Approach to the child with anemia

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**Definition of anemia**

Hb < 2 SD or P2.5 below the mean for a healthy of the same gender and age

**WHO Criteria**

Hemoglobin and hematocrit cutoffs used to define anemia in people living at sea level

<table>
<thead>
<tr>
<th>Age or sex group</th>
<th>Hemoglobin below:</th>
<th>Hematocrit below:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/dL</td>
<td>%</td>
</tr>
<tr>
<td>Children 6 months to 5 years</td>
<td>11.0</td>
<td>33</td>
</tr>
<tr>
<td>Children 5-11 years</td>
<td>11.5</td>
<td>34</td>
</tr>
<tr>
<td>Children 12-13 years</td>
<td>12.0</td>
<td>36</td>
</tr>
<tr>
<td>Nonpregnant women</td>
<td>12.0</td>
<td>36</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>11.0</td>
<td>33</td>
</tr>
<tr>
<td>Men</td>
<td>13.0</td>
<td>39</td>
</tr>
</tbody>
</table>

From WHO/UNICEF/UNU, 1997
The medical history in the child with anemia: Elements associated with specific causes of childhood anemia

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• In neonates and young infants, immune hemolytic disease, infection, and hereditary disorders are most common</td>
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<tr>
<td></td>
<td>• Anemia detected at three to six months of age suggests a hemoglobinopathy</td>
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<tr>
<td></td>
<td>• Nutritional iron deficiency is an unlikely cause of anemia before the age of six months in term infants</td>
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<tr>
<td></td>
<td>• In older children, acquired causes of anemia are more likely, particularly iron deficiency anemia (dietary or due to blood loss)</td>
</tr>
<tr>
<td>Sex:</td>
<td>• Some inherited causes of anemia are X-linked (eg, G6PD deficiency and X-linked sideroblastic anemia), and occur most commonly in males</td>
</tr>
<tr>
<td>Race/ethnicity:</td>
<td>• Hemoglobin S and C are most commonly seen in black and Hispanic populations</td>
</tr>
<tr>
<td></td>
<td>• Thalassemia syndromes are more common in individuals of Mediterranean and Southeast Asian descent</td>
</tr>
<tr>
<td></td>
<td>• G6PD deficiency is more common among Sephardic Jews, Filipinos, Greeks, Sardinians, Kurds, and black populations</td>
</tr>
</tbody>
</table>

| Symptoms | Changes in urine color, scleral icterus, or jaundice suggest a hemolytic disorder |
|          | Bloody stools, hematemesis, severe epistaxis, or severe menstrual bleeding suggest anemia from blood loss and/or iron deficiency |
|          | Infectious symptoms (eg, fevers, cough) suggest an infectious etiology of anemia |

| History of anemia | Prior episodes of anemia suggest an inherited disorder |
|                   | Anemia in a patient with previously documented normal CBC suggests an acquired etiology |
|                   | Hyperbilirubinemia in the newborn period suggests a hemolytic etiology; microcytosis at birth suggests chronic intrauterine blood loss or thalassemia |

| Underlying medical conditions | Underlying renal disease, malignancy, or inflammatory/autoimmune disorders may be associated with anemia |

| Drugs and toxin exposure | Anemia following exposure to oxidant drugs or fava beans suggests G6PD deficiency |
|                         | Exposure to paint, home renovations, or use of imported or glazed ceramics suggest lead toxicity |

| Family history | Family members with jaundice, gallstones, or splenomegaly suggests an inherited hemolytic anemia |

| Dietary history | In infants and young children, iron deficiency is suggested by the following: |
|                | • Use of low iron formula |
|                | • Introduction of unmodified cow’s milk before the age of one year |
|                | • Excessive milk intake (>24 ounces per day) |
|                | • Poor intake of iron-rich foods (meats or fortified infant cereal) |

| Travel history | Travel to/from areas of endemic infection suggests infectious etiology such as malaria or tuberculosis |

| Developmental history | Developmental delay is associated with iron deficiency, vitamin B12/folic acid deficiency, and Fanconi anemia |

