Anemia: Pathophysiology & Diagnostic Classification

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Key Concepts

A.) Define anemia

B.) Describe the metabolic and physiologic responses to anemia, with emphasis on those that give rise to the clinical findings

C.) Introduce the systemic classification of anemia on the basis of morphology and red blood cell production
Important Concepts from the Lecture:

A.) The metabolic and physiologic changes that occur in response to anemia
   1.) Changes in cardiac output and perfusion of different organs (e.g., brain, skin, kidney and muscle)
   2.) How increased RBC mass affects oxygen delivery
   3.) How decreased oxygen affinity affects the ability to deliver oxygen to tissues
Important Concepts from the Lecture (Continued):

A.) **Metabolic and physiologic responses to anemia (cont.)**

4.) How changes in blood volume and viscosity relate to oxygen transport (e.g., why a patient with a lower hematocrit may have more efficient oxygen transport and delivery than a patient with a higher hematocrit, but a smaller blood volume)

5.) An understanding of the oxyhemoglobin dissociation curve
B.) **How to classify anemias on the basis of etiology and RBC parameters:**

1.) **Decreased production**
   vs. RBC loss (increased destruction or bleeding)

2.) **RBC Size:**
   Macrocytic vs. microcytic vs. normocytic

3.) **Hemoglobin Content:**
   Hypochromic vs. normochromic

4.) **Shape:** Normal or abnormal
Part 1: The Metabolic and Physiologic Responses to Anemia

What is anemia?

Anemia from the Greek word (Ἀναιμία)(an-haîma) meaning "without blood", is a deficiency of red blood cells (RBCs) and/or hemoglobin.
Part 1: The Metabolic and Physiologic Responses to Anemia

What is anemia?
The Complete Blood Count:

1.) Hematocrit (Hct) or packed cell volume (PCV): Volume of packed red blood cells per unit of blood, expressed as a percentage.

   Example: 44 ml packed red blood cells/ 100 ml of blood
   
   = 44%

2.) Hemoglobin = grams of hemoglobin 
   dL of blood
Hematocrit (Hct) or packed cell volume (PCV): Volume of packed red blood cells per unit of blood, expressed as a percentage.

College students invent salad spinner centrifuge

Rice University undergraduates Lila Kerr and Lauren Theis turned an ordinary salad spinner into a device for diagnosing anemia.
What is anemia?
What is anemia?

Anemia

Red blood cells take up oxygen from the lungs and release carbon dioxide back to the lungs.

Lungs

Carbon dioxide

Oxygen

Red blood cells transport oxygen to the rest of the body.
What is anemia?
Who has anemia?
Part 1: The Metabolic and Physiologic Responses to Anemia

**Oxygen Delivery:**

\[ V_{O_2} = 1.39 \times Q \times Hb \times (S_{aO_2} - S_{vO_2}) \]

Oxygen carrying capacity: 1.39 ml O\_2 binds to 1 gm of Hb
Q = blood flow (ml/min)
Hb = hemoglobin (gm/dL)
S\_aO\_2 = % saturation of arterial blood (100 mm Hg)
S\_vO\_2 = % saturation of venous blood (40 mm Hg)
To Increase Oxygen Delivery:

1.) Increase in blood flow (or $Q$)

2.) Increase in red cell mass (or $Hb$)

3.) Increase oxygen unloading ($SaO_2 - SvO_2$)

$$V_{O_2} = 1.39 \times Q \times Hb \times (SaO_2 - SvO_2)$$
1.) Increase in blood flow (or $Q$)
   A.) Increased Cardiac Output
       Hg 7 gm/dL
       Clinical Findings:
       ↑ HR, ↑ Pulse pressure, murmurs, bruits, hyper-dynamic precordium, tinnitus or roaring
1.) Increase in blood flow (or Q)

B.) Changes in Tissue Perfusion

Oxygen Insensitive: skin (pallor), kidney

→

Oxygen Sensitive (heart, brain, muscle)

Clinical Findings:
Pallor
To Increase Oxygen Delivery:

1.) Increase in blood flow (or $\dot{Q}$)

2.) Increase in red cell mass (or Hb)

3.) Increase oxygen unloading $(SaO_2 - SvO_2)$

$V_{O_2} = 1.39 \times \dot{Q} \times Hb \times (SaO_2 - SvO_2)$
2.) Increase in red cell mass (or Hb)

EPO (kidney) $\rightarrow$ Reticulocytosis, immature RBCs

Clinically: Bony pain with expansion of the marrow
Expanded marrow cavity: “Hair on End” appearance
Erythropoiesis in bone marrow
Hyperviscosity: Red cell mass is too high!

