# Clinical Practice Recommendations for Pediatric Dyslipidemia CE

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## OBJECTIVES

1. Discuss common causes of primary and secondary dyslipidemia.
2. Recommend appropriate dyslipidemia screening options for pediatric patients.
3. Describe the efficacy and safety of currently available therapies and their potential role in the management of dyslipidemia in pediatric patients.

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## ABSTRACT

The leading cause of mortality in the United States is atherosclerotic cardiovascular disease (ASCVD). Atherosclerotic lesions begin during childhood and can place individuals at greater risk for ASCVD. Providers play an active role in preventing the progression of risk factors and future ASCVD events through appropriate clinical management of genetic and acquired dyslipidemias in the pediatric population. Health care providers need to be aware of current

recommendations related to screening for dyslipidemia, lifestyle modification strategies, pharmacologic treatment, and guidelines for ongoing monitoring. Most patients with mild to moderate dyslipidemia can be managed by a primary care provider. It is imperative that providers understand the pathophysiology, screening methods, and available treatment options to effectively manage the condition. Frequent reassessment of family history and adherence to lifestyle modifications and pharmacologic interventions is essential for effective treatment. J Pediatr Health Care. (2019) *33*, 494–504


## KEY WORDS

Dyslidemia, lifestyle modification, statins


Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of mortality in the United States, and although ASCVD events rarely occur during childhood, atherosclerotic lesions begin during childhood, and risk factors and behaviors are also present early in life (Jacobson et al., 2015). ASCVD has been noted in the pediatric population through autopsy data and imaging (Wilson, McNeal, & Blackett, 2015). Identifying this vulnerable population allows the opportunity to recognize and prevent the progression of risk factors and future ASCVD events through appropriate clinical management of genetic and acquired risk factors. Pediatric nurse practitioners should implement strategies to help modify risk factors and manage dyslipidemias.

## RISK FACTORS

Risk factors for ASCVD progress from childhood to adulthood, and although adopting a healthy lifestyle at an early age is the best preventative strategy for those without genetic dyslipidemias, there are other interventions that can be deployed for those at moderate to high risk with more complex dyslipidemias (Wilson et al., 2015). Moderate-risk patients include those with a body mass index (BMI) of 95% to 96%, Stage 1 and 2 hypertension without treatment, high-density lipoprotein cholesterol less than 40 mg/dl, Kawasaki disease with regressed coronary aneurysms, systemic lupus erythematosus, juvenile rheumatoid arthritis, human immunodeficiency virus infection, or nephrotic syndrome. High-risk patients include those with a BMI of 97% or greater, high blood pressure with treatment, Kawasaki disease with current coronary aneurysms, Type 1 or 2 diabetes mellitus, or end-stage renal disease; those who have had orthotopic heart or renal transplantation; and those who smoke (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute, 2011).


Pediatric nurse practitioners should implement strategies to help modify risk factors and manage dyslipidemias.


## PATHOPHYSIOLOGY

The two major forms of lipids are cholesterol and triglycerides (TGs). Cholesterol is essential to normal cell function and can be synthesized by each cell individually or added to the body through diet. However, increased levels of cholesterol and triglycerides (TGs) due to genetic or secondary causes can be detrimental to the human body.

Expected lipid level values in children younger than 19 years are different from those of adults and vary depending on age (Table 1). During infancy, both cholesterol and TG values are significantly lower than during adulthood. These levels increase significantly over the first year of life and then increase more slowly until ages 9 to 11 years, when they more closely reflect adult levels. Then the total and low-density lipoprotein cholesterol (LDL-C) levels decrease as much as 10% to 20% or more during puberty before returning to baseline around the second decade of life.

## PRIMARY DYSLIPIDEMIA

### Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder of cholesterol metabolism characterized by very high levels of LDL-C from birth. FH leads to premature ASCVD that affects 1 in every 200 individuals in the heterozygous form (HeFH; Bouhairie & Goldberg, 2015). The prevalence of HeFH in specific populations (French Canadian, South African, Dutch Afrikaner,

**TABLE 1. Acceptable, borderline-high, and high plasma lipid and lipoprotein ranges for children and adolescents**

| Category | Acceptable (mg/dl) | Borderline (mg/dl) | High (mg/dl) |
|---|---|---|---|
| Total cholesterol | <170 | 170–199 | ≥200 |
| Low-density lipoprotein cholesterol | <110 | 110–129 | ≥130 |
| Non–high-density lipoprotein cholesterol | <120 | 120–144 | ≥145 |
| Triglycerides | | | |
| 0–9 years | <75 | 75–99 | ≥100 |
| 10–19 years | <90 | 90–129 | ≥130 |
| High-density lipoprotein cholesterol | >45 | 40–45 | <40 |

