1 Approach to the Anemic Child

Anemia is the condition in which the concentration of hemoglobin or the red cell mass is reduced below normal. Anemia results in a physiological decrease in the oxygen-carrying capacity of the blood and reduced oxygen supply to the tissues. Causes of anemia are increased loss or destruction of red blood cells (RBCs) or a significant decreased rate of production. When evaluating a child with anemia, it is important to determine if the problem is isolated to one cell line (e.g., RBCs) or multiple cell lines (i.e., RBCs, white blood cells [WBCs], or platelets). When two or three cell lines are affected, it may indicate bone marrow involvement (leukemia, metastatic disease, and aplastic anemia), sequestration (i.e., hypersplenism), immune deficiency, or an immune-mediated process (e.g., hemolytic anemia and immune thrombocytopenic purpura).

Evaluation of anemia

The evaluation of anemia includes a complete medical history, family history, physical examination, and laboratory assessment. See Figure 1.1.

The diagnosis of anemia is made after reference to established normal controls for age (Table 1.1). The blood smear and red cell indices are very helpful in the diagnosis and classification of anemia. It allows for classification by the cell size (MCV, mean corpuscular volume), gives the distribution of cell size (RDW, red cell distribution width), and may give important diagnostic clues if specific morphological abnormalities are present (e.g., sickle cells, target cells, and spherocytes). The MCV, RDW, and reticulocyte count are helpful in the differential diagnosis of anemia. A high RDW, or anisocytosis, is seen in stress erythropoiesis and is often suggestive of iron deficiency or hemolysis. A normal or low reticulocyte count is an inappropriate response to anemia and suggests impaired red cell production. An elevated reticulocyte count suggests blood loss, hemolysis, or sequestration.

The investigation of anemia requires the following steps:

1. The medical history of the anemic child (Table 1.2), as certain historical points may provide clues as to the etiology of the anemia.

2. Detailed physical examination (Table 1.3), with particular attention to acute and chronic effects of anemia.

3. Evaluation of the complete blood count (CBC), RBC indices, and peripheral blood smear, with classification by MCV,

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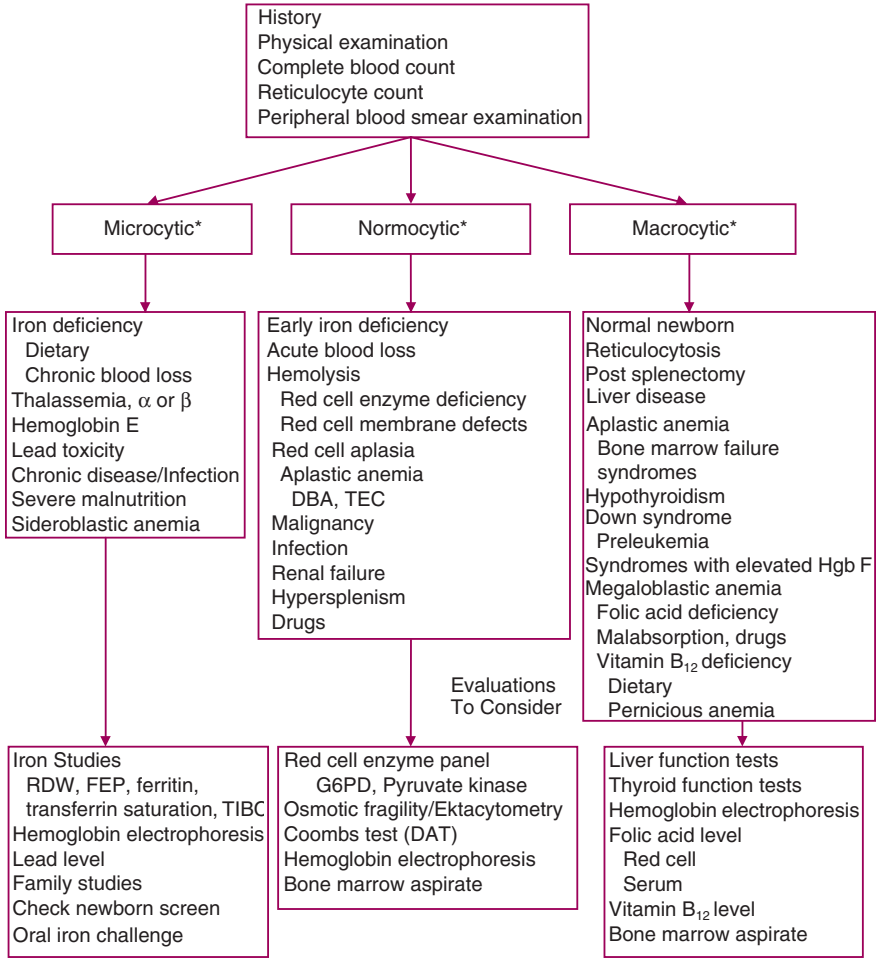

