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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 (e.g., 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. They allow for classification by the cell size (mean corpuscular volume [MCV]), give the distribution of cell size (red cell distribution width [RDW]), 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, reticulocyte count, and RBC morphology.

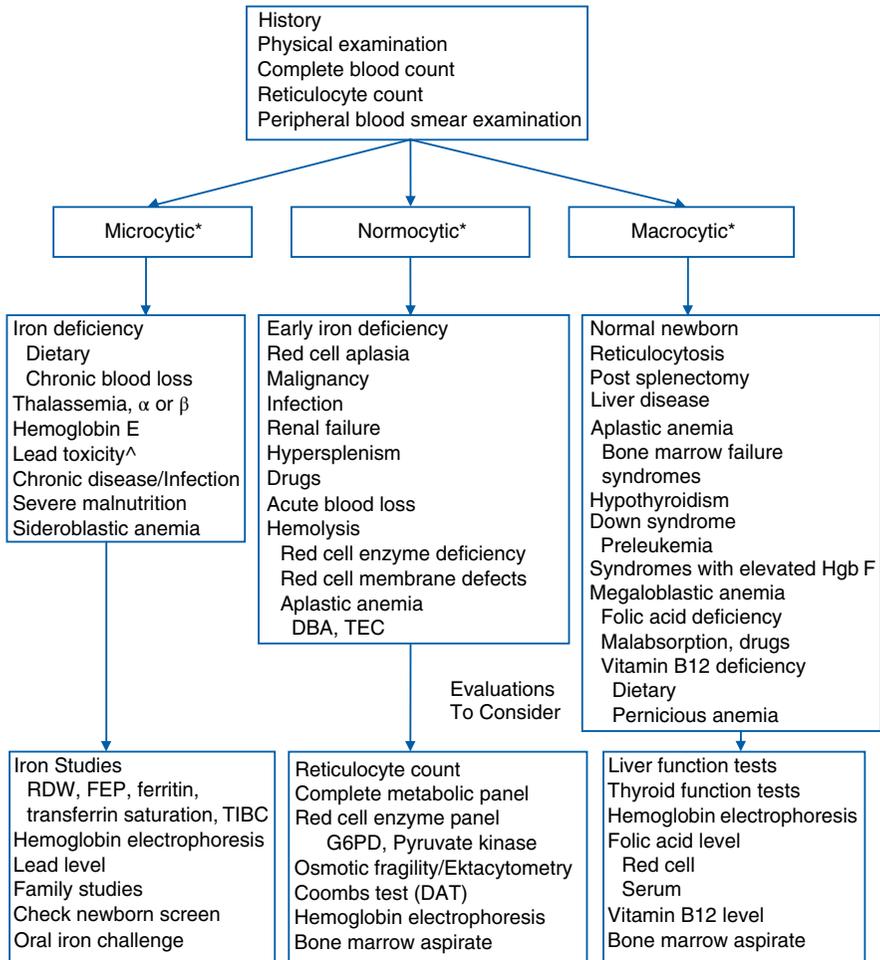


Figure 1.1 Diagnostic approach to the child with anemia (abbreviations: DBA, Diamond–Blackfan anemia; TEC, transient erythroblastopenia of childhood; RDW, red cell distribution width; FEP, free erythrocyte protoporphyrin; TIBC, total iron-binding capacity; G6PD, glucose-6-phosphate dehydrogenase deficiency;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

*Refer to Table 1.1 for age-based normal values.

^Microcytosis with lead toxicity has been noted secondary to concomitant iron deficiency; see text.

Consideration should also be given to the WBC and platelet counts as well as their respective morphologies.

