Journal of Clinical Lipidology (2015) 9, S5–S10

Journal of Clinical Lipidology

Pediatric guidelines for dyslipidemia

Stephen R. Daniels, MD, PhD*

Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA; and Children's Hospital Colorado, Aurora, CO, USA

KEYWORDS:
Pediatric;
Dyslipidemia;
Guidelines;
Familial hypercholesterolemia;
Evidence review

Abstract: Clinical guidelines are developed to assist clinicians in complex clinical decision making. Modern guideline development includes a systematic review and grading of relevant literature and then using the evidence review to construct recommendations for clinical care which are also graded regarding the level of evidence supporting them. Pediatric guidelines for dyslipidemia were first published in 1992. There was then a gap during which no formal guidelines were developed. In 2011, the National Heart, Lung, and Blood Institute Integrated Guidelines for Cardiovascular Disease Risk Reduction in Children were published. This included an evidence review and clinical recommendations regarding dyslipidemia. This review process began in 2006. The evidence review ended in 2008, and they were published in 2011 because of an extensive and prolonged review process. These guidelines recommend universal screening for dyslipidemia at age 9 to 11 y with a focus on identifying young individuals with genetic dyslipidemia such as familial hypercholesterolemia. The guidelines also include lifestyle recommendations and recommendations for pharmacologic treatment for children with markedly elevated low-density lipoprotein cholesterol. The guideline process should include review of the implementation of guidelines in practice and should also include ongoing review of the guidelines with respect to a growing evidence base with new research findings.

Clinical guideline development and implementation

Clinical guidelines are developed primarily to assist clinicians in complex clinical decision making. Guidelines require a compilation, review, and grading of relevant evidence. The evidence is then synthesized into recommendations for clinical care, which are also graded based on the level of supporting evidence. Clinical guidelines are not meant to be prescriptive because guidelines writing committees cannot capture every possible nuance in the way real patients present for care. In guideline construction, there is a grading process for the level of evidence and for the recommendation so that guideline users can understand where the evidence is stronger and where it is weaker. This is an aid to the clinician in clinical decision making. Sometimes, and this is more common for pediatric guidelines, there is a complete absence of evidence. In this circumstance, expert opinion is often used to supplement the evidence review. However, when expert opinion is used, it must be clearly demarcated.

The Institute of Medicine (IOM) has developed standards for the review of evidence and construction of guidelines.[1] The IOM standards emphasize efforts to reduce or eliminate real or perceived conflicts of interest. This has

* Corresponding author. Department of Pediatrics, University of Colorado School of Medicine, Children's Hospital Colorado, Aurora, CO 80045, USA.
E-mail address: Stephen.Daniels@childrenscolorado.org
Submitted February 20, 2015. Accepted for publication March 22, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.03.105

an important impact on construction of the guideline development group, but the group must also represent the range of knowledge and experience necessary to construct meaningful guidelines and often must represent a range of disciplines relevant to clinical content area. The IOM report emphasizes the prospective development of rules by which the evidence and recommendations should be graded. The IOM also recommends an extensive external review and vetting process once the initial evidence review and guideline construction process has been completed and before any implementation of the guidelines.

Once the Guideline Development Committee is empaneled, the process by which the evidence review is organized relies on the creation of key questions that a clinician would face in practice. The development of these key questions is one of the most important steps as the questions determine how the evidence review is conducted. The key questions also outline the clinical areas, which the guidelines will be able to address. In pediatric guideline construction, the development of key questions is especially important when there is concern about the impact of a risk factor in childhood on an adult outcome. Although questions about the evidence establishing the pediatric–adult link are of interest, it is important to recognize that to have any evidence to address such a question would take a randomized trial or a cohort study lasting at least several decades. Thus, such key questions may not be able to be answered and may not be worth asking in the context of pediatric guidelines.

Another challenge for pediatric guidelines is the level of evidence required to create a recommendation. In guidelines addressing adult health issues, guideline-writing committees will often only consider evidence coming from the most rigorous and bias-free studies and randomized controlled clinical trials. Although this type of evidence is quite important, unfortunately, such studies have often not been done in pediatric populations. This has led the American Academy of Pediatrics to establish an evidence-grading system that also allows for observational studies that are well done.[2] Pediatric evidence review also must frequently assess studies that evaluate intermediate or surrogate outcomes. It is, however, important to recognize the limitations of such studies and that results related to a single intermediate outcome, in particular, may not be the same as those with the true "hard" outcome of interest. When there is consistency of evidence across several types of intermediate outcomes, this may be more reassuring. Recently, there has also been interest in evidence that comes from so-called Mendelian randomization studies. These studies rely on identifying genetic polymorphisms that may determine a lifelong higher or lower exposure to a risk factor and then following the development of related outcomes over time. An example of this is the recent evaluation of the gene *PCSK9*, which determines the metabolism, and therefore the number, of low-density lipoprotein (LDL) receptors in the liver at birth and throughout life. When loss-of-function *PCSK9* mutations determine that the number of LDL receptors is high, then the circulating level of LDL cholesterol (LDL-C) is low. When gain-of-function mutations determine that the number of receptors is low, then circulatory concentrations of LDL-C are high. Such studies have demonstrated that those with lifetime low circulatory LDL-C have a very low lifetime risk of coronary heart disease. In fact, the risk is lower than the risk reduction seen with lipid lowering later in life with a statin medication. This kind of evidence may be helpful in the development of pediatric guidelines because the gene mutation of interest is not likely to be related to a variety of other environmental influences.

Once guidelines are developed, it is important to consider their implementation. Busy clinicians may not find it easy to implement guidelines in their practice. The electronic health record may help in this regard, but is not a complete answer. This suggests that guideline development and dissemination should be followed by specific implementation plans that are based on the evidence regarding changing physician behavior and the health system's support for such behavior change. This kind of behavioral research expertise is often lacking among the committee members and in the guidelines. Thus, developing implementation tools may require a separate process. Finally, guidelines should not be considered static documents. The evidence base is constantly expanding with the results of new relevant studies. At a minimum, guidelines should be re-evaluated every 3 to 5 y. In fact, developing a real-time system of ongoing evidence review and guideline modification should be a goal. In addition, study of the uptake of implementation of new guidelines by practitioners is also quite important.

Guidelines for pediatric dyslipidemia

History

The first set of pediatric guidelines for dyslipidemia was published in 1992.[3] These guidelines were developed by the National Heart, Lung and Blood Institute National Cholesterol Education Program (NCEP) and followed the development of screening, diagnosis, and treatment guidelines for adults, which were also developed by the NCEP. As was common for that time, both the adult and pediatric guidelines were more evidence informed than based on a systematic evidence review. There was substantial expert opinion in these reports, in part because the available evidence regarding pediatric dyslipidemia was so sparse.

These initial pediatric guidelines were adopted by the American Heart Association, the American Academy of Pediatrics, and other pediatric organizations. However, these guidelines did engender some controversy with concern about how clinically important dyslipidemia was for young patients.[4] There was also concern about whether the proposed approach to screening based on family history of dyslipidemia or premature cardiovascular disease (CVD)