Clinical Guidelines And Primary Care

Alfred O. Berg, MD, MPH, Series Editor

Screening And Management Of Cholesterol Levels In Children And Adolescents

Paul S. Frame, MD

The report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents commissioned by the National Cholesterol Education Program (NCEP) presents the rationale and guidelines for both a population approach and an individualized approach to lowering blood cholesterol in children and adolescents. Highlights of the report were published in *Pediatrics* in 1992,[1] and the full report was published as a supplement to that journal.[2] In addition, copies of the report have been widely distributed to primary care physicians. The approach and format of the report are similar to the earlier report published in 1988[3] by the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, also convened by the National Cholesterol Education Program.

Methods

The NCEP panel consisted of 12 members including 1 or more pediatricians, cardiologists, nutritionists, lipid researchers, nurses, and family physicians plus 5 ex-officio members representing the National Heart, Lung and Blood Institute. The specific methodology used in reviewing evidence and creating the guidelines is not described in the report. In the absence of any explicit discussion of methodology, it is assumed to be what has been described as "informal consensus development"[4] or "global subjective judgment."[5]

Submitted 15 June 1993.

From the Tri-County Family Medicine Program, Dansville, and the Department of Family Medicine and Department of Preventive and Community Medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY. Address reprint requests to Paul S. Frame, MD, Tri-County Family Medicine Program, Box 112, Park Avenue, Cohocton, NY 14826.

The report is divided into the following four sections: (1) Rationale for Attention to Cholesterol Levels in Children and Adolescents, (2) The Population Approach: Nutrition Recommendations for Healthy Children and Adolescents, (3) The Individualized Approach: Detection/Diagnosis/Evaluation, and (4) The Individualized Approach: Treatment. This review will discuss each section separately.

In reviewing this report I am accepting the philosophical position that preventive guidelines should be evidence based. Ideally the suggested intervention should be shown to produce the desired result, e.g., cholesterol reduction in children yields reduced coronary heart disease and overall mortality in adults. Furthermore, the demonstrated benefits should justify the costs and adverse effects of the intervention and be superior to other alternate strategies. In the example of cholesterol reduction in children, as in many preventive interventions, however, complete data for the entire chain of events are not available. It is necessary to combine data from multiple sources to create a causal pathway to evaluate the potential effectiveness of the intervention.[6] Figure 1 shows a diagram of the causal pathway for screening for cholesterol in children. In the absence of a study showing completeness of the entire pathway (path 5), it is necessary to know that each of the individual links (steps 1 to 4) are supported by solid evidence and that the benefits are greater than the adverse effects.

Section I. Rationale for Attention to Cholesterol Levels in Children and Adolescents

This section lays the foundation for the recommendations that follow in subsequent sections with a review of the evidence relating to elevated

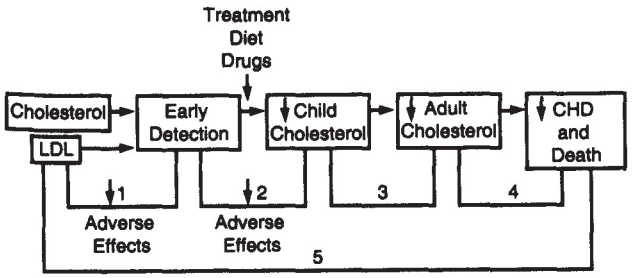

Figure 1. Causal pathway for cholesterol screening in children. LDL = low-density lipoprotein; CHD = coronary heart disease.

lipids and children. Evidence is presented in a stepwise fashion including the following major points:

1. Elevated blood cholesterol is directly related to coronary heart disease. Low-density lipoproteins are atherogenic; high-density lipoproteins are protective.
2. Children in the United States have higher cholesterol levels and higher intakes of saturated fatty acids than children in many other countries.
3. Autopsy studies have found fatty streaks; the precursors of atherosclerosis begin in childhood and adolescence.
4. There is a familial aggregation of lipid abnormalities.
5. Children with high cholesterol levels are more likely than the general population to have high levels as adults.