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

Interventions

Oral iron challenge

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

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 mo	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.

anemia and deficiencies in circulating and storage iron forms (such as an elevated total iron-binding capacity [TIBC], low serum iron, low transferrin saturation, and low ferritin). Iron absorption is impaired in certain chronic disorders (autoimmune diseases such as systemic lupus erythematosus, 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 30-60 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), practitioners have moved to newer (and

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 the abovementioned factors 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 (also predisposed to iron deficiency)
Sex	
Male	X-linked enzymopathies (i.e., G6PD deficiency)
Early jaundice (<24 h of age)	Isoimmune, infectious
Persistent jaundice	Suggests hemolytic anemia
Diet (Usually >6 mo unless history of prematurity)	
Pica behavior	Lead toxicity, iron deficiency
Excessive milk intake	Iron deficiency
Macrobiotic/vegan diets	Vitamin B12 deficiency
Goat 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 B12, or folate deficiency, vitamin E or K deficiency
Liver disease	Shortened red cell survival
Renal disease	Shortened red cell survival
Decreased red cell production (\downarrow EPO)	
Infectious diseases	
Mild viral infection (acute gastroenteritis, otitis media, pharyngitis)	Transient mild decreased hgb
Sepsis (bacterial, viral, mycoplasma)	Hemolytic anemia, decreased red cell production
Parvovirus	Anemia with reticulocytopenia

Abbreviations: EPO, erythropoietin; TORCH, toxoplasmosis, other, rubella, cytomegalovirus (CMV), herpes simplex virus; G6PD, glucose-6-phosphate dehydrogenase deficiency.

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
HEENT	Cavernous hemangioma	Microangiopathic hemolytic anemia
	Frontal bossing, prominent malar and maxillary bones	Extramedullary hematopoiesis (i.e., thalassemia major, congenital hemolytic anemia)
	Icteric sclerae	Congenital hemolytic anemia, hyperhemolytic crisis associated with infection (i.e., red cell enzyme deficiencies, red cell membrane defects, thalassemias, hemoglobinopathies), autoimmune hemolytic anemia
Chest	Angular stomatitis	Iron deficiency
	Glossitis	Vitamin B12 or iron deficiency
	Rales, gallop rhythm, tachycardia	Congestive heart failure, acute or severe anemia
Spleen	Splenomegaly	Congenital hemolytic anemia, infection, hematologic malignancies, portal hypertension
Extremities	Radial limb dysplasia	Fanconi anemia
	Spoon nails	Iron deficiency
	Triphalangeal thumbs	Red cell aplasia

perceived safer) formulations including ferrous gluconate and iron sucrose. Three additional compounds have been approved, one only in Europe (iron isomaltoside) and two in the United States (ferumoxytol and ferrous carboxymaltose). These newer agents have the potential benefit of total dose replacement in a very short and single infusion as compared to ferrous gluconate and iron sucrose which require multiple doses. Low-molecular-weight (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 1–2 doses of LMW iron dextran and has been shown safe. Refer to the Formulary for calculation of LMW iron dextran dosing.

Severe allergic reactions can occur with iron dextran and therefore a LMW product should be preferentially utilized. A test dose (10–25 mg) should be given prior to the first dose with observation of the patient for 30–60 minutes prior to administering the remainder of the dose. A common side effect is mild to moderate arthralgias the day after drug administration, especially