CBC: complete blood count; G6PD: glucose-6-phosphate dehydrogenase.
## Physical findings as clues to the etiology of anemia in children

<table>
<thead>
<tr>
<th>Finding</th>
<th>Possible etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Petechiae, purpura</td>
<td>Autoimmune hemolytic anemia with thrombocytopenia, hemolytic-uremic syndrome, bone marrow aplasia, bone marrow infiltration</td>
</tr>
<tr>
<td>Carotenemia</td>
<td>Suspect iron deficiency in infants</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Hemolytic anemia, hepatitis, and aplastic anemia</td>
</tr>
<tr>
<td>Cavernous hemangiomia</td>
<td>Microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Ulcers on lower extremities</td>
<td>Sickle cell disease (S and C hemoglobinopathies), thalassemia</td>
</tr>
<tr>
<td>Faces</td>
<td></td>
</tr>
<tr>
<td>Frontal bossing, prominence of the malar and maxillary bones</td>
<td>Congenital hemolytic anemias, thalassemia major, severe iron deficiency</td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
</tr>
<tr>
<td>Microcornea</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Tortuosity of the conjunctival and retinal vessels</td>
<td>Sickle cell disease (S and C hemoglobinopathies)</td>
</tr>
<tr>
<td>Microaneurysms of retinal vessels</td>
<td>Sickle cell disease (S and C hemoglobinopathies)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>Glucose-6-phosphate dehydrogenase deficiency, galactosemia with hemolytic anemia in newborn period</td>
</tr>
<tr>
<td>Vitreous hemorrhages</td>
<td>S hemoglobinopathy</td>
</tr>
<tr>
<td>Retinal hemorrhages</td>
<td>Chronic, severe anemia</td>
</tr>
<tr>
<td>Edema of the eyelids</td>
<td>Infectious mononucleosis, exudative enteropathy with iron deficiency, renal failure</td>
</tr>
<tr>
<td>Blindness</td>
<td>Osteopetrosis</td>
</tr>
<tr>
<td>Mouth</td>
<td></td>
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<tr>
<td>Glossitis</td>
<td>Vitamin B12 deficiency, iron deficiency</td>
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<tr>
<td>Angular stomatitis</td>
<td></td>
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<tr>
<td>Chest</td>
<td></td>
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<tr>
<td>Unilateral absence of the pectoral muscles</td>
<td>Poland’s syndrome (increased incidence of leukemia)</td>
</tr>
<tr>
<td>Shield chest</td>
<td>Diamond-Blackfan syndrome</td>
</tr>
<tr>
<td>Hands</td>
<td></td>
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<tr>
<td>Triphalangeal thumbs</td>
<td>Red cell aplasia</td>
</tr>
<tr>
<td>Hypoplasia of the thenar eminence</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Spoon nails</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Spleen</td>
<td></td>
</tr>
<tr>
<td>Enlargement</td>
<td>Congenital hemolytic anemia, leukemia, lymphoma acute infection, portal hypertension</td>
</tr>
</tbody>
</table>

Laboratory evaluation

- CBC , RBC indices
- Review of the peripheral blood smear
- Reticulocyte count
- used to focus the diagnostic and guide further testing to confirm the etiology of anemia
Complete blood count

most useful RBC parameter in anemia and is used to classify the anemia as follows:

- Microcytic anemia: anemia with low MCV [<70fl]
- Normocytic anemia: anemia with normal MCV [72-79 fl]
- Macrocytic anemia: anemia with high MCV [>85 fl]
Red cell Distribution Width (RDW)

- a quantitative measure of the variability of RBC sizes (anisocytosis)

- Normal values vary between 12 and 14 percent
Mean corpuscular hemoglobin concentration (MCHC)

