NCC Pediatrics Continuity Clinic
Curriculum: **Health Maintenance II**

Pre-Meeting Preparation:

Please read the following enclosures, corresponding to the screening procedures:

1) Hematocrit or Hemoglobin: "Iron Deficiency: Implications Before Anemia" *(PIR 2021)*
   → excerpt from "Diagnosis and Prevention of Iron-Deficiency and Iron-Deficiency Anemia in Infants and Young Children" *(Pediatrics 2010)*
2) Lead: "CDC calls on pediatricians to address challenges in lead poisoning prevention" (*AAP News, 2022*)
   → update on Maryland lead testing requirements (2020)
3) Tuberculosis: TB Risk-Assessment Questionnaire; "TST- CDC Fact Sheet"
   → excerpt from: AAP Clinical Report "Tuberculosis Infection in Children and Adolescents: Testing and Treatment" (*Pediatrics 2021)*
4) Dyslipidemia: Screening for Dyslipidemia *(Excerpts- AAP Statement);*

Homework:

* **Bring in an article or resource** addressing a "clinical controversy" or "current event" related to this week's screening procedures (e.g. unclear benefits of universal iron deficiency or lipid screening)

Conference Agenda:

- *Review* Health Maintenance II
- Complete Health Maintenance II Cases
- **Round-table discussion** of "clinical controversy"/ "current events" articles

Post-Conference: Board Review Q&A

Extra-Credit:

- Hct or Hgb: "Diagnosis & Prevention of Iron Deficiency" *(AAP Clinical Report; 2010)*
  - Letters to the Editor, AAP vs USPSTF *(Pediatrics, 2016)*
- Lead: "Prevention of Childhood Lead Toxicity" *(AAP Policy Statement; July 2016)*
  - State Lead-Testing Policies (*The Network for Public Health Law*)
- Tuberculosis: "Pediatric Tuberculosis" (*Francis J. Curry National TB Center, 2010)*
  - TB Screening Tests in Children *(Heartland National TB Center)* *see algorithms page 132-133*
  - Tuberculosis Infection in Children and Adolescents *(AAP Clinical Report, 2021)*
- Dyslipidemia: "Expert Panel on Integrated Guidelines for CV Health" (NHLBI, 2011)
  - Hyperlipidemia *(PIR, 2020)*
  - Universal Screening Among 9-to11-Year Children:Screening Results and Physician Management *(Clinical Pediatrics, 2022)*

Iron Deficiency: Implications Before Anemia

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EDUCATION GAP

Clinicians should recognize iron deficiency as a unique disease entity and understand the interconnection between iron deficiency and other systemic diseases.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recognize that iron deficiency is a separate entity that precedes iron deficiency anemia and in and of itself causes serious morbidity.
2. Identify iron deficiency as an associated sign for multiple underlying diseases, including inflammatory bowel disease and hereditary hemorrhagic telangiectasia.
3. Discuss the vulnerability of the brain to iron depletion.
4. Describe options for replenishing iron stores and the improvements in parenteral formulations of iron.

INTRODUCTION

Iron plays a role in multiple essential physiological functions, including oxygen transport, gene regulation, DNA synthesis, DNA repair, and brain function. Depletion of and inability to use iron disrupts these pathways and causes multiple morbidities. Iron deficiency anemia (IDA) is a well-known sequela, but iron deficiency alone, before the manifestation of microcytosis and anemia, may have negative implications for the health of pediatric patients.

Of children 0 to 4 years of age, 20.1% have IDA in industrialized countries and the same is true of 39% of children in nonindustrialized countries. (1) Iron deficiency, independent of anemia, affects 2.3 billion people worldwide, including 50% of younger children and female teenagers. The recognition that iron deficiency puts children at risk for a myriad of poor outcomes is an important step in delivering effective health-care.

IRON HEMOSTASIS

Iron is absorbed from the diet in primarily the duodenum and the jejunum. The body has been known to regulate the amount of absorption; it has been estimated that a diet with 10 to 20 mg of iron leads to approximately 1 mg of iron absorption.

AUTHOR DISCLOSURE Drs Tong and Vichinsky have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Dietary iron can take various forms when consumed. Heme iron, the iron associated with meat intake, represents approximately one-third of the dietary iron but contributes to two-thirds of the body iron. Heme iron is preferentially absorbed because it is soluble at the pH of the intestine. In contrast, the most common dietary form of iron, ferric or Fe3+ iron, must be chelated in the acidic environment of the stomach and stay chelated until it is absorbed via the β_3 integrin and mobilferrin pathway; without this chelation step, iron is insoluble in the intestine due to the small intestine's comparatively more alkalotic pH and cannot be absorbed. Ferrous or Fe2+ iron is the reduced form of ferric iron and is absorbed through a different pathway than the forms noted previously herein. Vitamin C (ascorbic acid) facilitates the reduction of ferric iron. Non-heme iron sources are, therefore, more difficult for the human body to absorb (can become insoluble, require chelation) compared with heme iron (soluble in the normal duodenal pH). (2)

Recent research elucidated one of the key players in the regulatory process, hepcidin, which is now considered the central regulator of iron, affecting how the gastrointestinal tract, liver, and macrophages contribute to iron homeostasis. Hepcidin regulates the activity of the iron exporter, ferroportin, located on the basolateral membrane of enterocytes, hepatocytes, and macrophages. The binding of hepcidin to ferroportin leads to the internalization of ferroportin, reducing the amount of iron available in the plasma. (3) High levels of hepcidin, therefore, lead to sequestration of iron, reducing the amount available for functions such as erythropoiesis and DNA synthesis.

Factors that influence the release of iron from the liver include intracellular and extracellular levels of iron, inflammation, and erythropoietic iron demands. High levels of iron and inflammation upregulate hepcidin production, whereas an erythropoietic signal downregulates hepcidin to make more iron available to bone marrow.

In cells, iron is processed as either transferrin-bound iron or non–transferrin-bound iron, both of which contribute to the labile iron pool. Ferritin is a major intracellular storage protein for iron, but if the pool of iron is too large, another pathway becomes available; free iron produces free radicals. This oxidative stress can damage organelles and impair cellular function.

IRON DEFICIENCY: CLINICAL CLASSIFICATION

Deficits in iron can be divided into 4 major categories: 1) Iron depletion describes a state in which the low level of iron affects nonhematologic pathways (brain, muscle); as such, one does not see the microcytic anemia that is classically seen in IDA. 2) Iron-restricted erythropoiesis applies to a state in which there is some impairment of hematologic function without evidence of anemia or microcytosis. 3) IDA represents the clinical picture with a decreased hemoglobin level, (4) at which point neurodevelopmental and musculoskeletal functions have already been hindered. 4) Functional iron deficiency defines a state in which iron stores are adequate but unavailable for biological use. The typical laboratory findings of each category can be seen in Table 1.

The epidemiology of true iron deficiency is hard to determine, but using anemia as a rough surrogate, the burden of disease is large. The 2001 World Health Organization report used an estimate of 30% to 40% of those with iron deficiency to manifest as cases of IDA. Iron deficiency is, therefore, thought to affect more than 2 billion people worldwide; the distribution varies according to age, sex, geography, and socioeconomic status, but in nonindustrialized countries, approximately 50% of children and teenaged girls have IDA. (1)

IRON DEFICIENCY: THE CONSEQUENCES

Iron deficiency affects a variety of physiological functions. Iron deficiency alone has been associated with long-lasting consequences on neurodevelopmental outcomes; standard test scores of 11- to 14-year-olds who had iron deficiency as infants demonstrate worse performance on 6 different tests, including the Full-Scale IQ and the Wide Range Achievement Test Arithmetic and Reading. (5) A group of infants was followed to 25 years of age, and the study demonstrated increased odds of failure to complete secondary school and of having neuropsychiatric deficits, including negative emotions, detachment, and poor self-rating of emotional health, compared with iron-sufficient control subjects. (6) Trying to isolate the effect of iron status in these studies is understandably difficult, and changes could be related to an unidentified confounder, but the associations are worth acknowledging with the potential of iron deficiency to affect individuals throughout their whole life. An iron-deficient state has further been linked to attention-deficit/hyperactivity disorder (ADHD) and restless legs syndrome (RLS). Visual and auditory deficits can also be seen. Physiologically, these changes may be mediated by neuronal hypomyelination and decreased neurotransmitter function. (7) In addition, in rats that model neonatal dendritic sprouting in the setting of iron deficiency, as simulated with deferoxamine chelation, investigators demonstrated shortening of the morphology of neuronal branches and a reduction in the number of primary dendrites in the hippocampus. (8) These sets of changes in the brain may underlie the impairments

Table 1. Classification of Iron States and Associated Laboratory Findings

LABORATORY FINDING	IRON DEPLETION	IRON-RESTRICTED ERYTHROPOIESIS	IRON DEFICIENCY ANEMIA	FUNCTIONAL IRON DEFICIENCY
Hemoglobin concentration	Normal	Normal	Reduced	Normal
Mean corpuscular volume	Normal	Normal to reduced	Reduced	Reduced
Serum iron concentration	Normal	Reduced	Reduced	Normal
Serum ferritin concentration	Reduced	Reduced	Reduced	Normal to elevated
Total iron binding capacity	Normal	Increased	Increased	Increased
Soluble transferrin receptor	Normal	Increased	Increased	Increased
Reticulocyte hemoglobin content	Normal	Decreased	Decreased	Decreased
Hepcidin	Reduced	Reduced	Reduced	Elevated

of neurodevelopment in children with iron deficiency and may contribute to the observed long-lasting negative impact of this micronutrient deficiency.