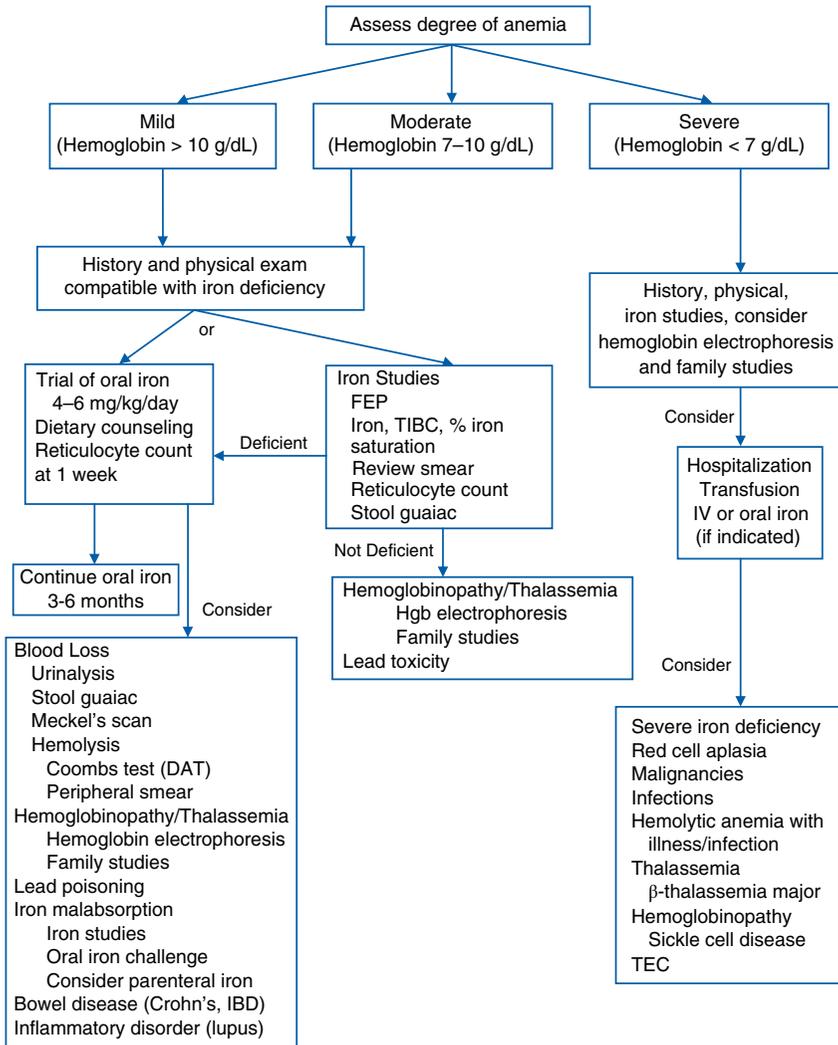


Figure 1.2 Evaluation of the child with microcytic anemia (abbreviations: FEP, free erythrocyte protoporphyrin; TIBC, total iron-binding capacity; DAT, direct antiglobulin test; IBD, inflammatory bowel disease).

in patients with autoimmune disease. Acetaminophen frequently alleviates the arthralgias. Iron dextran is contraindicated in patients with rheumatoid arthritis.

Iron sucrose or ferric gluconate should be considered in patients for whom multiple doses are more feasible. Both are limited

by a maximum dose beyond which there is increased risk of adverse events. Ferumoxytol and ferric carboxymaltose have both received approval by the United States Food and Drug Administration for the treatment of iron deficiency anemia as well as renal insufficiency in adults. Both have