Statements 2, 3, and 4 are not controversial and are supported by solid evidence. The NCEP panel's reporting of the evidence relating cholesterol reduction in adults to reductions in total mortality, however, is biased and incomplete. The statement is made, "Three studies have demonstrated clear reductions in total mortality as well as CHD mortality." In fact, all three of the studies cited (Oslo, Stockholm, and Coronary Drug Project) were secondary prevention trials of men who had previous myocardial infarctions.[7] The major intervention in the Oslo study was a reduction in tobacco use rather than cholesterol levels.[8]

The NCEP panel fails to mention the six randomized primary prevention trials that have shown no decrease or an increase in the total mortality rate in patients treated with cholesterol-lowering drugs.[7] Meta-analysis of these trials shows an increase in deaths from accidents, violence, and suicide in the treated groups, raising the possibility that cholesterol lowering might be harmful.[7]

The issue of whether high cholesterol levels in childhood predict high levels as adults (the tracking of cholesterol levels) is problematic. Evidence is presented that 43 percent of children aged 5 to 18 years with cholesterol levels above the 90th percentile will continue to have levels above the 90th percentile between the ages of 20 and 30 years. Consequently, more than one-half the children labeled as having and presumably given treatment for elevated cholesterol levels will have some regression toward average cholesterol levels without any treatment.

The NCEP panel does admit that no studies show lowering cholesterol in children will decrease coronary heart disease in adults. This fact alone might be considered adequate reason not to screen children for elevated cholesterol. The panel does not discuss the fact that adult data showing that a decrease in coronary heart disease (CHD) from cholesterol lowering is derived exclusively from studies of men, even though they recommend screening both boys and girls. Benefit from cholesterol reduction in the female population has not been demonstrated at any age.

Section II. The Population Approach: Nutrition Recommendations for Healthy Children and Adolescents

The NCEP panel recommends the following dietary program for all adolescents and children above the age of 2 years:

1. Nutritional adequacy should be achieved by eating a wide variety of foods.
2. Energy should be adequate to support growth and development and to reach or maintain desirable body weight.
3. Less than 10 percent of total calories should be derived from saturated fatty acids. Total fat should provide no more than 30 percent of total calories. Less than 300 mg of cholesterol should be consumed daily.

The recommendations basically mean all children older than age 2 years should follow what has been commonly known as the Step I diet. Chil-

dren younger than 2 years old are excluded from the recommendation because their rapid growth requires the high concentration of calories that can only be obtained from fats. To implement these recommendations the panel recommends a wide range of actions by schools, primary care providers, government, and the food industry.

It is true that from a population perspective small decreases in individual cholesterol levels have been calculated to have a major population effect. Theoretically, a 1 percent decrease in cholesterol levels should translate into a 2 percent decrease in coronary heart disease risk. The actual effect obtainable from implementing the population approach in the real world is unknown, as are the costs.

Because the Step I diet is the cornerstone of both the population and the individual approach to lowering cholesterol levels in children, it is important to point out that the cholesterol-lowering effect of the Step I diet is extremely limited. Ramsay and colleagues[9] have reviewed the published trials of the Step I diet both as an individual and a population intervention. In population trials with an educational intervention, cholesterol concentrations were reduced 0.6 to 2.0 percent during a 5- to 10-year period. Population trials combining education and individual dietary advice obtained results ranging from a 2.1 percent reduction in cholesterol concentration to a 1.0 percent rise in cholesterol concentration during a 4- to 10-year period. Five trials that used the Step I diet as an individual intervention achieved net cholesterol reductions ranging from 0.0 percent to 4.0 percent during a 6-month to 6-year period. Trials using a diet more intensive than the Step II diet were able to reduce cholesterol concentrations more than 13 percent in several high-risk or special situation populations.

All of these trials were conducted with adults, who probably are more motivated than children to change dietary behavior. No trials showing a reduction in cholesterol levels in children using the Step I diet have been reported. Given the adult data, it is unlikely the Step I diet would have an important cholesterol-lowering effect on individual children, although it might have a modest population effect.

Section III. The Individualized Approach: Detection/Diagnosis/Evaluation

The NCEP panel considers a total cholesterol level greater than 200 mg/dL or a low-density lipoprotein (LDL) level greater than 130 mg/dL to be high. These levels are approximately the 95th percentile. Total cholesterol levels between 170 and 199 mg/dL (LDL 110 to 129 mg/dL) are considered borderline. Total cholesterol levels less than 170 mg/dL or LDL cholesterol levels less than 110 mg/dL are considered acceptable. The panel recommends that screening start anytime after the age of 2 years and be repeated every 5 years for the following children:

1. Children whose parents or grandparents, at 55 years of age or younger, underwent diagnostic coronary arteriography and were found to have coronary atherosclerosis.
2. Children whose parents or grandparents, at 55 years of age or younger, suffered a documented myocardial infarction, angina pectoris, peripheral vascular disease, cerebrovascular disease, or sudden cardiac death.
3. Children of a parent found to have a blood cholesterol greater than 240 mg/dL regardless of the age of the parent.