Figure 1.1 Diagnostic approach to the child with anemia. (Abbreviations: DBA, Diamond–Blackfan anemia; TEC, transient erythroblastopenia of childhood; RDW, red cell distribution width; FEP, free erythrocyte protoporphyrin; TIBC, total iron binding capacity; G6PD, glucose-6-phosphate dehydrogenase deficiency; DAT, direct antiglobulin test).
*Refer to Table 1.1 for age-based normal values.

reticulocyte count, and RBC morphology. Consideration should also be given to the WBC and platelet counts as well as their respective morphology.

4. Determination of an etiology of the anemia by additional studies as needed (see Figures 1.1, 1.2, and 1.3).

Interventions

Oral iron challenge

An oral iron challenge may be indicated in the patient with significant iron depletion, as documented by moderate-to-severe anemia and deficiencies in circulating

Table 1.1 Red blood cell values at various ages.*

Age	Hemoglobin (g/dL)		MCV (fL)	
	Mean	−2 SD	Mean	−2 SD
Birth (cord blood)	16.5	13.5	108	98
1–3 d (capillary)	18.5	14.5	108	95
1 wk	17.5	13.5	107	88
2 wk	16.5	12.5	105	86
1 mo	14.0	10.0	104	85
2 mo	11.5	9.0	96	77
3–6 m	11.5	9.5	91	74
0.5–2 y	12.0	11.0	78	70
2–6 y	12.5	11.5	81	75
6–12 y	13.5	11.5	86	77
12–18 y female	14.0	12.0	90	78
12–18 y male	14.5	13.0	88	78
18–49 y female	14.0	12.0	90	80
18–49 y male	15.5	13.5	90	80

*Compiled from the following sources: Dutcher TF. Lab Med 2:32–35, 1971; Koerper MA, et al. J Pediatr 89:580–583, 1976; Marner T. Acta Paediatr Scand 58:363–368, 1969; Matoth Y, et al. Acta Paediatr Scand 60:317–323, 1971; Moe PJ. Acta Paediatr Scand 54:69–80, 1965; Okuno T. J Clin Pathol 2:599–602, 1972; Oski F, Naiman J. Hematological Problems in the Newborn, 2nd ed., Philadelphia: WB Saunders, 1972, p. 11; Penttilä I, et al. Suomen Lääkärilehti 26:2173, 1973; and Viteri FE, et al. Br J Haematol 23:189–204, 1972. Cited in: Rudolph AM (ed). Rudolph's Pediatrics, 16th ed., Norwalk, CT: Appleton & Lange, 1977.

Abbreviation: MCV, mean corpuscular volume.

and storage iron forms (such as total iron-binding capacity [TIBC], serum iron, transferrin saturation, and ferritin). Iron absorption is impaired in certain chronic disorders (autoimmune diseases such as lupus, peptic ulcer disease, ulcerative colitis, and Crohn's disease), by certain medications (antacids and histamine-2 blockers), and by environmental factors such as lead toxicity.

Indications for an oral iron challenge include any condition in which a poor response to oral iron is being questioned, such as in: noncompliance, severe anemia secondary to dietary insufficiency (excessive milk intake), and ongoing blood loss.

Administration of an oral iron challenge is quite simple: first, draw a serum iron level; second, administer a dose of iron (3 mg/kg elemental iron) orally; third, draw another serum iron level 30 to 60 minutes later. The serum level is expected to increase by at least 100 mcg/dL if absorption is adequate. The oral iron challenge is a quick and easy method to assess appropriateness of oral iron to treat iron deficiency—a safer, cheaper yet equally efficacious method of treatment as parenteral iron.

Parenteral iron therapy

Due to the potential risks of older parenteral iron preparations (specifically high molecular weight iron dextran), a reluctance remains to use the newer and much safer formulations. The majority of safety data exists with low molecular weight (LMW) iron dextran although many practitioners have moved to newer (and perceived safer)

Table 1.2 The medical history of the anemic child.