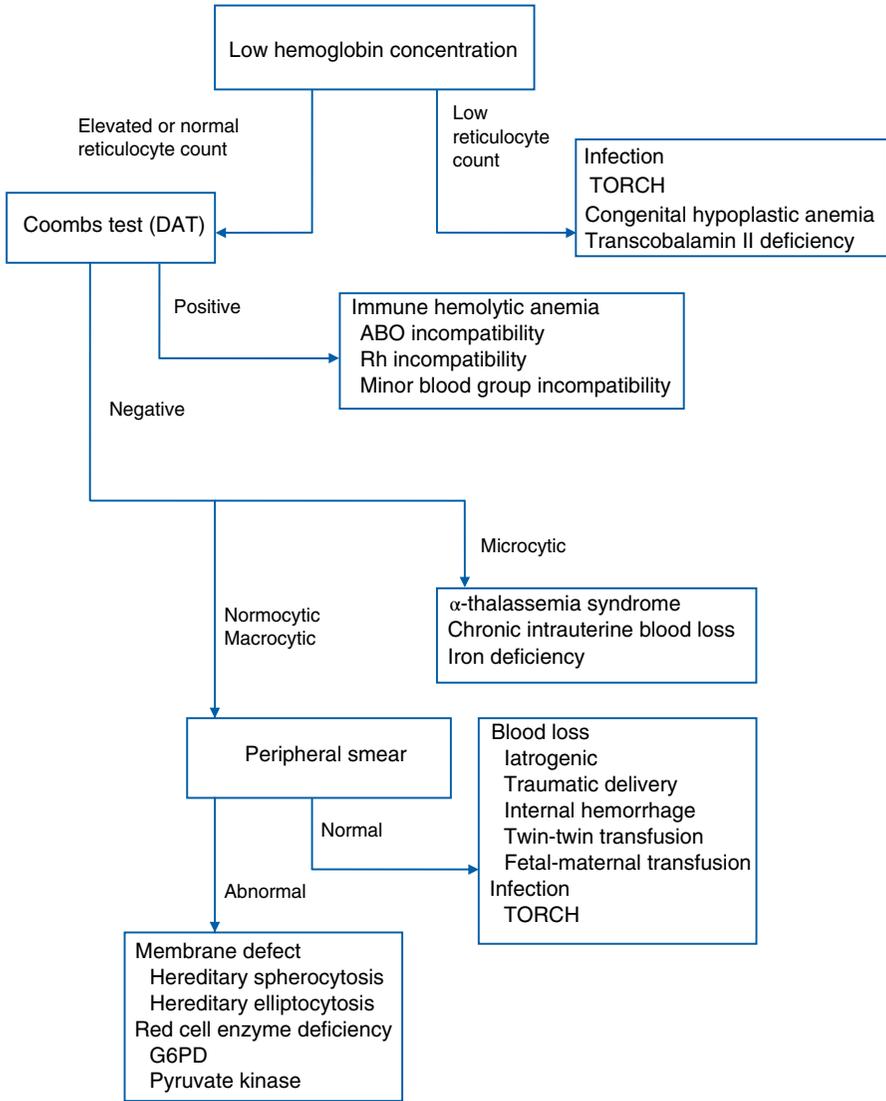


Figure 1.3 Approach to the full-term newborn with anemia (abbreviations: DAT, direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase deficiency; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex virus).

the benefit of total dose replacement given as a rapid infusion due to slow release of elemental iron. Neither is immunogenic and therefore no test dose is required. Studies

regarding utilization in pediatric patients are limited regarding appropriate per kg dosage, although the infusions appear safe and therefore will likely replace use of iron

sucrose and ferric gluconate in the future due to the convenience of single dose replacement. Refer to the Formulary for dosing parameters for these products.

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). EPO has also been used in autoimmune hemolytic anemia with low production as well as in chemotherapy-induced anemia when the family has religious beliefs that preclude transfusion. The use of EPO in this latter setting may reduce transfusion exposures but has not been validated.

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 1–2 weeks. Adequate iron intake (3 mg/kg/day orally or intermittent parenteral therapy) should be provided to optimize efficacy and prevent iron deficiency.

Transfusion therapy

Children with very severe anemia (i.e., 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 8–12 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 studies for review

1. You are seeing a 1-year-old for their well-child check in clinic. As part of routine screening, a fingerstick hemoglobin is recommended.

a. What questions in the history might help screen for anemia?

b. 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, scleral 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.

c. 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, TIBC) as well as lead toxicity (lead level) could be included or deferred until the anemia is better characterized utilizing the MCV and RDW on the CBC.