Note. *Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute (2011).*

Ashkenazi Jewish, and South Asian India) is as high as 1 in 100 due to the founder effect (Bouhairie & Goldberg, 2015), a reduced genetic diversity when a population has descended from a small number of colonizing ancestors. The homozygote variation (HoFH) is much rarer with a prevalence of one in every million (Bouhairie & Goldberg, 2015). There are over 12 million FH patients worldwide and an estimated 620,000 in the United States (Bouhairie & Goldberg, 2015). However, less than 10% of patients with FH are diagnosed due to limited clinician knowledge of the disorder or founder effect. Even patients who are diagnosed with FH have limited care options due to lack of overall awareness of the disorder. LDL receptor loss of function, apolipoprotein (Apo) B mutations, and gain of function in *PCSK9* are the common genetic mutations responsible for FH. Patients with HeFH are often asymptomatic and have LDL-C in the range of 155 to 500 mg/dl range (Nordestgaard et al., 2013). LDL-C elevations in HoFH are much more severe and are often greater than 500 mg/dl (Nordestgaard et al., 2013). Tendon xanthomas and premature corneal arcus may be present in HeFH, and planar, tubuerous, and tendon xanthomas; corneal arcus; and aortic stenosis may be present in HoFH.

## Hereditary Hypertriglyceridemia

Although secondary causes of hypertriglyceridemia are encountered much more frequently in primary care settings, genetic causes should be considered for elevation in TG level (>500 mg/dl). Alterations in function of lipoprotein lipase, ApoCII, and ApoA5 are causes of monogenic hyperchylomicronemia. Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by lipoprotein lipase (LPL) deficiency leading to extreme hypertriglyceridemia. In the absence of LPL, excessive levels of chylomicrons accumulate, and fasting plasma TG levels are well in excess of 1,000 mg/dl (Davidson et al., 2018). There are approximately 5,000 patients globally with FCS, and they usually present with nausea; vomiting; eruptive xanthomas; lipemia retinalis; hepatosplenomegaly; recurrent abdominal pain; failure to thrive; and severe, recurrent acute pancreatitis. Dysbetalipoproteinemia, caused by ApoE mutations, present with palmar tuberoeruptive xanthomas and an orange discoloration in palmar skin creases. TG elevations are typically between 500 and 2,000 mg/dl in children with dysbetalipoproteinemia.

Polygenic primary hypertriglyceridemias include familial hypertriglyceridemia and familial combined hyperlipidemia. These conditions result in more modest TG elevations and are much more common. Familial hypertriglyceridemia affects 1% of the population, with no typical physical findings and TG elevations of 250 to 1,000 mg/dl (Hegele et al., 2014). Familial combined hyperlipidemia also affects 1% to 2% of the population. These patients present with modest elevations of TG and cholesterol because of overproduction of ApoB and increased very-low-density lipoprotein particles (Hegele et al., 2014)

## Secondary Dyslipidemia

In many cases, dyslipidemia is caused by an underlying "nonlipid" disorder rather than an inborn disorder of lipid metabolism (Box 1). Uncontrolled diabetes, hypothyroidism, hepatic and renal dysfunction, and obesity are common causes of secondary dyslipidemia. Medications like oral contraceptives, protease inhibitors, retinoids, corticosteroids, and androgenic steroids may also cause secondary dyslipidemia (Wilson et al., 2015). Evaluation of secondary causes of dyslipidemia should be considered before initiating treatment strategies. Often, if management of secondary causes of dyslipidemia is maximized and/or pharmaceuticals are discontinued, lipid abnormalities resolve.

> In many cases, dyslipidemia is caused by an underlying "nonlipid" disorder rather than an inborn disorder of lipid metabolism

**BOX 1**. Secondary causes of dyslipidemia

- Exogenous
  - Alcohol
  - Isotretinoin
  - Beta blockers
  - Some oral contraceptives
  - Some antiretroviral agents
- Endocrine
  - Hypothyroidism
  - Hypopituitarism
  - Type 2 diabetes
  - Pregnancy
  - Polycystic ovarian syndrome
  - Lipodystrophy
- Renal
  - Chronic kidney disease
  - Nephrotic syndrome
- Infectious
  - Acute viral or bacterial infection
  - Human immunodeficiency virus
  - Hepatitis
- Hepatic
  - Obstructive liver disease/cholestatic conditions
  - Biliary cirrhosis
- Inflammatory disease
  - Systemic lupus erythematosus
  - Juvenile rheumatoid arthritis
- Other
  - Kawasaki disease
  - Anorexia nervosa
  - Solid organ transplantation
  - Childhood cancer survivor

