> It is not clear whether hs-CRP is a causative marker for atherosclerosis or simply a proxy marker

10. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29–38.
11. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; 352:20–28.
12. Institute for Clinical Systems Improvement. Lipid Management in Adults. Available at: www.guideline.gov. Accessed on February 7, 2005.
13. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110:227–239.
14. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003; 108:2292–2297.

■ CLINICAL COMMENTARY

hs-CRP may be useful as a risk marker in some moderately high-risk patients

Elevated hs-CRP is not a standard cardiovascular risk factor, but may be useful for patients with Framingham Risk scores of 10% to 20%. The updated National Cholesterol Education Panel Adult Treatment Panel III guidelines list elevated hs-CRP (>3 mg/L) as an influencing factor in deciding whether to use an LDL-lowering drug for moderately high-risk patients with LDL-cholesterol values <130 mg/dL.[13] However, no prospective studies prove that elevated hs-CRP should guide therapy. The JUPITER trial is a prospective, placebo-controlled trial evaluating cardiovascular events with statin therapy in primary prevention patients with LDL values <130 mg/dL and hs-CRP values >2 mg/L.[14] When this study is completed, the definitive clinical utility of hs-CRP will be known. Until then, hs-CRP is a risk marker that may be useful for some moderately high-risk patients.

Joseph Saseen, PharmD, FCCP, BCPS, *University of Colorado Health Sciences Center, Denver*

How should we follow up a positive screen for anemia in a 1-year old?

■ EVIDENCE-BASED ANSWER

Healthy infants who test positive for anemia on routine screening at 1 year of age are most likely iron-deficient and may be treated empirically with a trial of iron therapy (3–6 mg of elemental iron/kg/d). Documentation of response to iron confirms the diagnosis of iron-deficiency (strength of recommendation [SOR]: **B**; evidence from randomized controlled trials with some conflicting results; lack of evidence for long-term benefits/harms of screening strategies).

In these cases, further testing with a complete blood count, mean corpuscular volume, red cell distribution width (RDW), serum ferritin concentration, as well as hemoglobinopathy screening when appropriate, may be effective in determining the cause of anemia (SOR: **C**, expert opinion).

■ EVIDENCE SUMMARY

A prospective study of 1128 children identified as anemic with a screening hemoglobin level showed that subsequent testing—which included mean corpuscular volume, protoporphyrin, transferrin, and ferritin measurements—did not reliably distinguish potential responders from nonresponders to a 3-month trial of empiric iron therapy.[1] In fact, more than half of the responders would have been missed if treatment had been restricted to infants with abnormal mean corpuscular volume or iron studies.

Because of the simplicity, low cost, and relative safety of iron therapy for infants, this trial suggests that a therapeutic trial of iron be given first, reserving further work-up for the small number of infants that still have unexplained hemoglobin concentrations of <11.0 g/dL after a therapeutic trial. Similar results were found in a prospective controlled treatment trial among Alaskan Native children[2] as well as a trial of empiric iron therapy among infants with anemia.[3]

Another prospective study of 970 healthy infants identified 62 infants with a heel-stick capillary hematocrit of <33%. Of these, 31 had repeat hematocrit values of <33% as confirmed by subsequent heel-stick complete blood count measurement. Twenty of these anemic infants (65%) completed the study protocol, which included a 1-month trial of iron, a follow-up complete blood count, and hemoglobin electrophoresis for those infants with persistent microcytosis or positive sickle preparation (performed at initial screening for all African American infants). Six infants (30%) had an increase in hemoglobin concentration of 1.0 g/dL or more and were presumed to be iron-deficient; they went on to receive an additional 2 months of iron therapy. Two of these were found to have co-existing alpha-thalassemia. Of the remainder, 11 (55%) were determined to have a low-normal hematocrit (mean=31.5 ± 0.9), 1 had alpha thalassemia alone, 1 had coexisting alpha-thalassemia and hemoglobin AS, and 1 had hemoglobin SC. Review of data showed that abnormal diagnoses (iron deficiency, thalassemia, and sickle cell trait or disease) were found in 9 of 11 infants with high RDW and in none of the 9 with normal RDW. The authors concluded that RDW alone appears to be predictive of identifiable causes of anemia when used to screen healthy 12-month-old babies.[4]

A recent Cochrane review suggests there is a clinically significant benefit for the treatment of iron-deficiency anemia; however, there is a need for further randomized controlled trials with long-term follow-up.[5] A randomized controlled trial of iron supplementation vs placebo in 278 infants testing positive for iron-deficiency anemia demonstrated that once daily, moderate-dose ferrous sulfate ($FeSO_4$) therapy (3 mg/kg/d of elemental iron) given to fasting 1-year-old infants results in no more gastrointestinal side effects than placebo therapy.[6] Another study demonstrated that iron sulfate drops (40 mg elemental iron divided 3 times a day) or a single daily dose of microencapsulated ferrous fumarate sprinkles (80 mg elemental iron) plus ascorbic acid resulted in a similar rate of successful treatment of anemia without side effects.[7]

> Further work-up should be reserved for those infants having unexplained hemoglobin concentrations <11.0 g/dL

In a retrospective cohort study[8] of 1358 inner-city children aged 9 to 36 months who underwent screening, 343 (25%) had anemia (Hgb <11 g/dL); of these, 239 (72%) were prescribed iron and 95 (28%) were not. Responders were defined as those with a hemoglobin value of greater than 11 g/dL or an increase of 1 g/dL documented within 6 months of the initial screening visit. Follow-up rates for both groups were low (~50%), but of those prescribed iron, 107 of 150 (71%) responded to treatment compared with 27 of 48 (68%) of those who did not receive iron. Since similar response rates were seen among infants who did and infants who did not receive iron therapy, proving the benefit of routine screening followed by a trial of iron may be problematic in populations with higher rates of anemia, low follow-up rates, and high spontaneous resolution rates.