Immune system function has also been linked to low iron levels and can lead to decreased levels of the cytokine interleukin-6, diminished phagocytic activity, and impaired oxidative burst activity. (9) Impaired muscle metabolism due to decreased oxygen diffusion and reduced mitochondrial oxidative capacity is another manifestation. (10) Gastric atrophy, achlorhydria, chronic duodenitis, and villous atrophy have been seen in pediatric patients with IDA. (11)(12) In anemic women, compared with controls, an impaired response to cold stimulus has been observed; at baseline and after the cold stimulus, the group of anemic women had lower levels of thyroxine and triiodothyronine as well. The authors stipulate that this effect is mediated by decreased thyroid peroxidase in the setting of iron deficiency. (13)(14) Iron deficiency can contribute to chronic fatigue, especially in premenopausal women. This fatigue seems to respond to iron replenishment; in a group of nonanemic women with poor iron status (ferritin level 15 ng/mL [15 μg/L]), iron improved their fatigue score. (15)

EVALUATION OF IRON DEFICIENCY

There are multiple different tests that have been used to evaluate iron deficiency, including hemoglobin concentration, mean corpuscular volume (MCV), reticulocyte hemoglobin content, serum iron concentration, serum ferritin level, total iron binding capacity, soluble transferrin receptor, protoporphyrin level, and red blood cell distribution width (RDW). (16) Of these, ferritin concentration is the only one to be decreased in the setting of iron depletion without anemia, whereas changes from the normal range can routinely be seen in all of these parameters once IDA can be appreciated. Of note, though, the traditional ferritin cutoff value of 12 ng/mL (12 μg/L) has been shown to have 25% sensitivity, whereas a level of 30 ng/mL (30 μg/L) has improved sensitivity of 93% using bone marrow iron status as the "true" indicator of iron status. (17) In iron-restricted erythropoiesis, hemoglobin concentration and MCV can be normal, but the other parameters are typically affected.

Microcytic anemia can present in both IDA and anemia of chronic disease (ACD); in these cases, inflammatory markers prove useful in the differentiation of these entities. In ACD, cytokine, hepcidin, and ferritin levels tend to be elevated, with increased bone marrow iron content of macrophages. The soluble transferrin receptor level is usually normal in ACD. Nevertheless, both entities, ACD and IDA, present with decreased plasma iron.

The oral iron challenge can help differentiate patients who are iron deficient. After a dose of oral iron, peak serum iron levels are higher in those with iron deficiency compared with those who are iron sufficient. In patients with inflammatory bowel disease, the absorption of iron is less in patients with active disease than in those with inactive disease. The inflammatory milieu decreases iron absorption, which reinforces the importance of differentiating IDA and ACD due to differential response to therapeutic intervention. (18)

In pediatrics, risk assessment with a particular focus on diet history for iron deficiency is performed at 4, 15, 18, 24, and 30 months, and then annually. Laboratory tests are routinely performed at 9 to 12 months, 18 months in high-risk infants, during a growth spurt, and during menses (13–17 years old). Screening intervals are adjusted for high-risk individuals, athletes, vegans, patients with menorrhagia, patients with chronic disease, and obese patients. (19)(20) The screening laboratory tests that are recommended by the American Academy of Pediatrics are complete blood cell

(CBC) count, reticulocyte count, MCV, RDW, ferritin level, C-reactive protein level, and reticulocyte hemoglobin concentration (CHr). (19) CHr represents a newer test that is thought to be an early indicator of iron deficiency before anemia, and it outperforms MCV and ferritin as an early indicator when cases of MCV greater than 100 fL are excluded. (21) The CHr value tends to increase within 2 to 3 days of starting iron therapy. Normal values of CHr are typically greater than 28 pg. (16) Historically, the gold standard diagnostic test for IDA is the therapeutic trial of iron, in which patients are reevaluated 1 month after starting oral iron to look for a change in the CBC count parameters.

CAUSES OF IRON DEFICIENCY

Iron deficiency is the most common nutritional deficiency in the world. Interestingly, the IDA prevalence fell from 1990 to 2010, but in the subgroup of children younger than 5 years, the prevalence rose. (22) The steps that lead up to this can be numerous but stem primarily from diet. Single-food diets of infancy, in particular unfortified cow milk, nutritionally inadequate diet, and consumption of foods that interfere with iron absorption (tea, bran, fiber, antacids, phosphates, calcium) can all play a role.

Adequate iron intake for a newborn until 6 months of age is 0.27 mg daily, which is a calculated value. Stores of iron for full-term infants are sufficient until age 4 months, at which point it is suggested that exclusively breastfed infants have iron supplementation of 1 mg/kg per day until their diet includes more iron-rich sources. From 7 to 12 months, the daily recommendation is 11 mg, and from 1 to 3 years of age, 7 mg is suggested. (19) Nutritional requirements change with developmental requirements, dictating the need for higher dietary iron. These situations include prematurity, intrauterine growth restriction, infants of diabetic mothers, age 13 to 17 years, patients breastfed after 4 months of age, menstruation, and pregnancy. For example, premature babies have a goal of 2 mg/kg per day of iron intake until 1 year of age.

Iron deficiency has a wide range of causes (Table 2). Iron can be lost through the gastrointestinal system, genitourinary system (menorrhagia, hemosiderinuria), and pulmonary system (pulmonary hemosiderosis).

Impairment of iron absorption represents another etiology of iron deficiency. Subclinical celiac disease represented approximately 30% of 2,000 total cases of celiac disease diagnosed in children in 1990 to 1994 in Italy; the most common manifestation was iron malabsorption, as indicated by IDA. This was seen in 34.3% of the pediatric patients, with short stature representing the second most common sign at 29%. (23) *Helicobacter pylori*, one of the most prevalent chronic bacterial infections worldwide, oftentimes presents asymptomatically in children but can cause IDA. *H pylori* infection was more prevalent in children with IDA (31.3%) versus children without IDA (15.5%) in a study that examined the relationship between infection, iron deficiency, and short stature. (24) Infection with *H pylori* has been shown to cause gastritis and modify gastric ascorbic acid content; these factors contribute to the decreased gastric absorption due to the importance of low gastric pH in chelation of ferric iron and the role of ascorbic acid in reduction of ferric iron. (25) Initially, as many as 75% of patients with *H pylori*–associated IDA will not respond to oral iron, but *H pylori* treatment can improve the response; some studies have even demonstrated resolution of IDA without supplementation of iron. (26) Autoimmune gastritis and inflammatory bowel disease can also lead to insufficient iron stores.

Iron-resistant IDA is due to an autosomal recessive mutation in the *TMPRSS6* gene, which codes for a transmembrane serine protease that downregulates the BMP-SMAD signaling cascade known to have hepcidin as an end product. (27) Mutations, therefore, prevent the appropriate downregulation of hepcidin, resulting in failure of iron absorption even in iron-deficient states. Patients with iron-resistant IDA do not respond to oral iron and have a partial response to parenteral iron.

Localized cellular deficits in iron uptake or mitochondrial utilization of iron can also cause iron deficiency and have been noted in patients with RLS.

Dietary iron represents only a part of the story for developing iron deficiency, and the complex interplay between iron homeostasis and multisystem disorders underscores the importance of iron in many physiological processes.

PARTICULAR POPULATIONS AND BLEEDING

Certain patient populations are at increased risk for iron deficiency. Preterm infants are at increased risk due to the timing of iron accumulation in the fetus; 80% of iron stores are acquired during the third trimester of pregnancy, and preterm infants miss out on this critical time to build iron stores. (19) Looking at a cohort of mothers who did or did not have IDA in China, investigators demonstrated decreased mental development of infants at 12, 18, and 24 months of age as assessed on a mental development index in the IDA group. Mothers were also randomized to replenishment with folic acid/iron, folic acid, or macronutrient, and a subgroup analysis demonstrated reduction of the difference in mental