Note. *Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute (2011).*

## Screening for Pediatric Dyslipidemia

Guidelines for screening for dyslipidemia in the pediatric population have evolved over the past 26 years. Screening for family history for cardiovascular disease (CVD) can be challenging because of limited time for history taking during patient encounters and the need to address other health promotion and disease prevention topics that are recommended by the American Academy of Pediatrics (Wilson et al., 2015). Before 2011, there were two major approaches to screening for dyslipidemia in children: screening in selected populations and screening in the general the population. Traditionally, screening of high-risk children with multiple risk factors, a family history of CVD, or the presence of hypercholesterolemia were the recommendations. In 2010, the results of the Coronary Artery Risk Detection in Appalachian Communities project indicated that the targeted screening processes most likely resulted in missed opportunities; overlooked many with significant dyslipidemia; and failed to detect genetic dyslipidemias, which require pharmacologic treatment (Yoon, 2014). Initialization of universal screening would enable practitioners to diagnose, treat, and prevent future atherosclerotic disease (Daniels, 2015).

In 2011, the U.S. National Institutes of Health Heart, Lung, and Blood Institute (NHLBI) Expert Panel revised lipid cutoff values for children based on U.S. normative data. The panel of experts categorized the values as acceptable, borderline, and high (Table 1). Furthermore, the Expert Panel recommended additional universal screening" for all children and adolescents (Expert Panel, 2011). Subsequently, the National Lipid Association concurred with the NHLBI Expert Panel recommendation for universal screening (Jacobson et al., 2015). These organizations' views contrast with the most recent recommendation of the U.S. Preventive Services Task Force (2016), which rated the evidence as insufficient to recommend for or against routine/universal screening for lipid disorders in children or young adults age 20 years of age or younger.

## Selective Screening

### Target screening

Target screening for dyslipidemia in children, a strategy of primary prevention of development of early clinical manifestations of atherosclerosis, will allow us to slow or prevent the early development of CVD. The plasma levels of lipids and lipoproteins in children are influenced by various metabolic, genetic, and environmental factors. Additionally, lipid concentration is influenced by age, sex, and ethnicity (Gooding et al., 2015). Children and adolescents with unknown and positive family history results; a positive diagnosis of any disease that leads to early CVD; and the presence of risk factors such as obesity, hypertension, diabetes, smoking, poor dietary habits, and sedentary lifestyle should also be screened for dyslipidemia. All patients meeting these criteria, ages 2 to 21 years, should be screened by receiving a fasting lipid profile (de Ferranti, 2015; Jacobson et al., 2015). Selective screening based on family history and risk factors alone misses a considerable number (30−60%) of children with dyslipidemia (Expert Panel, 2011).

### Cascade screening

*Cascade screening* is defined as a systematic process for identifying individuals with a medical condition. In genetics, the process begins with an affected family member and entails an iterative or circular round of testing of closely related relatives, followed by testing of close relatives of those newly discovered as affected (Knowles, Rader, & Khoury, 2017). Cascade or reverse cascade screening for FH is a method of identifying people at any age who are at risk for a genetic condition by a process of systematic family tracing. Cascade screening relies on identifying patients for cholesterol testing, genetic testing, or both for all potentially affected relatives (Knowles et al., 2017). All children 2 years or older with a first- or second-degree relative with a recorded history of CVD before age 55 years in men and 65 years in women should at least have a fasting lipid profile to determine dyslipidemia status (de Ferranti, 2015).

## Universal screening

*Universal screening* of dyslipidemia refers to the detection of dyslipidemia in all or as many children as possible, regardless of family history of early CVD or value of the lipid profile of the parents or close relatives. Insufficient sensitivity of a family history of premature CVD, insufficient knowledge of the value of the lipid profile of the parents or close relatives, and overall health condition of the parents promote the importance of universal screening for dyslipidemia in children (Daniels, 2015). Universal screening of dyslipidemia can detect children with undiagnosed hereditary dyslipidemia, and subsequent lipid profile assessment of parents and relatives can uncover their cardiovascular risk (Gooding et al., 2015). According to the NHLBI guidelines, targeted or selective screening should be done in children ages 2 to 10 years who have a positive family or personal history result (Box 2). Universal screening is recommended for all children ages 9 to 11 years. It is not recommended during puberty or in early adolescence (ages 12−16 years), because it can produce a falsely low result due to the dip in lipid production during this time. However, if risk factors or an updated positive family are present, screening should be done. Universal screening is recommended once for 17- to 21-year-olds (Expert Panel, 2011).