■ RECOMMENDATIONS FROM OTHERS

The United States Preventive Services Task Force,[9] American Academy of Family Physicians,[10] and American Academy of Pediatrics[11] recommend screening infants for iron-deficiency anemia but do not address appropriate follow-up for positive screens.

The Centers for Disease Control and Prevention (CDC) guidelines recommend performing a confirmatory hemoglobin and hematocrit after a positive anemia screening. If anemia is confirmed and the child is not ill, then treat with iron replacement (3 mg elemental iron/kg/daily) for 4 weeks followed by a repeat test. An increase in hemoglobin concentration ≥1 g/dL or in hematocrit ≥3% confirms the diagnosis of iron-deficiency anemia. If iron-deficiency anemia is confirmed, they recommend continuing iron therapy for 2 more months (3 months total treatment), and rechecking hemoglobin or hematocrit 6 months after successful treatment is completed. Nonresponders, despite compliance with the iron

supplementation regimen and the absence of acute illness, should undergo further evaluation including mean corpuscular volume, RDW, and serum ferritin concentration.[12]

Stephen Scott, MD, Department of Family and Community Medicine, Houston, Tex; **Marlene Porter, MLS,** *Medical College of Ohio, Toledo*

■ CLINICAL COMMENTARY
Treating anemia without testing for the cause is the approach of most FPs

For infants 9 months to 1 year of age, there is no consensus regarding appropriate follow-up of positive screens for anemia. It is known that most of them have iron deficiency anemia and empiric treatment with iron supplements have been studied in several prospective trials.

It is also unclear which red cell indices should be tested for diagnosing the different types of anemia. One study found RDW testing alone could predict the cause of anemia. Based on my clinical experience with inner-city Hispanic babies, CDC guidelines seem to include appropriate follow-up. A Cochrane review suggests the need for further randomized controlled trials with long-term follow-up. There is evidence that treating anemia without initial testing for the cause is the approach of choice of most physicians, and there is some evidence that further testing may delay or result in nontreatment of infants who would have benefited from iron therapy.

Yasmeen Quadri, MD, Baylor College of Medicine, Houston, Tex

REFERENCES
1. Dallman, PR, Reeves JD, Driggers DA, Lo EY. Diagnosis of iron deficiency: the limitations of laboratory tests in predicting response to iron treatment in 1-year-old infants. *J Pediatr* 1981; 99:376–381.
2. Margolis HS, Hardison HH, Bender TR, Dallman PR. Iron deficiency in children: the relationship between pretreatment laboratory tests and subsequent hemoglobin response to iron therapy. *Am J Clin Nutr* 1981; 34:2158–2168.
3. Driggers DA, Reeves JP, Lo EY, Dallman PR. Iron deficiency in one-year-old infants: comparison of results of a therapeutic trial in infants with anemia or low-normal hemoglobin values. *J Pediatr* 1981; 98:753–758.
4. Choi YS, Reid T. Anemia and red cell distribution width at the 12-month well-baby examination. *South Med J* 1998; 91:372–374.
5. Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia (Cochrane review). *Cochrane Database Syst Rev Library*, Issue 2, 2004. 2001(2):CD001444.
6. Reeves JD, Yip R. Lack of adverse side effects of oral ferrous sulfate therapy in 1-year-old infants. *Pediatrics* 1985; 75:352–355.
7. Zlotkin S, Arthur P, Antwi KY, Yeung G. Treatment of anemia with microencapsulated ferrous fumarate plus ascorbic acid supplied as sprinkles to complementary (weaning) foods. *Am J Clin Nutr* 2001; 74:791–795.
8. Bogen DL, Krause JP, Serwint JR. Outcome of children identified as anemic by routine screening in an inner-city clinic. *Arch Pediatr Adolesc Med* 2001; 155:366–371.
9. US Preventive Services Task Force (USPSTF). Screening: Iron deficiency anemia. *Guide to Clinical Preventive Services.* Rockville, Md: USPSTF; 1996. Available at: www.ahrq.gov/clinic/uspstf/uspsiron.htm. Accessed on February 7, 2005.
10. American Academy of Family Physicians. Summary of Policy Recommendations for Periodic Health Examinations, revision 5.6, August 2004. Available at: www.aafp.org/x24975.xml. Accessed on February 7, 2005.
11. Kohli-Kumar M. Screening for anemia in children: AAP recommendations—a critique. *Pediatrics* 2001; 108:E56.
12. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1998; 47(RR-3):1–29. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/00051880.htm. Accessed on February 7, 2005.

■ CORRECTION
The authors of an article in the October 2004 issue of The Journal of Family Practice have requested a correction to the article's title and Practice Recommendation. The new title and recommendation (below) omit an earlier mention of breast cancer.

[Title]
Raloxifene reduces risk of vertebral fractures in postmenopausal women regardless of prior hormone therapy

[Practice Recommendation]
Consider prescribing raloxifene 60 mg/d for postmenopausal women, regardless of whether they have used hormone therapy, to reduce the incidence of vertebral fractures

The authors wish to note that raloxifene is not approved in the United States for use in reducing the incidence or risk of breast cancer.