2. You are seeing a 15-month-old for a routine well-child check visit. The family notes that the child has been well but appears pale to them. You ask the same questions as reviewed in case one, and the family notes a recent viral illness with no evidence of hemolysis, as there has been no history of dark-colored urine or jaundice. The dietary history is unremarkable and on review, the 1-year fingerstick hemoglobin was normal at 11.4 g/dL with a normal lead level at that time. There has been no noted diarrhea or blood loss, and the child is not on any medications. On exam, the child is pale but well appearing with a normal heart rate, respiratory rate, and blood pressure without scleral icterus or other signs of jaundice. There is no lymphadenopathy or hepatosplenomegaly. There are no petechiae or bruising.

lymphoblastic leukemia and aplastic anemia. Patients will have a decrease in erythroid precursors in the bone marrow and therefore a decrease in peripheral reticulocytes. TEC is an indolent process and thus patients will generally present with a well-compensated but often severe normocytic anemia. Spontaneous recovery occurs with reticulocytosis, and thus TEC in the recovery phase can be mistaken for a hemolytic anemia.

Multiple choice questions

1. You are seeing a patient at their one year clinic visit and perform a finger stick hemoglobin. The hgb is 9.2 g/dl. The child has been well without any recent illnesses or significant findings on exam. What is the next best step?

- a. Empirically start iron therapy
- b. Obtain further history
- c. Check a full CBC/diff
- d. Plan to repeat in one month
- e. Perform a lead level

Explanation: It is first important to understand underlying risk factors for anemia. These could include a dietary intake of significant milk consumption which would lead to iron deficiency or a family history of thalassemia. Also it is important to ask about a bleeding history to determine if there are ongoing losses. It is important to ask about any history of jaundice or scleral icterus which would point to a hemolytic anemia as well as other inflammatory conditions which could lead to anemia of chronic disease. Choice a. would likely be correct after obtaining more history; choice c. is reasonable in cases where the history is not suggestive or the hgb does not increase with empiric iron therapy; choice d. would not be correct without other interventions; choice e. is important to do but lead toxicity itself does not lead to anemia, rather it is concomitant iron deficiency. The answer is b.

2. You are seeing a patient in the hospital admitted at two months of age for sepsis rule out secondary to high fever with associated decreased feeds and decreased urine output. The child has a urinary tract infection. A CBC is checked the hgb is 9.0 g/dl. There is no relevant family history, the mother received good prenatal care and was not anemic during pregnancy and the baby was born full term. What is the next best step?

- a. Empirically start iron therapy
- b. Plan to repeat the CBC prior to discharge
- c. Plan to repeat the CBC in 1-2 months as an outpatient
- d. Provide reassurance to the family

Explanation: Although anemia in a young infant with an underlying infection can be due to bone marrow suppression, this level of hemoglobin is normal for age. The physiologic nadir of infancy occurs around 2-3 months of age as fetal hemoglobin goes away (fetal hemoglobin lives 60-90 days as compared to hemoglobin A which lives 90-120 days). A certain level of anemia occurs prior to the bone marrow ramping up production of hemoglobin A red blood cells. Choice a. is incorrect as iron deficiency would be unlikely in this age although can occur in a very preterm infant or if the mother had severe anemia during pregnancy. Choice b. and c. are not necessary since the hb is normal for age. The answer is d.

3. You are seeing a patient in follow up. At the one year visit the finger stick hemoglobin was 9.4 g/dl. Given a nutritional history of significant milk intake you previously decided to empirically start iron therapy at a dose of 3 mg elemental iron daily and see the child today, one month later for a repeat finger stick hemoglobin. The repeat hemoglobin is now 10.2 g/dl. What is the next best step?

- a. Stop iron therapy
- b. Send a full CBC/diff

- c. Continue iron therapy and see the patient back in one month
- d. Continue iron therapy and see the patient back in 2-3 months

Explanation: Given the level of hemoglobin and nutritional history, iron deficiency is the most likely diagnosis. Reticulocyte counts should increase in 1-2 days after commencement of iron therapy and hemoglobin should rise within one week. A rise in hb in one month is reassuring that the diagnosis and treatment plan are correct. Choice a. is incorrect because it is important to continue iron therapy for 2-3 months after resolution of anemia to replete liver iron stores; as this child is still anemic it is too early to stop iron therapy. Choice b. is unnecessary at this point since the hgb is appropriately increasing with therapy but may be necessary at a later point if the anemia persists on iron therapy. Choice c. is reasonable although given the amount of time of iron therapy required to replete stores and the improvement seen to date, it is not necessary to see the patient so frequently. The answer is d.