Based on guidelines of the NHLBI Expert Panel (2011), universal screening for dyslipidemia is recommended between the ages of 9 and 11 years and between 17 and 21 years. Children and adolescents should be tested by administering a nonfasting, non−high-density lipoprotein cholesterol (Daniels, 2015). The goal of this testing is to

**BOX 2**. Screening recommendations

Birth to 2 years

No lipid screening

2–8 years

Selective screening based on positive family history result of one of the following:

- Parent, grandparent, aunt/uncle, or sibling with premature ASCVD
- Parent with TC ≥ 240 mg/dl
- Patient with one of the following:
  - Diabetes
  - Hypertension, BMI ≥ 95th percentile
  - Smokes cigarettes
  - Exposed to secondhand smoke
  - Chronic kidney disease
  - Cardiac transplant
  - Kawasaki disease with current or regressed coronary aneurysms
  - Chronic inflammatory disease

9–11 years

Universal screening recommended. Further evaluation recommended for abnormalities

12–16 years

Universal screening NOT recommended
Selective screening recommended, if new knowledge of:

- Parent, grandparent, aunt/uncle, or sibling with premature ASCVD
- Parent with TC ≥ 240 mg/dl
- Patient with one of the following:
  - Diabetes
  - Hypertension, BMI ≥ 95th percentile
  - Smokes cigarettes
  - Exposed to secondhand smoke
  - Chronic kidney disease
  - Cardiac transplant
  - Kawasaki disease with current or regressed coronary aneurysms
  - Chronic inflammatory disease

17–21 years

Universal screening recommended once during this time period

Note. *ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; TC, total cholesterol. Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute (2011).*

reduce morbidity and mortality from heart disease in pediatric patients with FH through early diagnosis and effective disease management (Knowles et al., 2017). See Box 2 for an overview of all screening methods.

## INTERVENTIONS

### Lifestyle Modifications

For children with an LDL-C level of 130 mg/dl or greater, initial management consists of lifestyle modifications that focus on dietary changes; physical activity; and, in children with obesity, weight loss (Jacobson et al., 2015). Lifestyle modifications that prevent obesity will also have a positive impact on preventing/managing dyslipidemia. One of the best approaches is to guide parents to create a positive, healthy home environment that encompasses consuming a healthy diet; getting adequate sleep; stocking the home with healthy foods, beverages, and snacks; sharing family meals; promoting breakfast; and decreasing screen time.

The American Academy of Pediatrics encourages a family-based approach to educate and empower parents to promote behaviors related to healthy eating and childhood obesity prevention (Loth, Friend, Horning, Neumark-Sztainer, & Fulkerson, 2016). Research recommends that parents should be the primary focus of pediatric obesity prevention and treatment programs (Horning, Fulkerson, Friend, & Story, 2016). Parents can encourage self-regulation, provide positive non–food-based rewards, and model appropriate portion sizes.

Parents play an important role in dietary and activity levels with children of all ages. Children's consumption of calories at a meal is influenced by the portions they are served and the quality of food parents serve themselves. It is important to teach parents how to let their children self-regulate intake, how to serve proper portion sizes, and how to recognize positive parental feeding styles. Parents play a critical role in monitoring the food and beverages that enter the home. They also serve as the primary role models for healthy eating, screen time, and physical activity. Planning healthy home strategies is intentional and requires preplanning (Fruh, 2017).

### Home Environment and Household Routines

#### Creating a positive and healthy home environment

One of the best ways to achieve a healthy lifestyle with children is to create a healthy home environment. When parents create a healthy home environment, they themselves will more likely participate in healthy behaviors. Children often mimic the healthy behaviors adopted by their parents (Savage, Fisher, & Birch, 2007).

#### Dietary intake

Dietary modifications can improve dyslipidemia and can modestly improve abnormal lipid levels in children (Expert Panel, 2011). The specific dietary modifications focus on reducing total and saturated fat and cholesterol with an increased intake of dietary fiber through fruits, vegetables, and whole grains. For children who have not been placed on a low-saturated-fat diet, a diet that limits fat intake to 30% of total calories, saturated fat to 7% to 10% of total calories,

and total cholesterol to 300 mg per day should be implemented (Jacobson et al., 2015). If the child's fasting lipid levels after a 3-month trial intervention exceed the therapeutic target, a more restrictive diet is recommended. The more restrictive diet limits total fat to 25% to 30% of total calories, saturated fat to less than 7% of total calories, and cholesterol to less than 200 mg per day (Expert Panel, 2011).