History of	Consider
Prematurity	Anemia of prematurity (EPO responsive)
Perinatal risk factors	
Maternal illness (autoimmune)	Hemolytic anemia
Drug ingestion	Impaired production
Infections (TORCH [e.g., rubella, CMV], hepatitis)	
Perinatal problems	Acute blood loss
	Fetal–maternal hemorrhage
	Iron deficiency due to above or maternal iron deficiency
Ethnicity	
African-American	Hgb S, C; α- and β-thalassemia; G6PD deficiency
Mediterranean	α- and β-thalassemia; G6PD deficiency
Southeast Asian	α- and β-thalassemia; Hgb E
Family history	
Gallstones, cholecystectomy	Inherited hemolytic anemia, spherocytosis, elliptocytosis
Splenectomy, jaundice at birth or with illness	Inherited enzymopathy, G6PD, pyruvate kinase deficiencies
Isoimmunization (Rh or ABO)	Hemolytic disease of newborn (predisposed to iron deficiency)
Sex	
Male	X-linked enzymopathies (G6PD deficiency)
Early jaundice (<24 h of age)	Isoimmune, infectious
Persistent jaundice	Suggests hemolytic anemia
Diet (Usually > 6 mo)	
Pica (ice, dirt)	Lead toxicity, iron deficiency
Excessive milk intake	Iron deficiency
Macrobiotic diets	Vitamin B_{12} deficiency
Goat's milk	Folic acid deficiency
Drugs	
Sulfa drugs, anticonvulsants	Hemolytic anemia (G6PD deficiency)
Chloramphenicol	Hypoplastic anemia
Low socioeconomic status	
Pica	Lead toxicity, iron deficiency
Malnutrition	
Malabsorption	Anemia of chronic disease
Environmental	Iron, vitamin B_{12}, or folate deficiency, vitamin E or K deficiency
Liver disease	Shortened red cell survival
	Heinz bodies
Renal disease	Shortened red cell survival
Decreased red cell production (↓EPO)	
Infectious diseases	
Mild viral infection (acute gastroenteritis, otitis media, pharyngitis)	Transient mild decreased Hgb
Sepsis (bacterial, viral, mycoplasma)	Hemolytic anemia
Parvovirus	Anemia with reticulocytopenia (TEC)

Abbreviations: EPO, erythropoietin; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus; G6PD, glucose-6-phosphate dehydrogenase deficiency; TEC, transient erythroblastopenia of childhood.

Table 1.3 Physical examination of the anemic child.

System	Clinical sign or symptom	Potential underlying disorder
Skin	Pallor	Severe anemia
	Jaundice	Hemolytic anemia, acute and chronic hepatitis, aplastic anemia
	Petechiae, purpura	Autoimmune hemolytic anemia with thrombocytopenia, hemolytic uremic syndrome, bone marrow aplasia or infiltration
	Cavernous hemangioma	Microangiopathic hemolytic anemia
HEENT	Frontal bossing, prominent malar and maxillary bones	Extramedullary hematopoiesis (thalassemia major, congenital hemolytic anemia)
	Icteric sclerae	Congenital hemolytic anemia and hyperhemolytic crises associated with infection (red cell enzyme deficiencies, red cell membrane defects, thalassemias, hemoglobinopathies)
	Angular stomatitis	Iron deficiency
	Glossitis	Vitamin B_{12} or iron deficiency
Chest	Rales, gallop rhythm, tachycardia	Congestive heart failure, acute or severe anemia
Spleen	Splenomegaly	Congenital hemolytic anemia, infection, hematological malignancies, portal hypertension, resultant hypersplenism
Extremities	Radial limb dysplasia	Fanconi anemia
	Spoon nails	Iron deficiency
	Triphalangeal thumbs	Red cell aplasia

formulations including ferric gluconate and iron sucrose. Three additional compounds have been approved recently, 2 in Europe (ferric carboxymaltose and iron isomaltoside) and 1 in the United States (ferumoxytol). These newer agents have the potential benefit of total dose replacement in a very short and single infusion as compared to ferric gluconate and iron sucrose which require multiple doses. LMW iron dextran is approved as a total dose infusion for adults in Europe but not the United States. Due to the smaller dose generally required in pediatric patients, total iron replacement is feasible in 1 to 2 doses of LMW iron dextran. Calculation of the necessary dose is as follows:

$$\text{Dosage (mL)} = 0.0442 \times \text{LBW (kg)} \times (\text{Hgb}_n - \text{Hgb}_o) + [0.26 \times \text{LBW (kg)}],$$

where

LBW = lean body weight
- males: 50 kg + 2.3 kg for every inch over 5 ft in height
- females: 45.5 kg + 2.3 kg for every inch over 5 ft in height