The recommended initial screening tests are a lipoprotein analysis for those children with a family history of premature CHD and a total cholesterol measurement for those with a parental history of elevated cholesterol. Children with a high or persistently borderline total cholesterol reading should have a lipoprotein analysis. Subsequent treatment decisions are based on the LDL cholesterol level.

Treatment is recommended for all persistently borderline or high LDL levels initially using the Step I diet. The minimal goal of treatment is to reduce the LDL cholesterol to less than 130 mg/dL, whereas the ideal is to reduce LDL cholesterol below 110 mg/dL.

Choosing the age of 55 years as the definition of premature CHD and defining a parental cholesterol level of 240 mg/dL as the trigger for screening is an arbitrary decision based on efficiency considerations. Using a parental cholesterol level of greater than 240 mg/dL as the trigger for screening, 25.1 percent of children will need to be screened and 40.5 percent of children with an LDL level greater than 130 mg/dL will be detected. Thirty-seven percent of children screened will require at least one lipoprotein analysis. Lowering the trigger value would mean

more children would need screening, but a greater percentage of children with high LDL levels would be detected. Raising the trigger value would have the opposite effect.

The report includes a cost calculation that the initial implementation of this program on a national basis would cost $173 to $346 million with a subsequent annual cost of $11 to $23 million. These calculations, however, are only for laboratory costs and do not include physician fees or the costs of follow-up and treatment of detected cases. The actual costs would probably be several times greater than these figures.

The NCEP panel considered but rejected universal screening of all children, stating that "there was insufficient scientific and medical evidence to justify universal screening." Several concerns about universal screening were cited:

1. Tracking is imperfect in many children. Presumably tracking is better if there is a familial history of heart disease or lipid abnormality, but exact figures are not provided.
2. A large number of children would be labeled as needing counseling and treatment, including many who would not have high cholesterol levels as adults. This labeling could provoke unjustified anxiety in both parents and children.
3. Universal screening might lead to the overuse of drugs.
4. Given the efficacy of medical interventions in middle-aged individuals, there is sufficient opportunity to introduce medical treatment for most individuals at some time in their adult lives.

The cost or efficiency of screening is mentioned in the Appendix as a concern associated with universal screening but does not seem to have been a primary factor in the decision to reject this approach.

All of these arguments against universal screening also apply to screening a higher risk population only on a smaller scale. Although tracking might be more predictable in children with a family history of premature heart disease, it is still imperfect. Furthermore, a major cause of premature coronary heart disease is tobacco abuse, which is not mentioned in the report and is unrelated to high cholesterol levels. For many children a family history of premature CHD is caused by tobacco, not cholesterol. High-risk screening will label many children to be at risk who will not have high cholesterol levels as adults. Drug overuse is still a concern if 25 percent of children are being screened. Finally, if intervention in the third decade of life is effective, it is effective for high-risk individuals as well as normal-risk individuals. Indeed, most of the studies of cholesterol reduction in adults were done with high-risk populations.

Section IV. The Individualized Approach: Treatment

Although, the panel defines a high LDL cholesterol measurement as greater than 130 mg/dL (total cholesterol > 200 mg/dL), individual dietary intervention is recommended for all persistently borderline levels. Consequently, all children with an LDL cholesterol level greater than 110 mg/dL (total cholesterol > 170 mg/dL) would require dietary intervention. The Step I diet is the initial therapy for all children. If the LDL cholesterol level cannot be lowered below 130 mg/dL, the Step II diet should be initiated.

The panel recognizes that a multidisciplinary team approach is needed to obtain dietary compliance in children. They admit there is no long-term experience with children on the Step II diet. Nonetheless, they state that the Step I and Step II diets are safe and consistent with normal growth and development.

Incredibly, the report contains no data on the effectiveness of either the Step I or Step II diet in lowering cholesterol in children or any data on compliance with these diets by children in the community setting. As previously noted,[9] the Step I diet is minimally effective in adults. It is unlikely to be more effective in children.

Drug therapy is recommended only for low-risk children older than 10 years who continue to have LDL cholesterol levels greater than 190 mg/dL after intensive diet therapy or high-risk children (defined as a positive family history of premature heart disease or having two additional risk factors) who have LDL cholesterol levels greater than 160 mg/dL. Only the bile acid sequestrants, cholestyramine and colestipol, are recommended for use in children. The panel recognizes that compliance with taking bile acid sequestrants is difficult and suggests several en-

abling, prompting, and reinforcing strategies to improve medication compliance.