## Healthy Home Routines

A study identified that when preschool children were exposed to the three household routines of eating dinner regularly as a family, getting adequate nighttime sleep, and limiting screen time, they had lower obesity rates than children who were not exposed to these routines (Haines et al., 2013). Promoting healthy household routines needs to be encouraged by families to lower childhood obesity and improve hyperlipidemia.

### Sleep

Adequate nighttime sleep has been found to play a role in preventing obesity in children with a positive dose-response relationship between total sleep hours and obesity risk (Miller, Lumeng, & LeBourgeois, 2015). The American Academy of Pediatrics (2016) consensus group recommends the following guidelines regarding hours of sleep per 24 hours for children (which includes naps):

- infants 4–12 months of age: 12–16 hours;
- 1- to 2-year-olds: 11–14 hours;
- 3- to 5-year-olds: 10–13 hours;
- 6- to 12-year-olds: 9–12 hours; and
- 13- to 18-year-olds: 8–10 hours.

Given the relationship between sleep and obesity, it is essential that childhood obesity prevention efforts include educating parents on the importance of establishing a healthy sleep routine for themselves and their children.

### Home food environment, snacks, and beverages

Parents are the gatekeepers for food and beverage availability in the home (McIntosh & Zey, 1989). It is important that parents stock their homes with healthy foods. Families will consume the foods that are available in the home. The foods that are available in the home environment often become the foods that children learn to like and consume; therefore, the consumption of healthy foods such as fruits and vegetables is predicted by their home availability (Trofholz, Tate, Draxten, Neumark-Sztainer, & Berge, 2016; Williams et al., 2002). The availability of snacks significantly increases children's snack intake. Also, children's consumption of sugary drinks is associated with parent's soft drink habits and their availability in the home (Blaine, Kackurak, Davison, Klabunde, & Fisher, 2017). The exposure to healthy snacks like fruits and vegetables at age 2 to 4 years predicts food preferences at 8 years (Berge et al., 2015). Reducing the home availability of unhealthy snacks can play a role in preventing childhood obesity and improving general cardiovascular health (Blaine et al., 2017; Williams et al., 2002). Introducing healthy nutritional habits at a young age can produce lasting results that include lowering blood cholesterol levels and creating healthier families (Williams et al., 2002).

### Family meals

The promotion of healthy and frequent family meals is a protective factor for obesity because of the positive associations with healthy food intake (Berge et al., 2015; Ewald, Kirby, Rees, & Robertson, 2014; Loth et al., 2016). A study to encourage healthy family meals showed a promising reduction in excess weight gain in prepubescent children (Ewald et al., 2014). Research has also shown positive associations between family meal frequency, nutritional intake, and fruit and vegetable consumption among children, and inverse associations with consumption of soft drinks and high-fat foods among children (Ewald et al., 2014). It is important to teach parents how to purchase healthy food and prepare family meals on a limited budget and to give strategies for how to increase the frequency of healthy family meals.

### Screen time and other sedentary behaviors in the home environment

Limiting screen time can be an effective means of encouraging physical activity. Parents determine the amount of screen time for young children in the home (Xu, Wen, & Rissel, 2015). A longitudinal study spanning preschoolers through adolescents found that TV watching is an independent predictive factor of obesity (Xu et al., 2015). Additionally, a physically active lifestyle has health benefits that include lower blood pressure, increased life expectancy, and decreased risk of CVD (Williams et al., 2002). Encouraging decreased screen time, removing TVs and other screens from bedrooms, and turning off the TV while eating need to be discussed with parents.

### Summary

Family-based interventions that guide parents in behavior-change processes are most successful for children. It is important to target mothers as change agents related to children's diets and physical activity levels, because cholesterol tracks over many years, and children with high levels of LDL-C are more likely to become adults with high LDL-C (Williams et al., 2002). It is important to inform mothers of the impact their decisions will have on their own lives and their children's lives, and empowering them to make a change will have a significant impact on promoting health and managing/preventing dyslipidemia and obesity.

Family-based interventions that guide parents in behavior-change processes are most successful for children.

## Pharmacologic Therapy

Occasionally, lifestyle modifications are not sufficient to mitigate the risks of ASCVD, and pharmacologic therapy is needed to reduce LDL-C further. When pharmacologic therapy is initiated, it is important to continue the implementation of lifestyle modification as a synergistic mechanism to lower LDL-C or TG and, possibly, require lower dosages of medication. Children usually require pharmacologic intervention for elevated LDL-C or TG.