Table 2. Etiologies of Iron Deficiency

CAUSE	EXAMPLES
Inadequate dietary iron intake	Single-food diet in infancy, unfortified cow milk >20 oz
	Diet, fasting, malnutrition (iron is better absorbed from meat versus vegetables (30% versus 10%)
	Diet containing inhibitors of iron absorption: tea, bran, fiber, phosphates, calcium, antacids
Developmentally required increased iron requirements	Premature, intrauterine growth restriction, infant of diabetic mother
	Newborns breastfed after 4 mo
	Children aged 13–17 y
	Menstruation
	Pregnancy
Increased acquired iron requirements	Overweight/obese adolescents
	Adolescent athletes
Increased iron losses	Menorrhagia
	Gastrointestinal/genitourinary bleeding
	Hemosiderinuria from intravascular hemolysis
	Parasitic infections
	Exercise-related
	Pulmonary hemosiderosis
Decreased iron absorption	Celiac disease, inflammatory bowel disease
	Autoimmune atrophic gastritis
	Helicobacter pylori infection
	Iron-resistant iron deficiency anemia (hereditary)
	Chronic inflammation
Localized cellular mutations alter Fe iron uptake or mitochondrial transport	Restless legs syndrome

development index in the infants of mothers who had iron and folic acid supplementation but not in the infants of mothers who took only folic acid or macronutrient. (28) There has been much attention to the idea of delayed cord clamping as a means of providing more placental blood and iron to the neonate. A systematic review concluded that delayed cord clamping of greater than 2 minutes leads to elevated ferritin levels in the infant up to 6 months of age compared with early cord clamping (5–10 seconds). (29) A recent trial demonstrated effects up until 12 months of age with delayed cord clamping of greater than 3 minutes compared with an "extended" cord clamping (<60 seconds). At 8 months, delayed cord clamping was associated with higher ferritin levels and decreased risk of iron deficiency and IDA. At 12 months, delayed cord clamping was associated with decreased risk of IDA only. (30)

Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia) is an autosomal dominant condition that has a prevalence between 1 in 5,000 and 1 in 8,000, and it is much more common in the Afro-Caribbean population. Clinical manifestations include epistaxis, mucosal telangiectasias, and malformations of various organ systems, including pulmonary and gastrointestinal. Nosebleeds are more commonly the presenting symptom in children versus adults with this disease; in pediatrics, 90% of patients present initially with epistaxis, and the clinical finding of telangiectasia can lag from 5 to 20 years afterward. (31) These patients can present with epistaxis and IDA without other symptoms. This iron deficiency is an important risk factor for stroke in patients with pulmonary arteriovenous malformations and is associated with changes in platelet aggregation responses. (32)(33) Identification and

diagnosis of these patients can help initiation of preventive therapy.

Adolescent girls are thought to be at risk for IDA, especially those with menorrhagia. The objective definition of greater than 80 mL per cycle of blood loss is often difficult to apply in practice, but multiple visual scales can be used to estimate blood loss, including the pictorial blood loss assessment chart and the menstrual pictogram. (34) Other indicators include soaking of a pad in less than 2 hours, bleeding into clothes, or blood clots larger than 1 inch.

Athletes are another at-risk group; possible mechanisms are blood losses due to microscopic lesions in the gastrointestinal/genitourinary systems secondary to changes in circulation during exercise and sequestration of iron in the setting of inflammation-induced increases in hepcidin. (35) Rowland et al (36) followed high school runners through a season and found that the proportion of iron deficiency in both male and female runners increased. A meta-analysis looking at the effects of iron repletion linked improvement in exercise performance as measured by oxygen consumption. (37) Randomized double-blinded studies among female recruits to the army also demonstrated a beneficial effect in patients with IDA in terms of mood and exercise performance; it is notable that their study demonstrated no difference in recruits who had iron deficiency, which was defined as abnormalities in 2 of the 3 parameters of RDW, ferritin level, or transferrin saturation. (38) The International Olympic Committee has recommended a CBC count for all female athletes and a hemoglobin and ferritin screen for all endurance sport athletes. (39)

Obesity has also been linked to IDA in teenagers; both overweight and obese teenagers had an odds ratio of 2:1 for having iron deficiency (defined as 2 of 3 abnormal laboratory values) compared with patients with a BMI less than 85% with a prevalence of 3.5%, 7.2%, and 9.1% for normal BMI, overweight, and obese teenagers, respectively. (40) In Israel, the prevalence of iron deficiency, defined as a serum iron level less than 45 μg/dL (<8.05 μmol/L) in their study, in normal, overweight, and obese children was 4.4%, 12.1%, and 38.8%, respectively. (41) In 2012, the rate of obesity in children 6 to 11 years of age was 18% and in 12- to 19-year-olds was 21%. (42)(43) This is a significant portion of the youth who are at risk for iron deficiency and the associated biopsychological outcomes.

IRON HOMEOSTASIS IN NEUROLOGIC DISORDERS

Iron deficiency has been linked to ADHD and RLS; a possible link has been seen in animal models, in which a state of iron deficiency led to changes in dopamine receptor expression. ADHD and RLS have also been noted to be comorbid; of patients with ADHD, 44% had RLS symptoms, and of patients with RLS, 26% had ADHD symptoms. RLS has a prevalence of approximately 5% in pediatric patients, and most of these children have a family history. (44) Symptoms include sleep disturbances, restlessness, and inability to control limb movements. Intravenous iron therapy with low-molecular-weight dextran has demonstrated improvement in patients with iron deficiency and RLS. In a sample of 42 patients, 32 (76%) had subjective improvement of symptoms after a single infusion of iron dextran; 20 of 42 patients (48%) had improvement of symptoms lasting longer than 6 months. (45) There has been some debate as to the correlation of brain iron to peripheral iron; iron dextran, iron isomaltoside, or ferric carboxymaltose, with their higher incorporation into macrophages, may allow for greater iron delivery to the brain. (46) The overall mechanistic link is not straightforward because there seems to be a change in the way patients with RLS regulate brain iron, which implies that higher doses of intravenous iron may be required for symptomatic improvement. (46)

ADHD affects approximately 11% of children. (47) Recently, Adisetiyo et al (48) evaluated iron levels with a magnetic field correlation metric in patients with ADHD not taking medications, patients with ADHD, and control patients. The data demonstrate decreased iron levels in the putamen, caudate, and thalamus in patients with ADHD not taking psychostimulant medications compared with control patients and patients with ADHD taking psychostimulant medications. (48) A small study of 23 nonanemic children with ferritin levels less than 30 ng/mL (<30 μg/L) with ADHD demonstrated improvement on the Clinical Global Impression–Severity scale after 12 weeks of oral iron therapy compared with placebo. (49) Although the studies were small, there is evidence that addressing iron deficiency in RLS and ADHD provides symptomatic benefit.

MANAGEMENT

Dietary interventions to improve iron intake are also worth discussing. Foods rich in iron typically include flesh foods (animal products such as red meats and pork), legumes (beans, lentils), dried fruits (prunes, raisin, apricots), and iron-fortified cereals. Reducing consumption of beverages such as coffee or tea that can affect iron absorption can be recommended. In infants, we advise limiting daily cow milk consumption to less than 24 oz. A fairly small study evaluated the effect of dietary intervention versus oral iron versus placebo on the iron status of nonanemic women; they

demonstrated improvement of ferritin levels at 16 weeks of intervention in both the dietary intervention and oral iron groups. The authors, however, state that dietary intervention may not be the most practical approach to mild iron deficiency in the general public. The study provided an "intensive and expert individualized dietary program," and even with that support, the patients "achieved only a small increase in their intake of flesh foods." The authors also note that the serum ferritin level increased to a greater extent in the oral iron supplementation group. (50) Diet should, nevertheless, be incorporated into the management of those with iron deficiency.

Oral iron preparations are widely used in therapeutic trials for IDA. A recent Cochrane review suggested that iron supplementation for menstruating females reduces the risk of iron deficiency and anemia, reduces fatigue, and improves exercise performance. Iron supplementation demonstrated gastrointestinal adverse effects, but low doses (<30 mg of elemental iron daily) can provide benefit and reduce the risk of adverse effects. (51) Moretti et al (52) also evaluated iron absorption in iron-deficient women older than 18 years using dosing schedules of once a day or twice a day; they found that iron absorption decreased and hepcidin levels increased with daily dosing. Moretti et al plan to query alternate-day iron dosing given their findings. Longer-term follow-up of their dosing schedules is lacking. (52) The recommendations for iron supplementation in pediatrics is typically 3 to 6 mg/kg per day of elemental iron given on a schedule from daily to 4 times a day. Typically, patients treated for IDA return to the clinic 4 to 8 weeks later for a repeated hemoglobin measurement. Treatment courses should last for at least 3 months, and even after discontinuation of iron therapy it is reasonable to review and encourage consumption of iron-rich foods. There are multiple different iron preparations, with ferrous salts (ferrous sulfate, ferrous gluconate, ferrous fumarate) being the most common. As many are aware, compliance is a challenge with oral iron; polysaccharide complex was a product that was thought to be more palatable, but a study in 80 nutritionally iron-deficient anemic children demonstrated greater improvement in hemoglobin levels for patients taking ferrous sulfate versus polysaccharide complex. (53) Multiple intravenous preparations are also available and are safe and effective. Originally, the high-molecular-weight iron dextran was used and had many adverse effects, in particular, anaphylaxis. The next generation of parenteral irons, which includes low-molecular-weight dextran, ferric gluconate, and iron sucrose, all have favorable adverse effect profiles; adverse effects can be seen in approximately 1% of patients, with only 1 in 200,000 having a severe adverse effect. Nevertheless, patients, especially those with multiple drug allergies, should be monitored for symptoms of anaphylaxis. New third-generation forms (ferumoxytol, ferric carboxymaltose) are also now available. Iron sucrose remains the most commonly used. (54)

Iron should be given with caution when iron status is not known. Majumdar et al (55) looked at the impact of oral iron on weight gain and linear growth in iron-deficient and iron-replete individuals. Iron was of benefit to the iron-deficient group, but iron therapy was correlated with decreased weight gain and linear growth in the iron-replete group. Lozoff et al (56) also looked at iron-fortified versus iron-low formulas in children and found that those with higher pretreatment hemoglobin levels receiving iron-fortified formula had worse neuropsychiatric testing results at 10-year follow-up compared with those with similar hemoglobin levels who had low iron content formula. Among patients with pretreatment hemoglobin levels less than 10.5 g/dL (<105 g/L), those who had iron-fortified formula had improved testing at the follow-up point. (56) Iron therapy is safe, and the newer parenteral formulations have rare adverse effects; similar to any medication though, it must be used in the correct clinical context.

