventive Services Task Force 2016

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 was 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. This is a call for more research in this area.

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 several of the key questions are probably not answerable because the types of studies needed to answer the questions cannot reasonably be done. The USPSTF also 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.

The 2016 USPSTF review of cholesterol screening was improved in several ways compared to previous reviews (13-15). First, there was a separate analysis of the evidence to support screening for individuals with familial hypercholesterolemia. In previous USPSTF reviews, these individuals had been excluded from consideration. The 2016 USPSTF review also included a review of the evidence to screen for multifactorial dyslipidemia. The key questions were also modified somewhat from previous reviews. However, the answer for key questions, such as:

1) Does screening for dyslipidemia in asymptomatic children and adolescents delay or reduce the incidence of myocardial infarction or stroke in adulthood, or

2) Does treatment of dyslipidemia with lifestyle modification or lipid lowering medications in children and adolescents delay or reduce the incidence of adult myocardial infarction and stroke events?

These questions still require studies that are virtually impossible to do. Such studies would require randomization of young individuals and following them for decades to observe the outcomes. Utilization of these key questions make it quite difficult for the USPSTF to achieve anything other than an "I" statement for pediatric lipid screening.

There were several commentaries of the 2016 USPSF reviews that serve to put the results in broader context (16, 17). These commentaries pointed out that a statement of insufficient evidence for or against lipid screening was not particularly helpful for the clinician on the front line and that other health organizations, such as the American Heart Association and the American Academy of Pediatricians have recommended lipid screening in children and adolescents based on separate review and grading of the evidence.

It is important to note that an "I" statement from the USPSTF should not be taken as a recommendation against lipid screening. The USPSTF does recommend against screening when the evidence demonstrates that screening or treatment are ineffective or harmful. In the face of an "I" statement and given the high bar for evidence required by the USPSTF, it is up to individual clinicians and health organizations to weight the available evidence and decide on a course of action.

National Heart Lung and Blood Institute (NHLBI) 2011

In 2011, the results of an NHLBI panel, which performed a complete review and grading of the evidence for screening and treatment of

cardiovascular disease risk factors in children and adolescents, including dyslipidemia, were published as part of an integrated approach to CVD risk factor evaluation and management (18, 19). These Integrated Guidelines represent the most comprehensive, 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 should have their lipids tested one time between the ages of 9-11. 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 based on family history 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 presented 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 (20-22). In addition, uptake of the Integrated Guidelines has been less than optimum (23,24). 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 form of dyslipidemia, usually heterozygous FH. Children and adolescents 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. These children and adolescents should be treated with changes in lifestyle, including a more healthful diet and increased levels of physical activity. Estimates are that fewer than 1% of children and adolescents would qualify for statin treatment (25).

American Heart Association (AHA) and the National Lipid Association (NLA)

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 (25-27). 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 approximately 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.

American Heart Association/American College of Cardiology Cholesterol Clinical Practice Guidelines 2018

The most recent clinical practice guidelines regarding dyslipidemia are the American Heart Association/American College of Cardiology Cholesterol Clinical Practice Guidelines published in 2018 (28). These guidelines included a complete evidence review and systematic grading of the evidence and the recommendations. These guidelines largely focus on the management of blood cholesterol in adults, but also included a section on children. These guidelines indicate that, in children (age 10-19 years of age) and young adults (20-39 years of age), priority should be given to evaluation of lifetime risk of atherosclerotic cardiovascular disease and promotion of lifestyle risk reduction.

In the AHA/ACC 2018 guidelines, screening for dyslipidemia based on family history is given a B-nonrandomized level of evidence and a IIa strength of recommendation (28). Universal screening for dyslipidemia once between age 9-11 years and once between age 17-21 is given a B-nonrandomized level of evidence and a IIb strength of recommendation. The B-NR level of evidence indicates moderate quality of evidence from observational studies. The class IIa recommendation is a moderate recommendation, while a class IIb recommendation is considered weaker (might be reasonable).

For treatment of dyslipidemia in children and adolescents, lifestyle approaches receive a level A for the evidence and have a class I strength of recommendation. For children and adolescents age 10 and over with an LDL-C persistently above 190mg/dL or above 160mg/dL with a clinical presentation consistent with familial hypercholesterolemia who do not adequately respond to lifestyle change after 3-6 months, initiating statin therapy received a B-randomized level of evidence and a class IIa recommendation (22).