4. You are seeing a patient in follow up. At the one year visit the finger stick hemoglobin was 9.4 g/dl. Given a nutritional history of significant milk intake you previously decided to empirically start iron therapy at a dose of 3 mg elemental iron daily and see the child today, one month later for a repeat finger stick hemoglobin. The repeat hemoglobin is now 9.2 g/dl. The mother states that the child is taking the iron well, with vitamin C, and she has decreased milk intake to 16 oz (480 ml) on average in a 24 hour period. What is the next best step?

- a. Continue iron therapy for another month and recheck hb at that time
- b. Check a CBC/diff
- c. Stop iron therapy and check a CBC/diff
- d. Stop iron therapy and check iron studies in addition to a CBC/diff

Explanation: As iron deficiency is the most likely cause of anemia, an empiric trial of iron is the correct first step. Assessing compliance with iron therapy and nutritional recommendations is very important in follow up especially if the hgb is not improved. In many cases the family is unable to give the iron well and the excessive milk intake continues. Assuming a reliable family as in the case above, it is important to now check a CBC/diff to further characterize the anemia. It would also be important to test for ongoing losses at this point with a urinalysis and fecal occult blood test. Choice a. is incorrect since iron therapy should show improvement in the hgb in 1 week and if that is not the case it is best to avoid iron overload by unnecessarily continuing iron. Choice b. though correct is not as good a choice as choice c. Choice d. is reasonable although it would be first important to check for microcytosis on the full CBC—if microcytic then it would be reasonable to test iron studies (ferritin, TIBC) in addition to checking hemoglobin electrophoresis for β -thalassemia trait given the non-responsiveness to iron therapy. The answer is c.

5. You are seeing a 15-month-old for a routine clinic visit. The family notes the child has been more tired and pale recently. There was an antecedent viral illness about one month prior but the child is now otherwise well. The child had a normal finger stick hb at one year of age, eats a varied diet, has had no noted blood loss and had no signs of jaundice. The child is pale and tachycardic but otherwise well appearing without LAD or HSM. A finger stick hemoglobin is 5.4 g/dl. Follow up CBC shows a normocytic anemia with normal WBC/diff and platelet count. The retic count is very low. What is the most likely diagnosis?

- a. Transient erythroblastopenia of childhood
- b. Iron deficiency anemia

- c. Hemolytic anemia
- d. Anemia of chronic disease
- e. Aplastic anemia

Explanation: Transient erythroblastopenia of childhood (TEC) is a common etiology of normocytic anemia in infants and is due to unclear causes, possibly infection triggered bone marrow suppression. The normal MCV in addition to the low reticulocyte count in a well appearing child is suggestive of this diagnosis. TEC in recovery phase presents with a high reticulocyte and can be confused with hemolytic anemia. Choice b. is less likely since the anemia is normocytic and not microcytic. Choice c. is unlikely without a history of jaundice, scleral icterus or dark urine and with a low reticulocyte count. Choice d., although possible, is not suggested by a normal history without other medical diagnoses. Choice e. is also possible

with a normocytic anemia but typically presents with additional cytopenias. Often these patients have macrocytosis. The answer is a.

Suggested reading

- Camaschella, C. (2015). Iron deficiency: new insights into diagnosis and treatment. *Hematology Am. Soc. Hematol. Educ. Program* 1: 8–13.
- DeLoughery, T.G. (2014). Microcytic anemia. *N Engl. J. Med.* 371: 1324–1331.
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