FIGURE 40-4  Viscosity of heparinized normal human blood related to hematocrit (Hct). Viscosity is measured with an Ostwald viscosimeter at 37°C and expressed in relation to viscosity of saline solution. Oxygen transport is computed from Hct and $O_2$ flow ($1/\text{viscosity}$) and is recorded in arbitrary units.
FIGURE 40-5 Oxygen transport at various hematocrit levels in normovolemic, mildly hypervolemic, and severely hypervolemic individuals. The oxygen transport is estimated by multiplying hematocrit by cardiac output. As can be seen in 1, the optimal oxygen transport for the normovolemic subjects is at a hematocrit of about 45 percent with a progressive rise in the optimal hematocrit as the blood volume increases. A suboptimal hematocrit in a hypervolemic person (anemia of pregnancy), as in 2, may be associated with a higher oxygen transport than that of a normovolemic person with normal hematocrit. However, a high hematocrit without increase in blood volume (3) may be associated with an absolute reduction in oxygen transport and tissue hypoxia. Only high hematocrit coupled with high blood volume (4) enhances oxygen transport to the tissues. (Adapted from Murray et al.,\textsuperscript{37} and Thorling and Erslev.\textsuperscript{38})
To Increase Oxygen Delivery:

1.) Increase in blood flow (or $\dot{Q}$)

2.) Increase in red cell mass (or Hb)

3.) Increase oxygen unloading
   ($SaO_2 - SvO_2$)

$$V0_2 = 1.39 \times \dot{Q} \times Hb \times (SaO_2 - SvO_2)$$
3.) Increase oxygen unloading (\(\text{SaO}_2 - \text{SvO}_2\))
   A.) Decreased Oxygen Affinity
      2,3 - DPG

Fig. 1.59
Normal adult haemoglobin A: there are two \(\alpha\) and two \(\beta\) chains. 2,3-DPG fits into a pocket between the \(\beta\) chains and displaces oxygen.
Glycolysis: The source of 2,3-DPG
How & why does the RBC metabolize glucose:
No mitochondria, therefore glycolysis = sole source for energy

Anaerobic metabolism (90%):
Glycolytic pathway (Embden-Myerhoff)
Glucose → Pyruvate & Lactate

2, 3-DPG:
1° RBC phosphate generated via the Rapoport-Luebering (2,3-DPG shunt) in the glycolytic pathway

Aerobic metabolism (10%):
Pentose Phosphate (Hexose Monophosphate)
Shunt → NADPH

Why?
Generate energy (ATP) to maintain:
- cell shape, flexibility
- cation & H₂O content
Q: A 20-year-old African-American man presents complaining of weakness, mild lower abdominal pain and a change in the color of his urine. He noticed these symptoms abruptly this morning. Of note, he had been having some burning with urination for about the last week. He went to an urgent care center 2 days ago where he was prescribed trimethoprim-sulfamethoxazole for suspected prostatitis. He reports that "sickle cell" runs in his family. He also notes that he works at a fast food restaurant, where he eats two meals per day (usually hamburgers). He is afebrile. His blood work reveals a WBC of 10,000, hemoglobin of 9 g/dL, hematocrit of 28 %, MCV of 90 fl, and platelets of 200,000. His reticulocyte count is 12%. His LDH and indirect bilirubin are elevated. His haptoglobin is low at 5 mg/dl. His urine dipstick is positive for hemoglobin. His creatinine is normal.

Further testing is performed which reveals a negative direct antiglobulin test, a negative G6PD screen, and a hemoglobin electrophoresis that shows 59% HbA, 40% HbS, and 1% HbF. His peripheral smear shows:

The condition most likely responsible for this patient's hemolytic process is:
A. Glucose-6-phosphate dehydrogenase deficiency
B. Hemolytic-uremic syndrome
C. Sickle cell hemolytic crisis
D. Immune hemolytic anemia
To Increase Oxygen Delivery:

1.) Increase in blood flow (or $\dot{Q}$)

2.) Increase in red cell mass (or Hb)

3.) Increase oxygen unloading ($\text{SaO}_2 - \text{SvO}_2$)

$$V_0_2 = 1.39 \times \dot{Q} \times \text{Hb} \times (\text{SaO}_2 - \text{SvO}_2)$$
Oxyhemoglobin Dissociation Curve

2 important properties:

1.) **Oxygen affinity** \((P_{50})\): Convenient index of oxygen affinity = Partial pressure of oxygen at which hemoglobin is 1/2 or 50% saturated. If the curve is shifted to the right, \(P_{50}\) is increased and oxygen affinity is decreased (oxygen unloading is increase). Thus, \(P_{50}\) varies inversely with oxygen affinity.