CONCLUSIONS

Iron deficiency without IDA may impact development and physiological function. Dietary iron deficiency represents a significant global burden, and there are many children who are unscreened and untreated. Early treatment may prevent the negative outcomes associated with iron deficiency and relieve associated symptoms, but more trials are needed to determine the true benefit. Iron deficiency may represent a feature of underlying systemic illness, and in the context of appropriate history, it could alert clinicians to consider these possible etiologies in patients belonging to high-risk populations. IDA is only part of a much larger health-care problem, and once IDA appears, many physiological functions have already been impaired.

Summary

- Based on research studies, evidence quality C, iron deficiency without changes in hematologic parameters could have substantial implications for the health of children, in particular, their neurocognitive development.

- Based on research studies, evidence quality D, iron deficiency can be due to nutritional factors but can also represent a manifestation of a systemic illness such as hereditary hemorrhagic telangiectasia or celiac disease.
- Based on research studies and recent Cochrane reviews, evidence quality B, low-dose iron supplementation is appropriate for menstruating females.
- Based on research studies, evidence quality D, there are many children at risk for iron depletion who go unrecognized and unscreened.
- Based on research studies, evidence quality C, parenteral iron is safe and indicated in several conditions.

References for this article can be found at http://pedsinreview.aappublications.org/content/42/No. 1/11.

EXCERPT FROM AAP CPG ON IRON DEFICIENCY

link to full article here

dlers with ID do not have anemia (Table 2). It is also known that there is poor follow-up testing and poor documentation of improved Hb concentrations. In 1 study, 14% of the children had a positive screening result for anemia. However, only 18.3% of these children with a positive screening result had follow-up testing performed, and of that group, only 11.6% had documented correction of low Hb levels.[77] Therefore, for infants identified with a Hb concentration of less than 11.0 mg/dL or identified with significant risk of ID or IDA as described previously, SF and CRP or CHr levels in addition to Hb concentration should be measured to increase the sensitivity and specificity of the diagnosis. In addition, the AAP, the World Health Organization, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition also support the use of the measurement of TfR1 as a screening test once the method has been validated and normal values for infants and toddlers have been established.

Another step to improve the current screening system is to use technology-based reminders for screening and follow-up of infants and toddlers with a diagnosis of ID/IDA. Reminders could be incorporated into electronic health records, and there should be documentation that Hb concentrations have returned to the normal range. The efficacy of any program for minimizing ID and IDA should be tracked scientifically and evaluated through well-planned surveillance programs.

SUMMARY

Given that iron is the world's most common single-nutrient deficiency and there is some evidence of adverse effects of both ID and IDA on cognitive and behavioral development, it is important to minimize ID and IDA in infants and toddlers without waiting for unequivocal evidence. Controversies remain regarding the timing and methods used for screening for ID/IDA as well as regarding the use of iron supplements to prevent ID/IDA. Although further study is required to generate higher levels of evidence to settle these controversies, the currently available evidence supports the following recommendations.

1. Term, healthy infants have sufficient iron for at least the first 4 months of life. Human milk contains very little iron. Exclusively breast-fed infants are at increasing risk of ID after 4 completed months of age. Therefore, at 4 months of age, breastfed infants should be supple-mented with 1 mg/kg per day of oral iron beginning at 4 months of age until appropriate iron-containing complementary foods (including iron-fortified cereals) are intro-duced in the diet (see Table 3). For partially breastfed infants, the pro-portion of human milk versus for-mula is uncertain; therefore, begin-ning at 4 months of age, partially breastfed infants (more than half of their daily feedings as human milk) who are not receiving iron-containing complementary foods should also receive 1 mg/kg per day of supplemental iron.
2. For formula-fed infants, the iron needs for the first 12 months of life can be met by a standard infant formula (iron content: 10–12 mg/L) and the introduction of iron-containing complementary foods after 4 to 6 months of age, including iron-fortified cereals (Table 3). Whole milk should not be used before 12 completed months of age.
3. The iron intake between 6 and 12 months of age should be 11 mg/day. When infants are given complementary foods, red meat and vegetables with higher iron content should be introduced early (Table 3). To augment the iron supply, liquid iron supplements are appropriate if iron needs are not being met by the intake of formula and complementary foods.
4. Toddlers 1 through 3 years of age should have an iron intake of 7 mg/day. This would be best delivered by eating red meats, cereals fortified with iron, vegetables that contain iron, and fruits with vitamin C, which augments the absorption of iron (Tables 3 and 4). For toddlers not receiving this iron intake, liquid supplements are suitable for children 12 through 36 months of age, and chewable multivitamins can be used for children 3 years and older.
5. All preterm infants should have an iron intake of at least 2 mg/kg per day through 12 months of age, which is the amount of iron supplied by iron-fortified formulas. Preterm infants fed human milk should receive an iron supplement of 2 mg/kg per day by 1 month of age, and this should be continued until the infant is weaned to iron-fortified formula or begins eating complementary foods that supply the 2 mg/kg of iron. An exception to this practice would include infants who have received an iron load from multiple transfusions of packed red blood cells.
6. Universal screening for anemia should be performed at approximately 12 months of age with determination of Hb concentration and an assessment of risk factors associated with ID/IDA. These risk factors would include low socioeconomic status (especially children of Mexican American descent [Table 1]), a history of prematurity or low birth weight, exposure to lead, exclusive breastfeeding beyond 4 months of age without supplemental iron, and weaning to whole milk or complementary foods that do not include iron-fortified cereals or

foods naturally rich in iron (Table 3). Additional risk factors are the feeding problems, poor growth, and inadequate nutrition typically seen in infants with special health care needs. For infants and toddlers (1–3 years of age), additional screening can be performed at any time if there is a risk of ID/IDA, including inadequate dietary iron intake.

7. If the Hb level is less than 11.0 mg/dL at 12 months of age, then further evaluation for IDA is required to establish it as a cause of anemia. If there is a high risk of dietary ID as described in point 6 above, then further testing for ID should be performed, given the potential adverse effects on neurodevelopmental outcomes. Additional screening tests for ID or IDA should include measurement of:
   - SF and CRP levels; or
   - CHr concentration.
8. If a child has mild anemia (Hb level of 10–11 mg/d) and can be closely monitored, an alternative method of diagnosis would be to document a 1 g/dL increase in plasma Hb concentration after 1 month of appropriate iron-replacement therapy, especially if the history indicates that the diet is likely to be iron deficient.
9. Use of the TfR1 assay as screening for ID is promising, and the AAP supports the development of TfR1 standards for use of this assay in infants and children.
10. If IDA (or any anemia) or ID has been confirmed by history and laboratory evidence, a means of carefully tracking and following infants and toddlers with a diagnosis of ID/IDA should be implemented. Electronic health records could be used not only to generate reminder messages to screen for IDA and ID at 12 months of age but also to document that IDA and ID have been adequately treated once diagnosed.

ADDENDUM

Development of This Report

This report was written by the primary authors after extensive review of the literature using PubMed, previous AAP reports, Cochrane reviews, and reports from other groups.[1,6,7,48,77]

The report was also submitted to the following sections and committees of the AAP that were asked to comment on the manuscript: Committee on Fetus and Newborn (COFN); Committee on Psychosocial Aspects of Child and Family Health (COPACFH); Section on Administration and Practice Management (SOAPM); Section on Developmental and Behavioral Pediatrics (SODBP); Section on Gastroenterology, Hepatology, and Nutrition (SOGHN); Section on Hematology and Oncology (SOHO); and Section on Breast Feeding (SOBr).

Additional comments were sought from the Centers for Disease Control and Prevention (CDC), the Department of Agriculture (WIC), the National Institutes of Health (NIH), and the Food and Drug Administration (FDA), because these governmental agencies were involved in the development of the statement and will necessarily deal with its impact. As it was developed it was extensively reviewed and revised by members of the AAP Committee on Nutrition, who unanimously approved this clinical report. It is openly acknowledged that where the highest levels of evidence are absent, the opinions and suggestions of members of the Committee on Nutrition as well as other groups consulted for this statement were taken into consideration in developing this clinical report.

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AAP News™

CDC calls on pediatricians to address challenges in lead poisoning prevention

May 16, 2022

Paul Allwood, Ph.D., M.P.H., R.S., and Cdr. Matt Karwowski, M.D., M.P.H., FAAP

Article type: News

Topics: Environmental Health, Lead

Removing lead from gasoline and paint beginning in the 1970s led to significant declines in childhood blood lead levels (BLLs) across the United States. Underlying this great public health success, however, is a complicated and nuanced story of persistent disparities in exposure to lead, access to testing and services, and health outcomes.