The panel's concern about overuse of medication is commendable but might not be necessary as long as bile acid sequestrants are the only approved medications. A greater concern is that frustrated parents and physicians unable to lower cholesterol to recommended acceptable levels in children, either compliant or noncompliant with dietary therapy, will resort to expensive but not approved medications, such as the hydroxymethylglutaryl coenzyme A reductase inhibitors that have been shown to be effective and well tolerated in adults.

Conclusion

The population recommendations of the NCEP panel "feel good," although no evidence is presented that implementing them in the pediatric age group is effective or superior to implementing them in the adult years. Some authors have expressed concerns that the harms of cholesterol reduction in young persons might outweigh the benefits.[10] These potential harms have been ignored by the panel. The costs of implementing the recommendations are not specified but would certainly depend on the completeness and intensity of the intervention.

The evidence presented by the NCEP panel does not support the recommendation for individual screening of even selected children for elevated cholesterol levels and subsequent treatment with diet or drug therapy. No evidence is presented that the Step I or Step II diet will lower cholesterol levels in children. Adult data suggest the Step I diet has minimal effect. No evidence is presented that children will comply with either the Step I or Step II diet. No evidence is presented that detection and treatment of elevated cholesterol levels in children are superior to delaying screening and treatment to the adult years. No evidence is presented that children will comply with drug therapy for elevated cholesterol levels or that such treatment will lower cholesterol levels much less decrease adult coronary heart disease.

In the absence of evidence of benefit from cholesterol lowering in children, the potential adverse effects are of great concern. All of the concerns mentioned by the panel in rejecting universal screening apply to selective screening. Because of imperfect tracking, great numbers of children will have high cholesterol levels unnecessarily diagnosed and treated. The anxiety created by this labeling will be considerable and will be compounded by the failure, in many cases, to lower cholesterol levels with the Step I diet. Ironically, the overuse of drugs is a problem only if (1) the drugs are dangerous or (2) lowering cholesterol levels is really not important. Both of these ideas are rejected by the panel. The costs of screening 25 percent of children and providing follow-up for at least one-third of those tested have been grossly underestimated by the panel. Finally, as pointed out by Hulley and colleagues,[10] young adults are more likely to die of injuries and violence than heart disease. There is an unresolved question about the link between cholesterol lowering and the increased risk of death from accidents, suicide, and violence.[7]

Referring again to the causal pathway shown in Figure 1, there is evidence to support step 1. Screening children can yield early detection of lipid abnormalities. No evidence is presented that early detection can lower children's lipid levels (step 2) or that lower lipid levels in children will cause lower adult levels (step 3). There is partial evidence for step 4. It has been shown that decreasing adult cholesterol levels by drug therapy will decrease coronary heart disease, but it has not been shown that overall mortality will be decreased.

The NCEP recommendations for screening children for elevated blood cholesterol are premature given the current scientific evidence. Answers to many important research questions are needed before practitioners adopt these guidelines.

References

1. 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.
2. American Academy of Pediatrics. National Cholesterol Education Program: report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics 1992; 89(3 Pt 2):525-84.
3. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988; 148:36-69.
4. Woolf SH. Practice guidelines, a new reality in medicine. II. Methods of developing guidelines. Arch Intern Med 1992; 152:946-52.

5. Eddy DM. Practice policies: where do they come from? JAMA 1990; 263:1265,1269,1272 *passim*.
6. Woolf SH, Battista RN, Anderson GM, Logan AG, Wang E. Assessing the clinical effectiveness of preventive maneuvers: analytic principles and systematic methods in reviewing evidence and developing clinical practice recommendations. A report by the Canadian Task Force on the Periodic Health Examination. J Clin Epidemiol 1990; 43: 891-905.
7. Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. BMJ 1990; 301:309-14.
8. Hjermann I, Holme I, Leren P. Oslo Study Diet and Antismoking Trial. Results after 102 months. Am J Med 1986; 80(2A):7-11.
9. Ramsay LE, Yeo WW, Jackson PR. Dietary reduction of serum cholesterol concentration: time to think again. BMJ 1991; 303:953-7.
10. Hulley SB, Newman TB, Grady D, Garber AM, Baron RB, Browner WS. Should we be measuring blood cholesterol levels in young adults? JAMA 1993; 269:1416-9.