Children age 8 years and older are potential candidates for pharmacologic intervention to lower lipids after secondary causes of dyslipidemia (Bix 1) have been excluded, except in the case of HoFH, for which pharmacologic interventions are instituted at age 2 years. The average value of two separate fasting lipid panels and the presence or absence of moderate to high risk factors are used to determine which patients are appropriate for drug therapy.

### Elevated LDL-C

The first-line therapy for elevated LDL-C is 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins), which result in up-regulation of LDL receptors and reduced plasma LDL-C (Elkins & Friedrich, 2018). Initiation of statins results in substantial ASCVD risk reduction (Elkins & Friedrich, 2018). Six of the seven commercially available statins (excluding pitavastatin) are indicated for pediatric patients at varying ages and dosages (Table 2). Rosuvastatin and pravastatin have been approved by the U.S. Food and Drug Administration for use in children as young as 8 years; atorvastatin, lovastatin, simvastatin, and fluvastatin have been approved for use at 10 years of age (Bays, Jones, Orringer, Brown, & Jacobson, 2016). All of the statins with pediatric indications are available in generic form. The choice of a particular statin is a matter of provider preference but can be influenced by the degree of expected LDL-C reduction associated with the particular formulation and/or dosage.

The primary goal of treatment is to achieve an LDL-C level of 130 mg/dl or lower, ideally 110 mg/dl or lower, or a 50% or greater LDL-C reduction (Wilson et al., 2015). If the initial goal is not achieved, consideration should be given to doubling the dose of the statin, if the maximal dose has not already been achieved. However, doubling the dose of the statin will further reduce LDL-C only by approximately 6%.

If the combination of lifestyle modifications and maximally dosed statins provides an inadequate reduction of LDL-C, combination lipid-lowering therapy can be considered (Bays et al., 2016). Cholestyramine, a bile acid sequestrant (BAS), can be given as early as 6 years of age (Yoon, 2014). In children 10 years and older with FH, colesevelam, a BAS, or ezetimibe, a cholesterol absorption inhibitor, can be combined with statins to lower LDL-C in children 10 years and older with FH (Yoon, 2014). BASs bind bile salt to the gastrointestinal tract and prevent reuptake, leading to increased conversion of cholesterol to bile in the liver, up-regulation of the LDL receptor, and increased clearance of LDL-C from circulation (Yoon, 2014).

**TABLE 2. Pharmacotherapy options**

| Drug | Age | Dose | Indication | Expected LDL-C % reduction |
|---|---|---|---|---|
| Rosuvastatin | 8–9 years | 5–10 mg | HeFH | 44–52 |
| | 10–17 years | 5–20 mg | | 44–63 |
| Pravastatin | 8–13 years | 20 mg | HeFH | 30 |
| | 14–18 years | 40 mg | | 36 |
| Atorvastatin | 10–17 years | 10–20 mg | HeFH | 37–42 |
| | ≥10 years | 10–80 mg | HoFH | 37–60 |
| Fluvastatin | 10–16 years | 20–80 mg | HeFH | 20–36 |
| Simvastatin | 10–17 years | 10–40 mg | HeFH | 30–40 |
| Lovastatin | 10–17 years | 10–40 mg | HeFH | 20–30 |
| Colesevelam | 10–17 years | 3,750 mg | HeFH | 10–15 |
| Cholestyramine | 6–12 years | 80 mg/kg TID; maximum dose, 8 g/day | hypercholesterolemia | 20 |
| | adolescents | 4 g BID | | |
| Ezetimibe | 10–17 years | 10 mg | HeFH | 20 |

*Note. BID, twice per day; HeFH, heterozygous form of familial hypercholesterolemia; HoFH, homozygous form of familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; TID, three times per day. Modified from Bays, Jones, Orringer, Brown, & Jacobson (2016).*

Plant sterols and plant stanols, when taken at 2 g per day, have shown significant inhibition of cholesterol absorption and can lower LDL-C levels to 8% to 10% and TGs to 6% to 9% (Gylling et al., 2014). This LDL-C lowering is additive to that of statins in dyslipidemic patients. Plant sterols and stanols can be used in children older than 2 years in an adjunctive manner for those who fail to achieve LDL-C targets on statins or are statin intolerant (Expert Panel, 2011).