Pediatricians are well-positioned to address these contemporary challenges in lead poisoning prevention.

Ongoing exposure, disparities

Decades of lead use in consumer paint, motor vehicle fuels and other products has made lead a ubiquitous environmental hazard. Data from the American Healthy Homes Survey II estimate that millions of U.S. children have ongoing exposure to lead-based paint, placing them at risk for adverse health effects.

Data from the Centers for Disease Control and Prevention (CDC) demonstrate ongoing disparities in childhood BLLs. Children from low-income households, those living in housing built before 1978 and those who identify as African American are at greater risk for lead exposure. Children from certain other race/ethnicities, immigrants and refugees also are at higher risk due to exposures they faced in their country of origin as well as in the United States.

While these patterns remain important, data from CDC's state partners highlight that childhood lead exposure can occur across all racial and ethnic groups; urban, suburban and rural geography; and any family income level.

Importance of blood lead testing

Though primary prevention of lead exposure remains the goal for both medical and public health communities, strong evidence shows the value of secondary prevention, such as blood lead testing (Kaufmann RB, et al. *Pediatrics*. 2000;106:e79; Christensen K, et al. *WMJ*. 2019;118:16-20).

In October 2021, the CDC lowered the blood lead reference level from 5 micrograms/deciliter (mcg/dL) to 3.5 mcg/dL. However, no level of lead exposure or BLL is safe, and even low levels can impact neurodevelopment.

With approximately 500,000 U.S. children having a BLL of 3.5 mcg/dL or higher, the CDC and state health agencies recommend targeted blood lead testing to identify children exposed to lead.

However, inconsistent state and local testing and reporting policies, inadequate resources and loss to follow-up are important barriers that disproportionately affect certain populations. The COVID-19 pandemic and a recent recall affecting lead point-of-care testing kits have further impacted testing rates.

Overt lead toxicity is uncommon, with most contemporary lead exposure resulting in subclinical health effects. Therefore, some providers may feel lead exposure is less prevalent and less consequential. While it is important for providers to exercise clinical judgment when deciding which children to test, these decisions should be informed by local data, guidance from local or state health departments and the CDC, and evidence-based approaches such as those outlined in Bright Futures.

Factors such as a belief that one practices in a low-risk area, that only certain populations are at risk or that health effects are unlikely until BLLs reach higher levels can affect decisions on testing and delay or prevent recognition of children exposed to hazardous levels of lead (Markowitz M. *Pediatr Rev*. 2021;42:302-315; Neuwirth LS. *Int J Occup Environ Health*. 2018;24:86-100).

Pediatricians' role in prevention

Pediatricians can help address challenges in preventing childhood lead exposure — including disparities in exposure, testing and follow-up — in several ways:

- Continue to inform and educate families about lead exposure through day-to-day clinical interactions and via broader community outreach though AAP chapters and community-based organizations.
- Help ensure equitable screening, diagnosis and follow-up for children at greatest risk for lead exposure by following guidelines and partnering with local or state health department, health system and community to address disparities.
- Be a voice for policy, systems and environmental change through advocacy, educating policymakers and speaking as a trusted expert in your community.

The CDC is taking steps to increase awareness and promote blood lead testing by health care providers. These include sharing examples of lead exposure in children, with a focus on those who were not initially identified as at high risk; developing materials to encourage health care providers to test children at risk for lead exposures; and working with medical and social services.

Pediatricians have partnered with public health agencies to drive significant reductions in the U.S. population's exposure to lead since the 1970s. The CDC is optimistic that by reengaging with medical professionals, we can strengthen our partnership and redouble our efforts to address contemporary challenges in preventing childhood lead exposure.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the CDC.

Dr. Allwood is chief of Lead Poisoning Prevention and Surveillance at the CDC. Dr. Karwowski is chief medical officer of the Division of Laboratory Sciences in CDC's National Center for Environmental Health and CDC Liaison to the AAP Council on Environmental Health and Climate Change.

Perri Ruckart Dr.P.H., M.P.H., lead health scientist in the CDC's Lead Poisoning Prevention and Surveillance Branch, and Jonathan Lynch, M.B.A.-P.M., health communications specialist, Division of Environmental Health Science and Practice, contributed to this article.

Resources

- Information from the CDC on lead poisoning prevention
- CDC's recommended actions based on blood level results
- AAP information on lead exposure and prevention

Note 2022 Update to Maryland Guidelines (following pages) to align with 3.5 mcg/dL cut-off recommended by CDC

2020 Maryland Guidelines for the Assessment and Management of Childhood Lead Exposure

For Children 6 Months to 72 Months of Age

Maryland Department of the Environment

Test Blood Lead Level according to **Table 1**

↓

Confirm all capillary blood lead levels ≥ 5 mcg/dL with venous sample. Follow** **Table 2** for schedule

↓

Guidelines for Actions **Table 3** and **Table 5**

↓

Schedule Follow-up Venous Blood Lead Testing for all ≥ 5 mcg/dL **Table 4**

Table 1: Guidelines for Blood Lead Level Testing in Children 6 Months to 72 Months of Age (COMAR 10.11.04, as of 3/28/2016)

For ALL children born on or after 1/1/15, OR on Medicaid									
6 Months	**9 Months**	**12 Months**	**15 Months**	**18 Months**	**24 Months**	**30 Months**	**36 Months**	**48 Months**	**60 Months**
Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen
Test if indicated	Test if indicated	**Test Blood Lead Level**	Test if indicated	Test if indicated	**Test Blood Lead Level**	Test if indicated	Test if indicated	Test if indicated	Test if indicated
For children born before 1/1/15, AND not on Medicaid									
6 Months	**9 Months**	**12 Months**	**15 Months**	**18 Months**	**24 Months**	**30 Months**	**36 Months**	**48 Months**	**60 Months**
Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen	Screen
Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated	Test if indicated

Screening	• Perform Lead Risk Assessment Questionnaire (questions found in Lead Risk Assessment Questionnaire section of this document) • Clinical assessment, including health history, developmental screening and physical exam • Evaluate nutrition and consider iron deficiency • Educate parent/guardian about lead hazards
Inidcators for Testing	• Parent/guardian request • Possible lead exposure to symptoms of lead poisoning, either from health history, developmental assessment, physical exam or newly positive item on Lead Risk Assessment Questionnaire. (Questions can be found in Lead Risk Assessment Questionnaire section of this document.) • Follow-up testing on a previously elevated Blood Lead Level (Table 4) • Missed screening: If 12 month test was indicated and no proof of test, then perform as soon as possible after 12 months and then again at 24 months. If 24 month test was indicated and no proof of test, then perform test as soon as possible. • For more information about lead testing of pregnant and breastfeeding women, see: *http://www.cdc.gov/nceh/lead/publications/leadandpregnancy2010.pdf*

Table 2: Schedule for Confirmatory Venous Sample after Initial Capillary Test**

Capillary Screening Test Result	Perform Vernouse Test Within
< 5 mcg/dL	Not Required
5 - 9 mcg/dL	12 weeks
10 - 44 mcg/dL	4 weeks
45 - 59 mcg/dL	48 hours
60 - 69 mcg/dL	24 hours
70 mcg/dL and above	**Immediate Emergency Lab Test**

*** Requirements for blood lead reporting to the Maryland Childhood Lead Registry are located at COMAR 26.02.01. Reporting is required for all blood lead tests performed on any child 18 years old or younger who resides in Maryland.*

Table 3: Abbreviated Clinical Guidance for Management of Lead in Children Ages 6 Months to 72 Months *(Full Guidelins in Table 5)*

Blood Lead Level	Follow-up Testing	Management
< 5 mcg/dL	On schedule **Table 1**	• Continue screening and testing on schedule. Continue education for prevention. • If new concern identified by clinician, then retest blood lead level.
5 - 9 mcg/dL	3 months See **Table 4**	All of above AND: Investiage for exposure source in enviroment and notify health department. • For more detail consult **Table 5**
≥ 10 mcg/dL	See **Table 4**	Consult **Table 5**

Table 4: Schedule for Follow-up Venous Blood Lead Testing after Blood Lead Level ≥ 5 mcg/dL

Venous Blood Lead Level	Early follow-up testing (2-4 tests after identification)	Later follow-up testing after blood lead level declining
5 - 9 mcg/dL	1 - 3 months ***	6 - 9 months
10 - 19 mcg/dL	1 - 3 months ***	3 - 6 months
20 - 24 mcg/dL	1 - 3 months ***	1 - 3 months
25 - 44 mcg/dL	2 weeks - 1 month	1 month
≥ 45 mcg/dL	**As Soon As Possible**	**As Soon As Possible, based on treatement plan**

Seasonal variation in Blood Lead Levels exist, greater exposure in the summer months may necessitate more frequent follow-up.