Hgb_n = desired hemoglobin (g/dL) = 12 if < 15 kg or 14.8 if > 15 kg

Hgb_o = measured hemoglobin (g/dL)

The maximum adult dose is 2 mL and each milliliter of iron dextran contains 50 mg

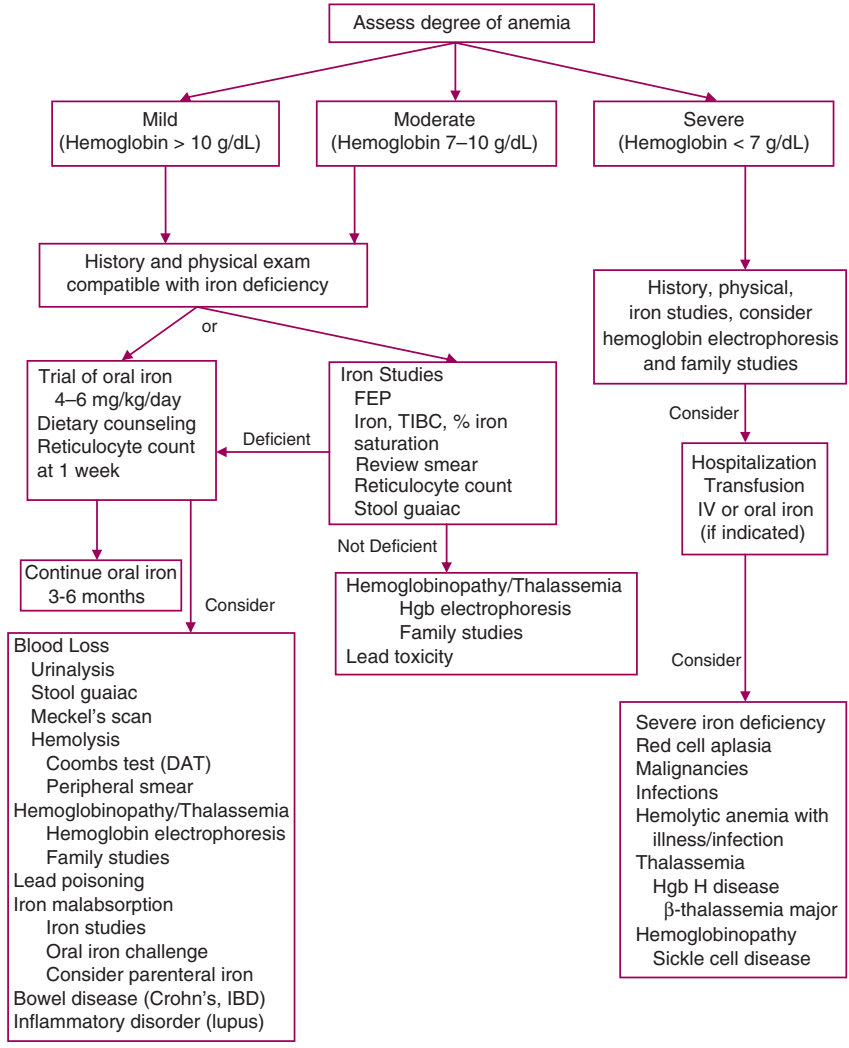

Figure 1.2 Evaluation of the child with microcytic anemia. (Abbreviations: FEP, free erythrocyte protoporphyrin; TIBC, total iron binding capacity; DAT, direct antiglobulin test; IBD, inflammatory bowel disease).

of elemental iron. Add 10 mg elemental iron/kg to replenish iron stores (chronic anemia states). Replacement may be given in a single dose, depending on the dose required. See the formulary for further information.