- Hypochromic anemia: low MCHC ($\leq 32$ g/dL)
- Normochromic anemia: MCHC normal range (33 to 34 g/dL)
- Hyperchromic anemia: high MCHC ($\geq 35$ g/dL)
Reticulocyte count

- the youngest red cells in the circulation, identified by the presence of residual RNA normal; 1.5%

- Reticulocyte index: \( \text{Retic count} \times \text{Hct Pt} \)
  
  Normal Hct

- Retic \( \uparrow \): Hemolysis/Blood loss
- Retic \( \downarrow \): Decreased production
White blood count and platelet count

- Leukocytosis
  suggests an infectious etiology or an acute leukemia
- Thrombocytosis
  common finding in iron deficiency
- Leukopenia, neutropenia, and/or thrombocytopenia
  abnormal bone marrow function/increased peripheral destruction
Blood smear

- A review of the peripheral smear is an essential part of any anemia evaluation

- an inexpensive but powerful diagnostic tool

- becoming a "lost art" but it provides rapid, reliable information
Blood smear

- The smear offers a window into the functional status of the bone marrow, the factory producing all blood elements.

- In some cases, the peripheral smear alone is sufficient to establish a diagnosis.

- A trained eye will also appreciate other subtleties of morphology that may be undetected by automated review.

Normal mature RBC are biconcave, round discs that are about 6 – 8 in diameter, which is only slightly smaller than the normal small mature lymphocytes (about 6 - 10 in diameter).

The term used to indicate red blood cells of normal size and shape is normocytic. The term used to indicate a normal color or central pallor (i.e., normal hemoglobin content) is normochromic.
Iron deficiency anemia

Normal RBC
Beta Thalassemia/Hb E

Normal RBC
Congenital spherocytosis  Normal RBC
RBC autoagglutination; AIHA

Normal RBC
Microangiopathic hemolytic anemia

[MAHA] ; DIC

Normal RBC
How to approach?
Approach from etiologic classification

1. Impaired red cell formation

1.1. Deficiency

a. Dietary intake

b. Demand

c. Absorption

IRON, folate, Vit B12, Vit C, Protein, Vit B6
Approach from etiologic classification

1.2. Bone marrow failure

a. Failure of a single cell line

  - Congenital red cell aplasia (Diamond-Blackfan anemia)
  
  - Acquired red cell aplasia (Transient erythroblastopenia of childhood: TEC)

b. Failure of all cell lines: Aplastic anemia
Approach from etiologic classification

1. 3 Bone marrow infiltrative disease

   leukemia, metastatic tumor

   lysosomal storage disease

   (Gaucher disease)
Approach from etiologic classification

2. Hemolytic anemia

2.1. Corpuscular

   a. membrane defect (Spherocytosis)
   b. enzymatic defect (G6PD)
   c. Hemoglobin defect (Thalassemia)

2.2. Extracorpuscular

   a. Immune: Autoimmune hemolytic anemia
   b. Nonimmune
Approach from etiologic classification