**** Some clinicians may choose to repeat elevated blood lead tests within a month to ensure that their Blood Lead Level is not rising quickly. (Advisory Committee on Childhood Lead Poisoning Prevention - CDC 2012)*

Table 5: Clinical Guidance for Management of Lead in Children Ages 0 - 6 years

Confirmed Blood Lead Level (mcg/dL)[1]	< 5	5 - 9	10 - 19	20 - 44	45 - 69	≥ 70
Primary Prevention: parent/guardian education about lead hazards[2]	X	X	X	X	X	X
Medical/nutritional history and physical	X	X	X	X	X	X
Follow-up blood lead monitoring[3]	X	X	X	X	X	X
Evaluate/treat for anemia/iron deficiency		X	X	X	X	X
Home environmental investigation		X[4]	X	X	X	X
Exposure/environmental history[5]		X	X	X	X	X
Coordinate care with local health department		X[5]	X	X	X	X
Nutritional counseling related to calcium and iron intake		X	X	X	X	X
Obtain developmental and psychological evaluation[7]			X	X	X	X
Consult with lead specialist, who will also evaluate for chelation therapy				X	X	X
Consider abdominal x-ray (with bowel decontamination if indicated)[8]				X	X	X
Urgent evaluation for chelation therapy					X	X
Hospitalize for medical emergency						X

[1] Refer to information about confirmation of capillary tests in Table 2.

[2] Includes discussion of pica and lead sources including house paints (before 1978), ceramics, paint on old furniture, soil, foreign travel, traditional folk medicines, certain imported items (candies, food, jewerly, toys, cosmetics, pottery), and parental occupations that can bring home lead dust and debris (e.g., painting, construction, battery reclamation, ceramics, furniture refinishers, radiator repair.)

[3] Refer to schedule of follow-up blood lead testing in Table 4.

[4] Initial confirmed blood lead of 5 - 9 mcg/dL may require home environmental investigation. Contact LHD for more guidance.

[5] Exposure/environmental history to identify potential lead sources. (See screening questions.) Consider Notice of Defect (information at right) for child living in pre-1978 rental property.

[6] Contact LHD for more information about care coordination for blood lead levels of 5 - 9 mcg/dL.

[7] Use validated developmental screen for levels 10 - 19 mcg/dL, such as Ages and Stages Questionnaire (ASQ). Refer children as appropriate for further evaluation. Children with BLL over 20 mcg/dL should be evaluated in consultation with an experienced clinician, specialist, or LHD regarding futher evaluation.

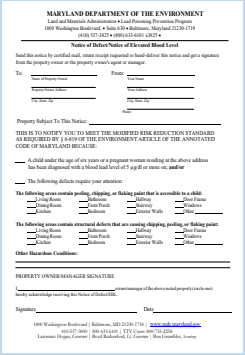
[8] https://www.cdc.gov/nceh/lead/advisory/acclpp/actions-blls.htm

Lead Risk Assessment Questionnaire Screen Questions:

1. Lives in or regularly visits a house/building built before 1978 with peeling or chipping paint, recent/ongoing renovation or remodeling?
2. Ever lived outside of the United States or recently arrived from a foreign country?
3. Sibling, housemate/playmate being followed or treated for lead poisoning?
4. Was child tested at 12 and/or 24 months?
5. Frequently puts things in his/her mouth such as toys, jewelry, or keys, eats non-food items (pica)?
6. Contact with an adult whose job or hobby involves exposure to lead?
7. Lives near an active lead smelter, battery recycling plant, or other lead-related industry, or road where soil and dust may be contaminated with lead?
8. Uses products from other countries such as health remedies, spices or food, or store or serve food in leaded crystal, pottery or pewter?

Table 6: Clinical Guidance for Lead Case Closure in Children Ages 0 - 6 years

For children with elevated blood lead levels, case closure will occur after implementation of environmental lead remediation and repeat testing demonstrates a blood lead level below 5mcg/dL. Testing should be repeated every 3 months until at least 2 consecutive tests results with a blood lead level below 5mcg/dL.



MARYLAND DEPARTMENT OF THE ENVIRONMENT

Notice of Defect/Notice of Elevated Blood Level

THIS IS TO NOTIFY YOU TO MEET THE MODIFIED RISK REDUCTION STANDARD AS REQUIRED BY § 6-819 OF THE ENVIRONMENT ARTICLE OF THE ANNOTATED CODE OF MARYLAND BECAUSE:

PROPERTY OWNER/MANAGER SIGNATURE

A Notice of Defect is a written notice that tells the landlord that there is chipping, flaking or peeling paint or structural defect in the home that is in need of repair. A Notice of Defect may also tell the landlord that a 'Person at Risk' (a child under the age of six or a pregnant woman) has a lead level of 5mcg/dL or above and that repairs need to be made in the home.*

*As of 7/1/20, the action level in Maryland was lowered from ≥ 10mcg/dL to ≥ 5mcg/dL to align with CDC's reference level. (COMAR 26.16.08.03).

The Notice of Defect must be sent by certified mail, return receipt (be certain to retain a copy of the return receipt) and the rental property owner has 30 days to repair the listed defects. It is illegal for a property owner to evict a tenant or raise the rent for reporting problems and/or defects in the home or that a child has been poisoned by lead. To download a copy of the Notice of Defect form, visit: *https://mde.maryland.gov/programs/LAND/Documents/LeadPamphlets/LeadPamphletMDENoticeOfTenantsRights.pdf*

For more information or assistance with filing a Notice of Defect, contact the Maryland Department of the Environment, Lead Poisoning Prevention Program or the Green & Healthy Homes Initiative.

Clinical Resources

Mid-Atlantic Center for Children's Health & the Environment
Pediatric Environmental Health Specialty Unit
866-622-2431
kidsandenvironment@georgetown.edu
https://kidsandenvironment.georgetown.edu

Mount Washington Pediatric Hospital Lead Treatment Program
410-367-2222
www.mwph.org/health-services/lead-treatment

Maryland Poison Control
800-222-1222
www.mdpoison.com

American Academy of Pediatrics - Policy Statement: Prevention of Childhood Lead Toxicity
https://pediatrics.aappublications.org/content/pediatrics/138/1/e20161493.full.pdf

American Academy of Family Physicians
https://www.aafp.org/afp/2010/0315/p751.html

Regulatory Programs and Resources

Maryland Department of Health
866-703-3266
dhmh.envhealth@maryland.gov
http://phpa.dhmh.maryland.gov/OEHFP/EH/Pages/Lead.aspx

Maryland Department of the Environment
Lead Poisoning Prevention Program
410-537-3825 | 800-776-2706
http://www.mde.state.md.us/programs/Land/LeadPoisoningPrevention/Pages/index.aspx

Local Health Departments
http://dhmh.maryland.gov/PAGES/DEPARTMENTS.ASPX

Center for Disease Control and Prevention
https://www.cdc.gov/nceh/lead/default.htm

Green & Healthy Homes Initiative
410-534-6447 | 800-370-5223
www.greenandhealthyhomes.org

National Center for Healthy Housing - Lead Resources
https://nchh.org/information-and-evidence/healthy-housing-policy/state-and-local/lead

Maryland
DEPARTMENT OF HEALTH
Larry Hogan, Governor · Boyd K. Rutherford, Lt. Governor · Dennis R. Schrader, Secretary

January 25, 2022

RE: Guidance for Providers Regarding New CDC Blood Lead Reference Level and Other Matters Pertaining to Lead Testing for Children

Dear Colleague,

This letter provides guidance to health care providers regarding blood lead testing in children in Maryland, including the recent change to the reference value for blood lead announced by the U.S. Centers for Disease Control and Prevention (CDC), the status of point of care (POC) testing with Magellan Diagnostics, and re-emphasizes the importance of blood lead testing in light of the impact of COVID-19 and the availability of new resources for health care providers in managing children with lead exposures.

Clinical Guidance on New CDC Blood Lead Reference Level

Following the recommendations of the federal Lead Exposure and Prevention Advisory Committee (LEPAC), the CDC announced in an October 28, 2021 press release that it was updating its blood lead reference value (BLRV) from 5 micrograms/deciliter (µg/dL) to 3.5 µg/dL. This change reflected improvements in blood lead levels in children across the country. MDH is now recommending that providers follow this guidance in clinical practice. Providers should manage children according to the CDC's Recommended Actions Based on Blood Lead Level, which provides detailed guidance on clinical actions for a given blood lead level. In particular, MDH emphasizes the importance of obtaining a confirmatory venous sample at the recommended time interval for capillary specimens performed as point of care (POC) tests (Table 1), as well as a follow-up blood lead test at the recommended interval or sooner to ensure that there is no ongoing lead exposure (Table 2). Both of these schedules can be found in the CDC guidance, and are also shown below.

MDH and the Maryland Department of the Environment (MDE) remind providers that **there is no change at this time in the legal definition of elevated blood lead level in Maryland, which remains 5 µg/dL.** MDE continues to notify parents, property owners, and local health departments about children with blood lead levels of 5 µg/dL or greater, and continues to conduct environmental investigations for those children. **Thus, it is essential that providers follow up on children with blood lead levels of 3.5 - 4.9 µg/dL to ensure that their blood lead levels are not increasing, indicating ongoing exposure.**

Table 1: Recommended Schedule for Obtaining a Confirmatory Venous Sample for a Capillary Fingerstick or Heelstick			Table 2: Schedule for Follow-Up Blood Lead Testing following a Confirmed Blood Lead at or above the Blood Lead Reference Value[a]		
Blood Lead Level (µg/dL)	**Time to Confirmation Testing**		**Venous Blood lead Levels (µg/dL)**	**Early follow up testing (2-4 tests after identification)**	**Later follow up testing after BLL declining**
≥3.5–9	**Within 3 months***		**≥3.5–9**	**3 months****	**6–9 months**
10–19	**Within 1 month***		**10–19**	**1–3 months****	**3–6 months**
20–44	**Within 2 weeks***		**20–44**	**2 weeks–1 month**	**1–3 months**
≥45	**Within 48 hours***		**≥45**	**As soon as possible**	**As soon as possible**

*The higher the BLL on the initial screening capillary test, the more urgent the need for confirmatory testing using a venous sample.