2.) **Cooperativity**: When hemoglobin is partially saturated with oxygen, the affinity of the remaining hemes in the tetramer for oxygen increase markedly. This phenomenon is explained by the existence of 2 Hb conformations:

   i.) Deoxy or T = tense form
   ii.) Oxy or R = relaxed form
The graph illustrates the relationship between the oxygen saturation of hemoglobin (HbO₂) and the partial pressure of oxygen (P₅₀). The curve shows that as the partial pressure of oxygen increases, the hemoglobin saturation also increases. At P₅₀ = 26 mm Hg, the graph indicates the point where 50% of the hemoglobin is saturated with oxygen.

Key points:
- HbF: Hemoglobin F
- HbS: Hemoglobin S
- 2,3 DPG: 2,3-Diphosphoglycerate
- pH: Hydrogen ion concentration
- Bohr effect: Shift of hemoglobin oxygen dissociation curve to the left, facilitating oxygen release in the tissues

Factors affecting the curve:
- ↑ oxygen
- ↓ temperature
- ↓ oxygen
- ↑ temperature

The graph also highlights the difference between venous and arterial blood, with arterial blood having a higher oxygen saturation than venous blood.
Oxyhemoglobin Dissociation Curve

2 important properties:

1.) Oxygen affinity \((P_{50})\): Convenient index of oxygen affinity

\[ P_{50} = \text{Partial pressure of oxygen when the hemoglobin is 50\% saturated.} \]

If the curve is shifted to the right, \(P_{50}\) is increased and oxygen affinity is decreased. Thus, \(P_{50}\) varies inversely with oxygen affinity.
\( P_{50} = 26 \text{ mm Hg} \)
2.) Cooperativity: When hemoglobin is partially saturated with oxygen, the affinity of the remaining hemes in the tetramer for oxygen increases significantly. This phenomenon is explained by the existence of 2 Hb conformations:

i.) Deoxy or T = tense form
ii.) Oxy or R = relaxed form
FIG. 5–20. Diagrammatic representation of the subunit interaction in hemoglobin as oxygen is added. Deoxyhemoglobin (upper left), with low oxygen affinity, is in the T (taut) conformation, constrained by salt bridges (shown as interconnecting lines) and the 2,3 DPG molecule. As O₂ is added, salt bridges are broken, and eventually the DPG molecule is expelled, resulting in the R (relaxed) configuration with higher oxygen affinity.
Bohr effect

\[
\text{P}_{50} = 26 \text{ mm Hg}
\]
**NO & Hemoglobin**

**Cell Free Zone:**
Pressure/velocity gradients in laminar flow drive red cells to the center of the vessel, creating this “cell free zone”

**NO synthesis:**
Endothelial cells synthesize by NOS. NO → smooth muscle, activates guanylate cyclase → vasodilation
Part 2: Classification of Anemia

Diagnostic Approach To Anemia:
General considerations

1.) Is there decreased RBC production, increased loss (RBC destruction or RBC loss – i.e. bleeding)?

2.) Is the anemia
   - Microcytic (small red blood cell size)?
   - Macrocytic (large red blood cell size)?
   - Normocytic (normal red blood cell size)?
Part 2: Classification of Anemia

Diagnostic Approach To Anemia:

General Considerations:

3.) Is the anemia
   - Hypochromic (decreased Hb per RBC)?
   - Normochromic (normal Hb per RBC)?

4.) Is the anemia associated with
   - Normal RBC morphology?
   - Abnormal RBC morphology?
These questions can be answered using a few readily available clinical tests:

1.) Is the patient anemic?
    Complete blood count (CBC), Hb, Hct

2.) Is there decreased RBC production, increased RBC destruction, or RBC loss?
    Reticulocyte count

3.) Is the anemia micro, macro, or normocytic?
    RBC Indices
These questions can be answered using a few readily available clinical tests:

4.) Is the anemia hypo or normochromic? 
   RBC Indices

5.) Is the RBC morphology normal or abnormal? 
   Peripheral blood smear
The Complete Blood Count:

1.) Hematocrit (Hct) or packed cell volume (PCV):
    Volume of packed red blood cells per unit of blood, expressed as a percentage.