3. Blood loss

3.1. Acute: hemorrhage

3.2. Chronic: GI hemorrhage
Approach from blood smear

**Hypochromic**
- IDA
- Thalassemia
- Lead toxicity
- Cu deficiency
- Severe PEM

**Macrocytic**
- Aplastic anemia
- Megaloblastic anemia
- Pure red cell aplasia
- Drugs (Phenytoin)

**Normocytic**
- Acute blood loss
- Renal failure
- CNT disease
- Liver disease
- Hemolysis (enz. def.)

*Specific morphologic abnormality*
## Approach from MCV & RDW

<table>
<thead>
<tr>
<th>MCV Low</th>
<th>MCV Normal</th>
<th>MCV High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RDW Normal</strong></td>
<td><strong>Microcytic</strong> Homogeneous</td>
<td><strong>Normocytic</strong> Homogeneous</td>
</tr>
<tr>
<td>Heterozygous thalassemia</td>
<td>Normal</td>
<td>Inherited bone marrow failure syndromes</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>Chronic disease</td>
<td>Preleukemia</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Chronic liver disease</td>
<td></td>
</tr>
<tr>
<td>Nonanemic hemoglobinopathy (e.g., AS, AC)</td>
<td>Nonanemic hemoglobinopathy (e.g., AS, AC)</td>
<td></td>
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<tr>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Chronic myelocytic leukemia</td>
<td>Chronic myelocytic leukemia</td>
<td></td>
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<tr>
<td>Hemorrhage</td>
<td>Hemorrhage</td>
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<tr>
<td>Hereditary spherocytosis</td>
<td>Hereditary spherocytosis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>RDW High</th>
<th>Microcytic Heterogeneous</th>
<th>Normocytic Heterogeneous</th>
<th>Macrocytic Heterogeneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Early iron or folate deficiency</td>
<td>Folate deficiency</td>
<td></td>
</tr>
<tr>
<td>S β-thalassemia</td>
<td>Mixed deficiencies</td>
<td>Vitamin B₁₂ deficiency</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin H</td>
<td>Hemoglobinopathies (e.g., SS)</td>
<td>Immune hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Red cell Fragmentation disorders</td>
<td>Myelofibrosis</td>
<td>Cold agglutinins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sideroblastic anemia</td>
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</tbody>
</table>

**Abbreviations:** MCV, mean corpuscular volume; RDW, red cell distribution width, which is coefficient of variation of RBC distribution width (normal, 11.5–14.5%).
Approach from Reticulocyte count

Reticulocyte count

High

Bilirubin

Normal

Hemorrhage

High

Hemolytic anemia

Direct antiglobulin test

Negative

(Table 7-2)

(a) Corpuscular

Hemoglobinopathies
Hemoglobin electrophoresis
Enzymopathies
Enzyme assays
Membrane defects
Morphology, autohemolysis, osmotic fragility

(b) Extracorpuscular

Idiopathic
Secondary (drugs, infection, microangiopathic)

Positive

(Table 9-1)

Extracorpuscular

Autoimmune hemolytic anemia
Primary
Secondary (e.g., connective tissue disease, drugs)
Isoimmune Hemolytic Disease
Rh, ABO, mismatched transfusion

Low

White cell and platelet count

Low

Bone marrow depression
Malignancy
Aplastic anemia
Congenital
Acquired

Normal

Increased

Pure red cell aplasia
Diamond blackfan
Transient erythroblastopenia of childhood (TEC)

Infection

Modified from Lanzkowsky Manual of Pediatric Hematology and Oncology 2011
Low HGB level (≤2.5th percentile for age, race, and sex)

Does the child truly have anemia?*

Yes

Are other cell lines affected?

No

What is the MCV?

Low MCV

Normal MCV

High MCV

Further evaluation and confirmatory tests

- Review dietary history
- Therapeutic trial of iron
- Serum ferritin, iron, and TIBC levels
- HGB electrophoresis

Further evaluation and confirmatory tests

- Indirect bilirubin, LDH, haptoglobin levels
- DAT
- G6PD screening test
- Osmotic fragility
- HGB electrophoresis

Further evaluation and confirmatory tests

- Review medications
- Review dietary history
- Serum B12 and folate levels
- Thyroid function tests
- Osmotic fragility
- HGB electrophoresis
- DAT
- Bone marrow biopsy/aspirate

Further evaluation and confirmatory tests

- Hemoglobinopathy (eg, hereditary spherocytosis, elliptocytes)
- Enzymopathy (eg, G6PD deficiency, pyruvate kinase deficiency)
- Hemoglobinopathy (eg, sickle cell disease)
- Autoimmune hemolytic anemia
- Microangiopathic hemolytic anemia
- Drug (eg, anticonvulsants, zidovudine, methotrexate)
- Vitamin B12/folate deficiency
- Sickle cell disease (especially if treated with HU)
- Immune hemolytic anemia
- Diamond-Blackfan anemia
- Sickle cell disease
- Hypothyroidism
- Pernicious anemia
- Myelodysplastic syndromes