## Elevated TGs

Children with TG levels of 500 mg/dl or greater are at risk for developing secondary pancreatitis, and although there are no medications approved by the U.S. Food and Drug Administration to treat hypertriglyceridemia in pediatric patients, fibric acid derivatives (fibrates) and/or omega-3 fatty acids can be considered in consultation with a lipid specialist (Wilson et al., 2015). These medications both primarily decrease hepatic TG production. However, some primary hypertriglyceridemic disorders (FCS and familial LPL deficiency) are caused by insufficient LPL activity and result in decreased clearance of dietary-derived chylomicrons from circulation and will have little response to any pharmacotherapeutic intervention. Pre-prandial orlistat, a pancreatic lipase inhibitor, in addition to a very-low-fat diet, has shown increased triglyceride circulatory clearance and decreased risk of pancreatitis (Blackett, Wilson, & McNeal, 2015).

Fibrates significantly decrease TG levels by activating peroxisome proliferator-activated receptor-$\alpha$, part of a group of nuclear receptor proteins that act as transcription factors, via three separate mechanisms: suppressed production of the LPL inhibitor ApoC-III, reduced hepatic secretion of very-low-density lipoprotein C, and reduced hepatic TG production via $\beta$-oxidation (Elkins & Friedrich, 2018). Fibrates are often one of the first-line treatment options to help mitigate the risk of pancreatitis in patients with very high TG levels. Their ability to lower serum TG is dependent on baseline TG levels; average TG reduction is 40% to 50%, but reductions of up to 62% have been shown in isolated hypertriglyceridemia (Elkins & Friedrich, 2018).

Omega-3 fatty acids are available in the form of nonprescription dietary supplements and prescription therapy. Both lower TG levels in a dose-dependent manner; however, dietary supplements are not as rigorously regulated and can provide inconsistent levels of omega-3 fatty acids. Therefore, prescription products should primarily be used to lower plasma TG levels (Elkins & Friedrich, 2018). Although prescription omega-3 fatty acids are not indicated for pediatric use, they have been safely used to lower TG in this population. The exact mechanism by which omega-3 fatty acids lower TG levels is unknown but is thought to include increased $\beta$-oxidation of fatty acids, increased LPL hydrolysis through the activation of proliferator-activated receptor-$\alpha$, and inhibition of ApoC-III (Elkins & Friedrich, 2018). Reductions in serum TG up to 45% have been observed with the use of omega-3 fatty acids (Elkins & Friedrich, 2018).

## Drug Safety

The risks of pharmacologic treatment in children appear to be low and similar to risks in adults (Jacobson et al., 2015). The primary adverse effects of statins in the adult population are muscle-related symptoms, hepatic dysfunction, and hyperglycemia, and they are more prevalent with higher-dose statins that are not approved for pediatric patients (Elkins & Friedrich, 2018). Muscle toxicity and myalgia are the most common adverse effects of statins, and fear of muscle symptoms is a commonly cited reason for delaying or not initiating statin therapy (Johnson et al., 2017). However, the extent of these adverse effects is unknown because of the limited frequency and duration of statin use in pediatric patients. Johnson et al. (2017) found no clinically meaningful difference in pediatric patients' creatinine kinase (CK) levels when taking or not taking statins or after initiation of statin therapy. Furthermore, patients who did experience muscle symptoms or significant elevations of CK were often able to be rechallenged with statin therapy and continue taking statins without prolonged adverse effects.

Statins should be avoided during pregnancy, and sexually active females should undergo pregnancy counseling before statin use. Concerns of statins decreasing cholesterol synthesis and affecting brain development and function have been unfounded in pediatric homozygous FH trials when statin use begins as early as 2 years of age.

The nonsystemic absorption of BAS leads to primarily gastrointestinal adverse effects, most frequently constipation, gas, and bloating, and can be mitigated with increased dietary fiber and fluid consumption (Yoon, 2014). However, the discontinuation rates are as high as 30% because of gastrointestinal adverse effects (Yoon, 2014). Because of the mechanism of action, BAS can increase plasma TGs and should be used cautiously in those with TG levels greater than 250 mg/dl and not used if TG levels are greater than 500 mg/dl.

The most commons adverse reactions with fibrate therapy include myopathy, cholelithiasis, and elevations in creatinine (Elkins & Friedrich, 2018). Myopathy is the most serious adverse reaction associated with fibrates, is more prevalent with concomitant statin therapy, and may cause rhabdomyolysis if fibrates are not discontinued when myopathy develops (Elkins & Friedrich, 2018). An average creatinine elevation of 12% is noted with fibrate therapy; however, this elevation is reversible upon discontinuation of therapy and is not thought to indicate intrinsic renal dysfunction (Elkins & Friedrich, 2018).

The use of omega-3 fatty acids has produced no serious safety issues, minimal treatment discontinuation, no effect on hepatic function, and no serious drug–drug interactions. An elevation of LDL-C up to 45% has been noted in omega-3 fatty acids containing docosahexaenoic acid ethyl esters; however, this increase was not observed in formulations of omega-3 fatty acids that contain eicosapentaenoic acid ethyl ester alone (Elkins & Friedrich, 2018).