[a]Seasonal variation of BLLs exists and may be more apparent in colder climate areas. Greater exposure in the summer months may necessitate more frequent follow ups.

**Some case managers or healthcare providers may choose to repeat blood lead tests on all new patients within a month to ensure that their BLL level is not rising more quickly than anticipated.

Status of Blood Lead Testing Using Magellan Diagnostics Blood Lead Test Kits

MDE and MDH continue to monitor the expanded recall of LeadCare blood lead test kits by Magellan Diagnostics in October, 2021. Providers should follow the recommendations of the CDC on follow up testing of children tested with LeadCare test kits between October 27, 2020 and the present time. Questions about the recall or about retesting children with a lead level of <5 µg/dL should be directed to MDE (Dr. Rena Boss-Victoria at 410-537-3880 or rena.boss-victoria@maryland.gov) or MDH (toll-free 1-866-703-3266 or mdh.envhealth@maryland.gov).

New State Resources for Providers in Managing Children with Lead Exposure

The COVID-19 pandemic has resulted in a nearly 17% drop in testing children in Maryland for lead poisoning from calendar year 2020 compared to 2019. Fewer children saw their physicians for blood lead testing as well as for completing well child check-ups and updating their immunizations. Health care providers are reminded that Code of Maryland Regulations 10.11.04 requires licensed health care providers to test all children ages 1 and 2 years (12 and 24 months) for lead, either by a capillary test or a venous blood draw.

MDH, Maryland Department of the Environment, and the Maryland Commission on Lead Poisoning Prevention also remind Maryland's health care providers and parents that there are new state resources and services for children with lead poisoning, including home visiting programs to help parents and families, and funding to remove lead from homes at no cost to families. Providers who want to refer children for these programs should contact MDH (1-866-703-3266).

Please consider these suggestions to increase blood lead testing. Delays in identifying children with elevated blood levels can result in significant impairment to a young child's developing brain. If you have questions, call the Environmental Health Help Line at 1-866-703-3266. More information is also available on the MDH Lead Poisoning Prevention home page,

the MDE Lead Poisoning Prevention home page, and the CDC Lead Poisoning Prevention Program home page.

Sincerely,

Clifford S. Mitchell, MS, MD, MPH
Director, Environmental Health Bureau

TB Elimination
Tuberculin Skin Testing

What is it?

The **Mantoux tuberculin skin test** (TST) is the standard method of determining whether a person is infected with *Mycobacterium tuberculosis*. Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice.

How is the TST Administered?

The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The TST is an intradermal injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm in diameter.

How is the TST Read?

The skin test reaction should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will need to be rescheduled for another skin test.

The reaction should be measured in millimeters of the induration (palpable, raised, hardened area or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

How Are TST Reactions Interpreted?

Skin test interpretation depends on two factors:

- Measurement in millimeters of the induration
- Person's risk of being infected with TB and of progression to disease if infected

Classification of the Tuberculin Skin Test Reaction

An **induration of 5 or more millimeters** is considered positive in

- » HIV-infected persons
- » A recent contact of a person with TB disease
- » Persons with fibrotic changes on chest radiograph consistent with prior TB
- » Patients with organ transplants
- » Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)

An **induration of 10 or more millimeters** is considered positive in

- » Recent immigrants (< 5 years) from high-prevalence countries
- » Injection drug users
- » Residents and employees of high-risk congregate settings
- » Mycobacteriology laboratory personnel
- » Persons with clinical conditions that place them at high risk
- » Children < 4 years of age
- » Infants, children, and adolescents exposed to adults in high-risk categories

An **induration of 15 or more millimeters** is considered positive in any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.

What Are False-Positive Reactions?

Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:

- Infection with nontuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

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What Are False-Negative Reactions?

Some persons may not react to the TST even though they are infected with *M. tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to, the following:

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within 8-10 weeks of exposure)
- Very old TB infection (many years)
- Very young age (less than 6 months old)
- Recent live-virus vaccination (e.g., measles and smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles and chicken pox)
- Incorrect method of TST administration
- Incorrect interpretation of reaction

Who Can Receive a TST?

Most persons can receive a TST. TST is contraindicated only for persons who have had a severe reaction (e.g., necrosis, blistering, anaphylactic shock, or ulcerations) to a previous TST. It is not contraindicated for any other persons, including infants, children, pregnant women, persons who are HIV-infected, or persons who have been vaccinated with BCG.

How Often Can TSTs Be Repeated?

In general, there is no risk associated with repeated tuberculin skin test placements. If a person does not return within 48-72 hours for a tuberculin skin test reading, a second test can be placed as soon as possible. There is no contraindication to repeating the TST, unless a previous TST was associated with a severe reaction.

What is a Boosted Reaction?

In some persons who are infected with *M. tuberculosis*, the ability to react to tuberculin may wane over time. When given a TST years after infection, these persons may have a false-negative reaction. However, the TST may stimulate the immune system, causing a positive, or boosted reaction to subsequent tests. Giving a second TST after an initial negative TST reaction is called two-step testing.

Why is Two-Step Testing Conducted?

Two-step testing is useful for the initial skin testing of adults who are going to be retested periodically, such as health care workers or nursing home residents. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection.

Can TSTs Be Given To Persons Receiving Vaccinations?

Vaccination with live viruses may interfere with TST reactions. For persons scheduled to receive a TST, testing should be done as follows:

- Either on the same day as vaccination with live-virus vaccine or 4-6 weeks after the administration of the live-virus vaccine
- At least one month after smallpox vaccination

Additional Information

1. American Thoracic Society and CDC. Diagnotic standards and classification of tuberculosis in adults and children. (PDF) A*m J Respir Crit Care Med 2000*; 161. http://ajrccm.atsjournals.org/cgi/content/ful/161/4/1376
2. CDC. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR* 2005; 54 (No. RR-17). www.cdc.gov/tb/publications/guidelines/infectioncontrol.htm
3. CDC. Mantoux Tuberculin Skin Test: Training Materials Kit (2003).
4. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49 (No. RR-6). www.cdc.gov/MMWR/PDF/rr/rr4906.pdf

http://www.cdc.gov/tb

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Summary of Recommendations Regarding Testing

Table 4 shows potential strategies for testing. Some specific points are as follows:

- Only children who have a risk factor for TBI or are at risk for progressing to disease, are suspected of having TB disease, or who have an immunosuppressive disease or about to start immunosuppressive therapy should be tested with a TST or an IGRA.
- There is no compelling evidence to support the use of one IGRA (QFT, T-SPOT) over the other.
- If the child of any age has been exposed to an infectious case of TB disease, he or she should be evaluated and, if determined not to have TB disease, given a full course of treatment of TBI if either a TST or IGRA result is interpreted to be positive.
- Even with a negative initial test result, contacts of a person with known TB disease should be retested in 8 to 10 weeks, usually with the same test, regardless of whether the initial test used was a TST or IGRA.
- ^ For exposed contacts with impaired immunity (eg, HIV infection) and all contacts younger than 5 years, treatment of possible TBI should be initiated, even if the initial TST or IGRA result is negative, once TB disease is excluded (often referred to as "window prophylaxis"). If the TST or IGRA result still is negative with repeat testing in 8 to 10 weeks, treatment can be discontinued. If a TST or IGRA result of a contact becomes positive, the regimen for TBI should be completed.
- For children who have received a BCG vaccine and have no known exposure to a contagious TB case and no other TB risk factor other than birth in a foreign country, 2 strategies can be used[9]:
  (1) an IGRA can be used and the result acted on; or
- (2) a TST can be performed, and if the result is negative, no further testing is necessary; if the result is positive, an IGRA should be performed and its result acted on.
- When evaluating a child of any age for TB disease, both a TST and one or both IGRAs can be performed to maximize sensitivity. However, neither method can be used to rule out TB disease, and a negative result of either the TST or an IGRA should be considered especially unreliable in a child younger than 3 months.
- Indeterminate/invalid IGRA results are more common in very young children (younger than 2 years) and immunosuppressed patients. When an IGRA result is indeterminate/invalid, either a repeat IGRA test using the same or the other IGRA can be performed, ensuring proper technique of specimen collection and processing, or a TST can be performed.
- For children without TB risk factors other than foreign birth who have an unexpected low-level positive IGRA result (QFT <1.00 IU/mL, T-SPOT with 5–7 spots), a second diagnostic test, either an IGRA or a TST, should be performed; the child is considered infected only if results of both tests are positive.[9]
- Although IGRAs are more expensive than the TST, their use may be more cost-effective than the TST because of time savings for the family and the elimination of many false-positive results.[94]
- A TB specialist should be involved when there is a question about testing interpretation.
- Early communication with public health authorities during evaluation for a positive test result in children is strongly encouraged.