These newest guidelines are essentially in line with the 2011 Integrated Guidelines from the NHLBI. However, they also emphasize that more high-quality evidence is needed. This should drive research efforts in the areas of screening and management for pediatric dyslipidemia.

CONCLUSION

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.

REFERENCES

1. Sniderman AD, Furberg CD. Why guideline-making requires reform. JAMA. 2009;301:429- 31.
2. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Health Technol Assess. 2004;8:iii-iv, 1-72.
3. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89:495- 501.
4. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6-19 yr. The Lipid Research Clinics Program Prevalence Study. J Chronic Dis. 1981;34:27-39.
5. Ritchie SK1, Murphy EC, Ice C, Cottrell LA, Minor V, Elliott E, Neal W. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. Pediatrics. 2010;126:260-5.
6. The Writing Group for the DISC Collaborative Research Group. Efficacy and safety of lowering dietary intake of fat and cholesterol in children with elevated low-density lipoprotein cholesterol. The Dietary Intervention Study in Children (DISC). The Writing Group for the DISC Collaborative Research Group. JAMA. 1995;273:1429-35
7. McCrindle BW1, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr. 2003;143:74-80.
8. American Academy of Pediatrics. Committee on Nutrition. American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. Pediatrics. 1998;101(1 Pt 1):141-7.
9. Daniels SR, Greer FR; Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198-208.
10. Kavey RE, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K; American Heart Association. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation. 2003;107:1562- 6.
11. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, Hayman LL, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee; American Heart Association Council of Cardiovascular Disease in the Young; American Heart Association Council on Cardiovascular Nursing. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115:1948-67.
12. US Preventive Services Task Force. Screening for lipid disorders in children: US Preventive Services Task Force recommendation statement. Pediatrics. 2007;120:e215-9.
13. US Preventive Services Task Force. Screening for lipid disorders in children and adolescents: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:625-33.
14. Lozano P, Henrikson NB, Dunn J, Morrison CC, Nguyen M, Blasi PR, Anderson L, Whitlock EP. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: Evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;316(6):645-55.
15. Lozano P, Henrikson NB, Morrison CC, Dunn J, Nguyen M, Blasi PR, Whitlock EP. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: Evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;316(6):634-44.
16. Urbina EM, de Ferranti SD. Lipid screening in children and adolescents. JAMA. 2016;316(6):589-91.
17. Daniels SR. On the US Preventive Services Task Force Statement on screening for lipid disorders in children and adolescents: One step forward and 2 steps sideways. JAMA Pediatrics. 2016;170(10):932-34.
18. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics. 2011;128 Suppl 5:S213-56.
19. Gidding SS, Daniels SR, Kavey RE; Expert Panel on Cardiovascular Health and Risk Reduction in Youth. Developing the 2011 Integrated Pediatric Guidelines for Cardiovascular Risk Reduction. Pediatrics. 2012;129:e1311-9.
20. Newman TB, Pletcher MJ, Hulley SB. Overly aggressive new guidelines for lipid screening in children: evidence of a broken process. Pediatrics. 2012;130:349-52.

21. McCrindle BW1, Kwiterovich PO, McBride PE, Daniels SR, Kavey RE. Guidelines for lipid screening in children and adolescents: bringing evidence to the debate. Pediatrics. 2012;130:353-6.
22. Gillman MW, Daniels SR. Is universal pediatric lipid screening justified? JAMA. 2012;307:259-60.
23. Valle CW, Binns HJ, Quadri-Sheriff M, Benuck I, Patel A. Physicians' Lack of Adherence to National Heart, Lung, and Blood Institute Guidelines for Pediatric Lipid Screening. Clin Pediatr (Phila). 2015;54:1200-5.
24. de Ferranti SD, Rodday AM, Parsons SK, Cull WL, O'Connor KG, Daniels SR, Leslie LK. Cholesterol screening and treatment practices and preferences: A survey of United States pediatricians. J Pediatr. 2017;185:99-105.
25. McCrindle BW1, Tyrrell PN, Kavey RE. Will obesity increase the proportion of children and adolescents recommended for a statin? Circulation. 2013;128:2162-5.
26. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, McCrindle B, Raal F, Rader D, Santos RD, Lopes-Virella M, Watts GF, Wierzbicki AS; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015;132:2167-92.
27. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:133-40.
28. Writing Committee, Cholesterol Clinical Practice Guidelines. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive summary. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1046-e1081.
29.