Further evaluation and confirmatory tests

- Toxic granulations, bandemia, or atypical lymphocytes → Infection
- Basophilic stippling → Lead poisoning

Further evaluation and confirmatory tests

- Spherocytes → Hereditary spherocytosis or autoimmune hemolytic anemia
- Fragmented cells → Microangiopathic anemia
- Sickle cells → Sickle cell disease
- Elliptocytes → Hereditary elliptocytosis
- Heinz bodies → G6PD deficiency

Further evaluation and confirmatory tests

- Hemolytic Anemias
- Hemorrhage

Referral to algorithm for anemia in children with other cell lines affected

Additional Resources:

- Iron deficiency
- Thalassemia
- Sideroblastic anemia
- Anemia of chronic disease
- Infection
- Drugs
- Lead poisoning
- Acute blood loss
- Anemia of chronic disease
- Renal disease
- TEC
- Microangiopathic hemolytic anemia
- Drug (eg, anticonvulsants, zidovudine, methotrexate)
- Vitamin B12/folate deficiency
- Sickle cell disease (especially if treated with HU)
- Immune hemolytic anemia
- Diamond-Blackfan anemia
- Liver disease
- Hypothyroidism
- Pernicious anemia
- Myelodysplastic syndromes

Notes:

*If low HGB level is suspect, confirm with repeat sample and consider additional testing.

**Consider referral to a hematologist.

***Low or normal reticulocyte count (≤1%)
DIAGNOSTIC APPROACH

- History
- Physical Examination
- Initial laboratory tests

Still the new paradigms in recognition and treatment of Pediatric anemia
Iron deficiency anemia

- most common nutritional deficiency in children
- WHO estimates that anemia affects 1/4 of the world's population and is concentrated within preschool-aged children and women
- majority of the anemia is due to iron deficiency
- can have important consequences to health and development
Iron deficiency anemia

Definition

Iron deficiency

Serum ferritin <12 micrograms/L (up to five years old), and <15 micrograms/L (five years and older)

Anemia

Hb that is <2 SD or P2.5 or more below the mean for a healthy population of the same age and sex
Causes of IDA

1. Low intake (milk: 0.75 mg iron/l)

2. Inadequate/Impaired absorption

3. Increased demand

4. Blood loss
CLINICAL MANIFESTATIONS OF IDA

• Most common presentation: asymptomatic, well-nourished infant or child with mild to moderate hypochromic microcytic anemia

• Much less frequent are infants with severe anemia, and lethargy, pallor, irritability, cardiomegaly, poor feeding, tachypnea
CLINICAL MANIFESTATIONS OF IDA

- Neurodevelopment
  - Impaired psychomotor and/or mental development
  - Cognitive impairment can occur in adolescent/negative impact on infant social-emotional behavior/associated with ADHD
  - A meta-analysis of randomized trials in older children and adults showed evidence of modest improvement of attention, concentration and cognitive function with iron supplement*

CLINICAL MANIFESTATIONS OF IDA

- Immunity and infection
  - effects on immune function and susceptibility to infection
  - defects in leukocyte and lymphocyte function, including defective IL-2 and IL-6 production
risk for bacterial infection under conditions of maximal iron saturation

- iron-binding proteins in humans (transferrin and lactoferrin) have bacteriostatic effect, which are lost when they are saturated with iron binding side
- competitive for binding iron over iron-binding siderophores in bacteria
- in a systematic review of randomized controlled trials, iron supplementation had no apparent harmful effect on the incidence of infectious illnesses in children but association with increase risk of diarrhea*

CLINICAL MANIFESTATIONS OF IDA

- Exercise capacity decreased
- Pica and pagophagia
- Thrombosis

- In a large case-control study from a comprehensive Stroke Registry in Canada, previously healthy children with stroke (arterial or venous) were 10 times more likely to have IDA than healthy children. (May be related to thrombocytosis in IDA)*