TABLE 4 Suggested Uses of TST and IGRA in Children

TST preferred, IGRA acceptable[a]
Children younger than 2 y[b]
IGRA preferred[a]
Children 2 y or older, especially those who have received BCG vaccine
Children of any age who are unlikely to return for the TST reading
Both[c] the TST and an IGRA should be considered when:
The initial and repeat IGRA results are indeterminate or invalid
The initial test (TST or IGRA) result is negative and:
There is clinical suspicion of TB disease[c] (to maximize sensitivity)
The child has a risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biological agent, such as a TNF-α antagonist)[c,d]
An initial TST is positive and:
The child has a history of BCG vaccination
Additional evidence is needed to increase adherence with therapy

[a] In situations of testing obligated by law or credentialing bodies in person unlikely to be uninfected with TB, IGRA is preferred.[9]

[b] Many experts will use an IGRA in children of any age, especially if the child has received a BCG vaccine but have no other significant risk factors other than foreign birth. However, data from children in this age group are few.

[c] A positive result of either test is considered significant in these groups.

[d] The clinician should obtain the complementary test (eg, if a TST was initially performed, then IGRA should be obtained for a complete set).

Screening for Dyslipidemia *(See Extra Credit "Expert Panel")*

A. Recommendations for Lipid Assessment *(based on Table 9-5 from article)*

Age	Recommendation
Birth- 2yrs	No lipid screening
2-8yrs	Selective screening with Fasting Lipid Profile (FLP) of children with close FamHx lipid disorders ± premature heart disease *OR* personal RFs for CVD (*see Table C*)
9-11yrs	**Universal Screening x 1** with Non-fasting Lipid Profile (NLP) of Non HDL-C
12-16yrs	Selective screening with FLP if new knowledge of +FamHx or personal RFs
17-21yrs	**Universal Screening x 1** with NLP of Non HDL-C

B. Lipid & Lipoprotein Concentration (mg/dL) Cutoffs *(based on Table 9-1 from article)*

Category	Acceptable	Borderline	High
TC	<170	170-199	≥ 200
LDL-C	< 110	110-129	≥ 130
Non HDL-C*	< 120	120-144	≥ 145
TG			
0-9 years	< 75	75-99	≥ 100
10-19 years	< 90	90-129	≥ 130
HDL-C	> 45	40-45	<40

*** Non HDL-C = TC- HDL-C**

C. Risk Factors for Cardiovascular Disease *(based on Tables 9-6, 9-7 from article)*

HIGH LEVEL RISK FACTORS & CONDITIONS

Parent/grandparent history of CV disease < 55 year in males, < 65 year in females:
coronary atherosclerosis, MI, peripheral vascular disease, or cerebrovascular disease
BMI > 97th percentile (> 95th %ile still moderate risk)
Diabetes Mellitus, type 1 or type 2
Hypertension
Current smoker
Chronic renal disease/end-stage renal disease
s/p any solid organ transplant
History of Kawasaki's disease with coronary aneurysms (regressed aneurysms *moderate* risk)

MODERATE LEVEL RISK FACTORS & CONDITIONS

Pre-diabetes: impaired fasting glucose ≥100; impaired glucose tolerance 2hr
Polycystic Ovarian Syndrome
Chronic Inflammatory Disease (SLE or JRA)
HIV Infection
Nephrotic syndrome

POTENTIAL RISK FACTORS & CONDITIONS

h/o cancer or congenital heart disease
Passive smoker
Unknown Family History

Health Maintenance II Quiz

1. For each blood test, list the AAP recommendations for risk assessment and actual testing:
   a. H/H:

   b. Pb:

   c. TB:

   d. Lipids:

2. What are the TWO most common age-groups for nutritional iron deficiency and what is the etiology in each of these age groups?

3. Fill in the parameters (Normal, Increased, or Decreased) for the hematologic and biochemical markers for iron deficiency anemia. Which marker is the first to be abnormal?

- Hemoglobin _____
- MCV _____
- RDW _____
- Reticulocytes _____
- Serum Ferritin _____
- Serum iron _____
- TIBC _____
- TFN saturation _____

MHS-Genesis FYI: Order an "Iron Group," iron panel does not exist

4. Match the action with the blood lead levels (more than one correct answer):

A. < 10 µg/dL	1. Referral to local health department: _____
B. 10-14 µg/dL	2. Immediate hospitalization: _____
C. 15-19 µg/dL	3. Chelation indicated: _____
D. 20-45 µg/dL	4. Detailed environmental history: _____
E. 45-69 µg/dL	
F. >70 µg/dL	

5. Match the following populations with the criteria for positive TST:
   a. Child with no risk factors: _____
   b. Healthy child < 4 years: _____
   c. Dr. Jones patient on high-dose steroids: _____

6. Flashforward: How can you code for these screening tests? Which garners the most RVUs?
   a. Newborn Screen: _____
   b. Hgb/Hct: _____
   c. Tuberculin Skin Test: _____

Health Maintenance II *Mini*-Cases

Case 1: You are seeing the 3 year old son of an Egyptian military attaché for a well child visit. What screening would you perform? Consider the *entire* periodicity schedule.

Case 2: A 12 month old child has a blood lead level of 14 µg/dL on capillary testing that is 14 µg/dL on follow-up venous testing. Name 4 specific steps the parents can take to decrease lead exposure in their child.

Case 3: A mother asks about screening her 18 month old and 5 year boys for "cholesterol" after their 38 year old father undergoes a coronary catheterization for angina. What do you tell her and what screening will you order?

Bonus: What is the rationale for universal screening at 9-11yrs?

Case 4: You screen a 12mo with PMHx of Hemoglobin C trait on his newborn screen and obtain the CBC below. He was recently weaned from breast milk to whole milk, and mother reports that he takes 32-40oz per day. He still prefers Gerber purees—mostly fruits and vegetables— to table foods. Lead screening was normal. **What is your working diagnosis? What additional testing do you want, if any? What interventions, if any will you take today?**

CBC W/Diff	**Result**
WBC	10.3
RBC	4.85
Hemoglobin	**9.6 (L)**
Hematocrit	**29.0 (L)**
MCV	**59.9 (L)**
MCH	**19.9 (L)**
MCHC	33.1
RDW CV	**25.0 (H)**
Platelets	**730 (H)**
MPV	7.3
Neutrophils	**32.4 (L)**
Lymphocytes	**53.9 (H)**
Monocytes	7.2
Eosinophils	6.4
Basophils	**0.1 (L)**
Neutrophils	3.4
Lymphocytes	**5.6 (H)**
Monocytes	0.7
Eosinophils	**0.7 (H)**
Basophils	0.0

Differential Manual	**Result**
Eosinophils	**6 (H)**
Basophils	1
Lymphocytes Atypical	2
Anisocytosis	2+
Poikilocytosis	1+
Microcytes	3+
Hypochromia	2+
Target Cells	1+
Schistocytes	RARE
Neutrophils Segmented	33
Lymphocytes	53
Monocytes	5

Health Maintenance II Board Review

1. You are seeing a 1-year-old patient in your clinic for a health supervision visit. You explain the recommended screening tests for this visit to the medical student who accompanies you.

Of the following, the MOST appropriate recommended screening test at this visit is:
A. blood lead concentration by fingerstick
B. blood lead concentration by venipuncture
C. complete blood count with differential count
D. serum ferritin
E. serum iron

2. A medical student notes on rounds that a 2-year-old girl admitted for pneumonia has a complete blood count (CBC) that includes a hematocrit of 35% (0.35), hemoglobin of 11.5 g/dL (115.0 g/L), mean corpuscular volume of 68.0 fL, and platelet and white blood cell counts that are normal for age. During the bedside encounter with the child's mother, you advise her to start the child on a multivitamin with iron and have her primary care physician obtain another CBC in a month or so. The medical student asks why you recommended iron supplementation when the child has a normal hematocrit.

Of the following, the BEST reason to prescribe supplemental iron therapy for this child at this time is to prevent
A. diminished cognitive abilities
B. fatigue
C. rapid progression to anemia
D. recurrent infections
E. short stature

3. As you are leaving the supermarket, the cashier tells you that she is worried because her child recently had a positive tuberculin skin test. She had to take him to the health department for skin testing because he had been in contact with her father, who recently was diagnosed with active pulmonary tuberculosis. They told her that the boy's skin test was positive at "25," but his chest radiograph was normal. She is concerned because the doctor told her that the case is a little unusual because of the type of tuberculosis her father has. She asked the physician at the health department to write it down, and she hands you a paper that says "INH resistant." The mother asks you what type of medication her boy should receive.

Of the following, the MOST appropriate antituberculous agent to prescribe for this boy is
A. ciprofloxacin
B. ethambutol
C. isoniazid
D. pyrazinamide
E. rifampin

4. A family has just relocated to your community, and you are evaluating their 12-year-old son for the first time this afternoon. Family history reveals that the boy's father and grandmother had premature cardiovascular disease. The boy's parents are concerned about his risk of heart disease.

Of the following, the MOST important next step in this child's evaluation is:
A. Echocardiography
B. Electrocardiography
C. Fasting lipoprotein analysis
D. Random cholesterol measurement
E. Referral to the cardiology clinic