### Monitoring

Frequent laboratory follow-up is recommended in patients who undergo pharmacologic therapy (Wilson et al., 2015). Fasting lipid profiles and hepatic enzymes should be monitored at baseline, 1 month, 2 months, and then every 3 to 4 months thereafter. Hepatic enzyme levels should remain less than three times the upper limit of normal. CK level should be monitored at baseline, at 1 month after initiating statin therapy, and if myalgia symptoms occur.

Physical examination, including height, weight, BMI, and blood pressure, should be monitored at each visit. Nurse practitioners should also review medication compliance, tolerance, and possible adverse effects at each office visit. The patient's family history and risk factors should frequently be updated to ensure that appropriate treatment recommendations are being followed.

### When to Refer

Children with LDL-C levels of 250 mg/dl or greater and/or TG levels of 500 mg/dl or greater should be referred to a lipid specialist (see http://www.learnyourlipids.com/content/specialists/) for specialized management (Expert Panel, 2011).

## CONCLUSION

Primary care providers are often the first health care professionals to diagnose and manage dyslipidemia. Most patients with mild to moderate dyslipidemia can be managed by a primary care provider. It is imperative that providers understand the pathophysiology, screening methods, and available treatment options to effectively manage the condition. Frequent reassessment of family history and adherence to lifestyle modifications and pharmacologic interventions is essential for effective treatment. Some patients with more complex lipid abnormalities will require referral to a lipid specialist.

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## CE QUESTIONS

1. Which of the following are moderate risk factors for atherosclerotic cardiovascular disease?
   a. Kawasaki disease with regressed coronary aneurysms
   b. Human immunodeficiency virus infection
   c. Nephrotic syndrome
   d. All of the above
2. Which one of the populations does not have an increased prevalence of familial hypercholesterolemia due to the founder effect?
   a. Pacific Islanders
   b. French Canadian
   c. Dutch Afrikaner
   d. Ashkenazi Jewish
3. Which of the following is a genetic mutation responsible for the development of familial hypercholesterolemia?
   a. Lipoprotein lipase deficiency
   b. PCSK9 gain of function mutation
   c. Apo E mutation
   d. Apo CII mutation
4. During a 6-year-old females' well visit, her mother mentions that her 32-year old husband recently suffered a heart attack and has high cholesterol. The patient has no positive risk factors for dyslipidemia and a normal physical examination. The most appropriate next step for this patient is which of the following?
   a. None, due to normal exam findings
   b. A non-fasting non-high density lipoprotein cholesterol
   c. A fasting lipid profile
   d. Refer the child to a lipid specialist
5. An obese 12-year-old male presents with a history of a sedentary lifestyle, and a food questionnaire reveals poor dietary habits. In conjunction with prescribing interventions to improve diet and exercise. The practitioner would screen him by which of the following methods?
   a. Cascade screening
   b. Universal screening
   c. Targeted screening
   d. Genetic testing
6. Universal lipid screening is recommended during puberty because of normal changes in lipid levels.
   a. True
   b. False
7. Which one of the following dietary modification is recommended to modestly improve abnormal lipid levels in children?
   a. Saturated fat limited to 7-10% of dietary intake
   b. Total cholesterol limitation of less than 300 mg/day
   c. Dietary fat limited to less than 30% of total calories
   d. All of the above
8. Which of the following medications would be most appropriate for an 8-year-old boy diagnosed with HeFH whose LDL-C is 200 mg/dL after six months of lifestyle modifications?
   a. Atorvastatin 10 mg
   b. Rosuvastatin 5 mg
   c. Pravastatin 40 mg
   d. Pitavastatin 1 mg
9. Which of the following should be monitored on every follow-up visit for dyslipidemia?
   a. Creatinine kinase
   b. Glucose
   c. Blood pressure
   d. Total bilirubin
10. A 9-year-old healthy boy without significant medical history presents for evaluation. His father experienced a myocardial infarction at age 40 and was placed on a

high potency statin. The patient's fasting lipid profile revealed: Total Cholesterol - 370 mg/dL; High Density Lipoprotein-C- 45 mg/dL; triglyceride (TG)- 25 mg/dL; and Low Density Lipoprotein-C 335 mg/dL. Based on these results you would recommend which of the following?

a. Refer the patient to a pediatric lipid clinic
b. Do more inter-office testing
c. Prescribe a statin
d. Start him on a low cholesterol diet

Answers available online at ce.napnap.org.