    Example: 44 ml packed red blood cells/ 100 ml of blood
    = 44%

2.) Hemoglobin = grams of hemoglobin
dL of blood
3.) **Reticulocyte** = Young RBC

Anemia due to hemolysis or bleeding is characterized by the presence of a reticulocytosis. The reticulocyte count is used to assess the appropriateness of the bone marrow response to anemia. The normal reticulocyte count in a patient with a normal Hb and Hct is about 1%. Approximately 1% of circulating RBCs are removed daily and replaced by marrow young RBCs or reticulocytes (approximately 20 cc of RBCs /day).
4.) **Mean Cell (or Corpuscular) Volume (MCV):**

The MCV reflects the average size or volume of the RBC expressed in fl. MCV will tell you if the patient is micro, macro, or normocytic. MCV is calculated as follows:

\[
\text{MCV} = \frac{\text{Hct}}{\text{RBC Count}} = \frac{\text{Volume of packed red cells (\% X 10)}}{\text{Red cell count (x 10}^{12}/\text{l})}
\]
5.) **Mean Cell Hemoglobin (MCH):**

The MCH indicates the *weight* of Hb in the average red cell. MCH is calculated as follows:

\[
MCH = \frac{Hb \times 10}{RBC\ text\ count} = \frac{Hb \ (gm/dl \times 10)}{Red\ cell\ count \ (x\ 10^{12}/l)}
\]
6.) **Mean Cell Hemoglobin Concentration (MCHC):**

The MCHC indicates the *concentration* of Hb in the average red cell or the ratio of the weight of the Hb to the volume in which it is contained (chromicity), expressed in percent as follows:

\[
\text{MCHC} = \frac{\text{Hb}}{\text{Hct}} = \frac{\text{Hb (gm/dl X 100)}}{\text{Volume of packed red cells (ml per 100 ml)}}
\]
7.) Normal red blood cell morphology: is characterized by a donut shape with the center 1/3 of the red cell being pale or without hemoglobin. This is assessed on peripheral smear.
Common Causes for Various Types of Anemia

1.) **Hypochromic, microcytic:**
   - Iron Deficiency
   - Thalassemia syndromes
   - Sideroblastic anemia
   - Transferrin deficiency

2.) **Macrocytic:**
   - Megaloblastic Anemias (Folic acid/ B\textsubscript{12} deficiencies)
   - Liver Disease
   - Reticulocytosis
   - Normal newborn
   - Bone marrow failure syndromes
   - Drugs (AZT, Trimethoprin sulfate)
Common Causes for Various Types of Anemia (Continued):

3.) **Normocytic, normal morphology:**
   - Hemorrhage or blood loss
   - Unstable hemoglobins
   - Infections
   - Chronic disease

4.) **Normocytic, abnormal morphology:**
   - Hemoglobinopathies, (SS, SC, CC)
   - Hereditary Spherocytosis
   - Autoimmune hemolytic anemia
   - Some enzymatic deficiencies
Q: A 52-year-old woman presents to you with complaints of fatigue of several months duration. Past history is unremarkable, except for menorrhagia for the past two years. Mild pallor is evident on physical exam.

Which ONE of the following general statements is true?  
A. Iron stores decline with aging.  
B. Iron deficiency is a direct stimulus for erythropoietin production.  
C. Iron deficiency is associated with an increase in Hemoglobin F.  
D. She may admit to pagophagia or restless legs
A 72-year-old gentleman with a history of hypertension, coronary disease, and a mitral valve replacement presents complaining of fatigue and dyspnea on exertion. On examination, he is pale. His vital signs reveal a temperature of 36.5°C, pulse 95/minute, respiratory rate 20/min, and BP 146/78. There is no jugular venous distension and his lungs are clear. His heart is regular, rate, and rhythm with a II/VI systolic murmur. Prosthetic heart sounds are present. There is no peripheral edema.

WBC—5,550
Creatinine—1.6 mg/dL (at baseline)
Hgb—6.7 g/dL
Plt—236,000
Direct antiglobulin test—negative
Reticulocyte count—6.8%
Iron, TIBC, % saturation—normal
Ferritin—99 ng/ml

Which of the following is the most appropriate next step in this patient's work-up/treatment?
A. Obtain an echocardiogram
B. Start prednisone at 1 mg/kg/day
C. Begin plasmapheresis
D. Obtain a bone marrow biopsy
E. Obtain a hemoglobin electrophoresis