Laboratory screening

- The American Academy of Pediatric

- Universal laboratory screening for IDA is recommended for all children at 9 to 12 m of age

- Method

  - The minimum laboratory is measurement of Hb levels
    
    (<11 g/dL are abnormal)

  - most cost-effective measurement is CBC
A presumptive diagnosis of IDA

- risk + hemoglobin <11 g/dL, low MCV,
  elevated RDW

- elevated RDW is the earliest hematologic manifestation of IDA
DIAGNOSIS

- **To confirm the diagnosis**
  - Assess risk factors for lead exposure and measure blood lead level if this was not recently done
  - If dietary deficiency seems likely and there is no evidence of lead toxicity, perform an empiric trial of oral iron supplementation
Empiric treatment

- infants and toddlers up to 24 months of age with presumptive diagnosis of IDA
  - directly to empiric trial because iron deficiency is a particularly likely cause of anemia in this age group
- children 24 months and older
  - evaluating MCV, RDW, a reticulocyte count, peripheral blood smear, and testing stool for occult blood before empiric trial
Empiric treatment

- children with severe anemia (Hb<7g/dl ), complicated medical history, or features atypical for IDA
  - perform additional laboratory testing before the therapeutic trial

The most reliable criteria for diagnosis of IDA is the Hb response to an adequate therapeutic trial of oral iron*

*Lanzkowsky Manual of Pediatric Hematology and Oncology, 2011*
Additional laboratory testing

- serum iron, ferritin, total iron-binding capacity, and transferrin saturation, (most of these can be affected by factors other than iron status)
- test several stools for occult blood
- Other laboratory tests, such as soluble transferrin receptor (sTfR) and reticulocyte Hb concentration may prove to be more reliable measures of iron deficiency, but they are not routinely used
The diagnosis is confirmed;

- if a trial of oral iron supplementation (3 mg/kg elemental iron per day) produces a Hb rise of >1 g/dL within four weeks for children with mild anemia, or within two weeks for those with severe anemia.
ORAL IRON THERAPY

• 3 essential steps for successful treatment
  ● Appropriate dose and scheduling of oral iron therapy
  ● Dietary modifications
    address the underlying etiology of the iron deficiency
  ● Follow-up assessment for response
ORAL IRON THERAPY

- Dose and scheduling
  - Standard recommended dosing is 3 to 6 mg/kg elemental iron per day
  - use ferrous sulfate and the 3 mg/kg dose because it was effective in a RCT of 80 young children (ages 9 to 48 months) with nutritional IDA

UpToDate, 2017
ORAL IRON THERAPY

- Side effects
  - abdominal pain
  - constipation
  - Diarrhea

- low-dose iron supplementation (e.g., 3 mg/kg) and iron-fortified formulas rarely cause gastrointestinal symptoms

UpToDate, 2017
Follow-up assessment for response

- depends on the severity of the IDA

- **mild anemia** (Hgb $\geq 9$ g/dL) should be reevaluated by checking Hgb or CBC at 4 wks

- **moderate or severe anemia** (Hgb <9 g/dL) should be retested one or two weeks
Follow-up assessment for response

- Responders
  - **Mild anemia** \((\text{Hb} \geq 9 \text{ g/dL})\): The Hb should rise at least 1 g/dL within four weeks of treatment
  - **Moderate or severe anemia** \((\text{Hb} < 9 \text{ g/dL})\): The Hb should rise at least 1 g/dL within the first two weeks of treatment
  - A reticulocyte response may be seen as soon as 72 hours after treatment initiation.
Follow-up assessment for response

- therapeutic iron should be continued
- continuing iron therapy for about one month after all CBC parameters have normalized (Hgb, MCV, and RDW)
- Total duration of therapy is typically at least three months
Thank You