Severe allergic reactions can occur with iron dextran and the low molecular weight product should be preferentially utilized. A test dose (10 to 25 mg) should be given prior to the first dose with observation of the patient for 30 to 60 minutes prior to administering the remainder of the dose. A common side effect is mild to moderate arthralgias the day after drug administration, especially in patients with autoimmune disease. Acetaminophen frequently

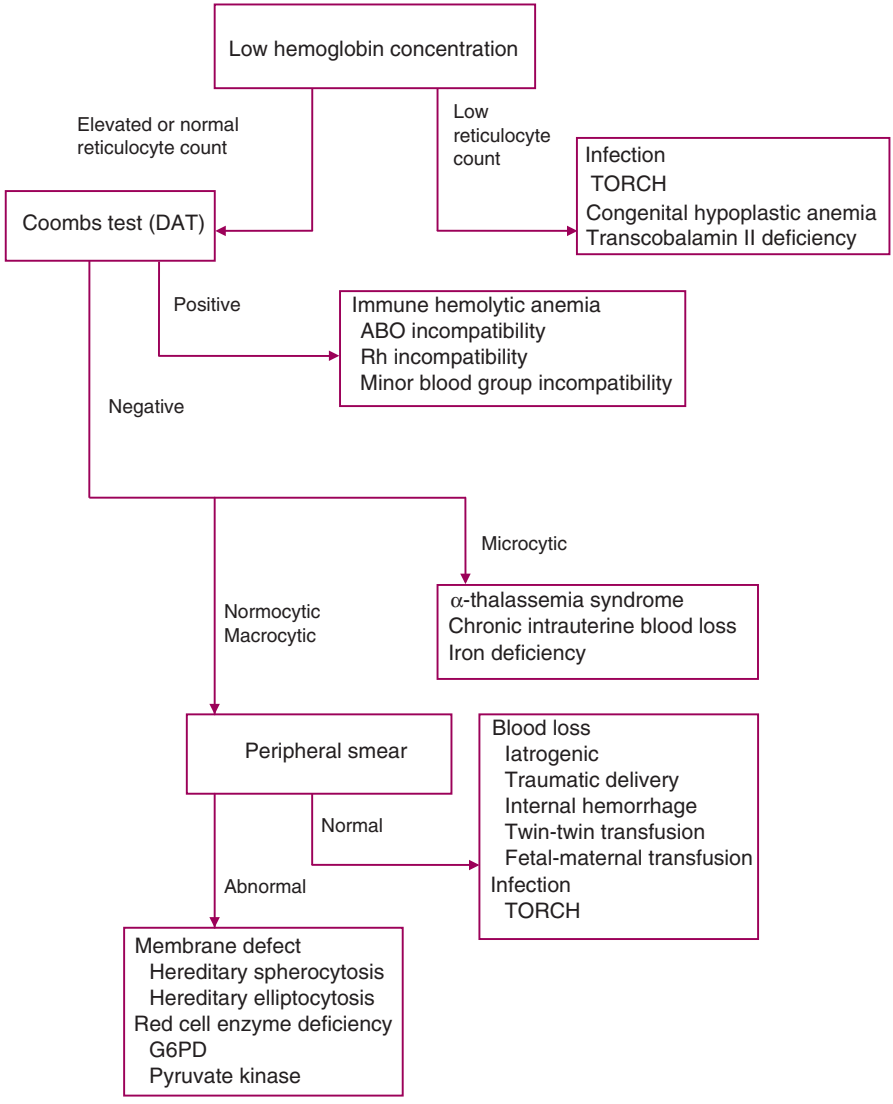

Figure 1.3 Approach to the full-term newborn with anemia. (Abbreviations: DAT, direct antiglobulin test; G6PD, glucose-6-phosphatase deficiency; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus).

alleviates the arthralgias. Iron dextran is contraindicated in patients with rheumatoid arthritis.

Iron sucrose or ferric gluconate can be considered in inpatients in which multiple doses are more convenient and feasible than the outpatient setting. With continued usage and safety data, ferumoxytol will likely replace the currently used products due to the much larger maximum dose that

can be given, lack of need for a test dose, and excellent side effect profile.

Erythropoietin

Recombinant human erythropoietin (EPO) stimulates proliferation and differentiation of erythroid precursors, with an increase in heme synthesis. This increased proliferation creates an increased demand in iron availability and can result in a functional iron deficiency if not given with iron therapy.

Indications for EPO include end-stage renal disease, anemia of prematurity, anemia of chronic disease, anemia associated with treatment for AIDS, and autologous blood donation. EPO use for the treatment of chemotherapy-induced anemia remains controversial and is not routinely recommended in pediatric patients (see Chapter 25).

The most common side effect of EPO administration is hypertension, which may be somewhat alleviated with changes in the dose and duration of administration.

Typical starting dose of EPO is 150 U/kg three times a week (IV) or subcutaneous (SC). CBCs and reticulocyte counts are checked weekly. Higher doses, and more frequent dosing, may be necessary. Response is usually seen within 1 to 2 weeks. Adequate iron intake (3 mg/kg/d orally or intermittent parenteral therapy) should be provided to optimize effectiveness and prevent iron deficiency.

Transfusion therapy

Children with very severe anemia (Hgb < 5 g/dL) may require treatment with red cell transfusion, depending on the underlying disease and baseline hemoglobin status, duration of anemia, rapidity of onset, and hemodynamic stability. The pediatric literature is scarce as to the best method of transfusing such patients. However, it appears to be common practice to give slow transfusions to children with cardiovascular compromise (i.e., gallop rhythm, pulmonary edema, excessive tachycardia, and poor perfusion) while being monitored in an ICU setting. Transfusions are given in multiple small volumes, sometimes separated by several hours, with careful monitoring of the vitals and fluid balance. For those children who have gradual onset of severe anemia, without cardiovascular compromise, continuous transfusion of 2 mL/kg/h has been shown to be safe and result in an increase in the hematocrit of 1% for each 1 mL/kg of transfused packed RBCs (based on RBC storage method). The hemoglobin should be increased to a normal value to avoid further cardiac compromise (i.e., Hgb 8 to 12 g/dL). Again, the final endpoint may be dependent on several factors including nature of anemia, ongoing blood loss or lack of production, baseline hemoglobin, and volume to be transfused. Care should be taken to avoid unnecessary exposure to multiple blood donors by maximal use of the unit of blood, proper division of units in the blood bank, and avoidance of opening extra units for small quantities to meet a total volume. See Chapter 5 for product preparation, ordering, and premedication. A posttransfusion hemoglobin can be checked if necessary at any point after the transfusion has been completed. Waiting for "reequilibration" is anecdotal and unnecessary.

Case study for review

You are seeing a one year old for their well child check in clinic. As part of routine screening, a fingerstick hemoglobin is recommended.

1. What questions in the history might help screen for anemia?
2. What about the physical examination?

Multiple questions in the history can be helpful. Dietary screening for excessive milk intake is important in addition to asking about intake of iron-rich foods such as green leafy vegetables and red meat. One should also ask about pica behavior such as eating dirt or ice and include questions regarding the age of the house to help screen for lead paint exposure and ingestion. Any sources of blood loss should also be explored including blood in the urine or stool as well as frequent gum or nose bleeding (more likely in an older child). Finally, family history should be explored regarding anemia during pregnancy, previous history of iron deficiency in siblings, and history of hemoglobinopathies.

Physical examination to search for anemia should be focused. Pallor, especially subconjunctival, perioral, and periungual should be checked. Tachycardia, if present, would be more consistent with acute anemia rather than well-compensated chronic anemia. Splenomegaly, sclera icterus, and jaundice may point to an acute or chronic hemolytic picture.

You do the fingerstick hemoglobin in clinic and it is 10.2 g/dL. The history is not suggestive of iron deficiency and the exam is unremarkable.

3. What are the reasonable next steps?

Depending on the prevalence of iron deficiency in your population, it would be reasonable at this point to give a 1 month trial of oral iron therapy. The family should be counseled that oral iron tastes bad and should be given with vitamin C (i.e., orange juice) and not milk to improve absorption. If there is a low likelihood of iron deficiency, a family history of thalassemia or sickle cell disease, or a suggestive newborn screen, an empiric trial of oral iron supplementation should not be performed. Similarly, if there are signs that are consistent with a hemolytic process or a significant underlying disorder, further workup should be done. In these cases, it would be correct to next perform a CBC. If there are concerns for sickle cell disease or thalassemia, it would be reasonable to also perform hemoglobin electrophoresis. If there are concerns for hemolysis, labs including reticulocyte count, total bilirubin, lactate dehydrogenase, and a direct Coombs should be performed. Finally, if there is concern for a systemic illness such as leukemia, a manual differential should be requested. Further workup for iron deficiency (ferritin and TIBC) as well as lead toxicity could be included or deferred until the anemia is better characterized utilizing the MCV and RDW on the CBC.

Suggested Reading

Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. Hematology Am Soc Hematol Educ Program 338–347, 2010.

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