Top 10 Anemias to Know for Boards
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Introduction

Clinical stuff

Anemia (from *an-* , without, and *emia*, blood) is a reduction below normal in hemoglobin or red blood cell number. Patients with anemia can present in different ways, depending on what kind of anemia they have and how severe it is. The general signs and symptoms of anemia relate to the underlying lack of oxygen-carrying capacity: fatigue, weakness, dizziness, tachycardia, pallor of skin and mucous membranes. It's important to remember that if an anemia is fairly mild, symptoms will not be present. Also, if the anemia is chronic and slowly-progressive, the cardiovascular system adjusts to the new diminished level of oxygen, and symptoms will only appear when the anemia becomes quite severe.

In addition to the general symptoms of anemia, some specific findings may be present. If the anemia is hemolytic, the patient may be jaundiced. Patients with iron-deficiency anemia may show spoon-shaped nails (koilonychia), a smooth tongue, or pica (a craving to eat dirt and other non-food items). And patients with megaloblastic anemia may develop a big, beefy tongue.
The Complete Blood Count (CBC)

The CBC is comprised of a bunch of different indices. You get all of these on every report, whether you ask for them specifically or not (that’s just the way the machine does it!). Some of these indices are really useful (like the hemoglobin, MCV and RDW), and some of them are rarely if ever used (like the mean platelet volume). You should know what each one measures, and be able to recognize the normal range.

**Red blood cell count (RBC)**
- Total number of red blood cells in blood
- Normal ranges: male 4.5-6.0 x 10^12/L, female 3.8-5.2 x 10^12/L

**Hemoglobin (Hgb)**
- Concentration of hemoglobin in blood
- Normal ranges: male 13-18 g/dL; female 12-16 g/dL
- Hgb below normal = anemia

**Hematocrit (Hct)**
- Volume of “packed” red blood cells.
- In the old days, was performed by spinning a tube of blood and estimating the amount of total blood volume taken up by the red cells (not a great method – because if the cells are of unusual shape, they may not pack as well as normal red cells, producing an artificially elevated Hct)
- Now calculated by machine (MCV x RBC)
- Normal ranges: male 40-52%, female 35-47%

The most useful red cell indices are the hemoglobin, MCV and RDW.
Mean red blood cell volume (MCV)
- Average size of red blood cells
- Normal range: 80-100 fL (1 fL = 10⁻¹⁵ L)
- Differentiates between microcytic (MCV < 80), normocytic (MCV 80-100) and macrocytic (MCV > 100) anemias

Mean cell hemoglobin (MCH)
- Weight of Hgb in the average red blood cell
- Normal range: 26-34 pg (1 pg = 10⁻¹² g)
- Not a frequently used parameter

Mean cell Hgb concentration (MCHC)
- Concentration of Hgb in the average red blood cell
- Normal range: 32-36 g/dL
- Calculated by machine (Hgb/Hct)
- Differentiates between hypochromic (MCHC < 32) and normochromic (MCHC 32-36) anemias
- There is no such thing as a hyperchromic red cell (you can’t put excess hemoglobin into a cell, or it would burst!)
- You can see this nicely on a blood smear: normochromic cells have a “zone of central pallor” (that white dot in the middle of the cell) that is no more than 1/3 the diameter of the red cell. Hypochromic red cells have just a thin rim of hemoglobin.

Red cell distribution width (RDW)
- Standard deviation of the MCV
- Tells you how much the red blood cells differ from each other in size. If they are all pretty similar in size, the RDW is low. If some are little and some are big, the RDW is high.
- Normal range = 12-13.5%
- Differentiates between anemias with minimal anisocytosis (difference in cell size) (RDW 12-13.5%) and those with increased anisocytosis (RDW > 13.5%).
**White blood cell count (WBC)**
- Total number of leukocytes in blood
- Normal ranges: adult: $4.5-11 \times 10^9/L$, newborn: $9 - 30$, child over 1: $5.0-17.0$
- A high WBC is seen in many conditions. Some are benign, such as infection and inflammation. Others are malignant, such as leukemia.

**Differential (“diff”)**
- Amounts of each white blood cell type in blood
- Normal ranges:

<table>
<thead>
<tr>
<th></th>
<th>Percentage of WBC</th>
<th>Absolute (x $10^9/L$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>45-75</td>
<td>2-8</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20-50</td>
<td>1-4</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1-8</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0-6</td>
<td>0-0.5</td>
</tr>
<tr>
<td>Basophils</td>
<td>0-1</td>
<td>0-0.3</td>
</tr>
</tbody>
</table>

**Platelet count (Plt)**
- Total number of platelets in blood
- Normal range = $150-450 \times 10^9/L$
- Causes of a low platelet count are numerous and include splenomegaly, idiopathic thrombocytopenic purpura, disseminated intravascular coagulation, and bone marrow failure. Causes of a high platelet count are also numerous, and include reactive thrombocytosis (as seen in iron-deficiency anemia) and essential thrombocythemia.

**MPV (mean platelet volume)**
- Average size of platelets
- Normal range depends on the platelet count! (Normally, if the platelet count falls, the body compensates a little by trying to make bigger platelets.)
- Not used all that often.
The Blood Smear

There are three main things you need to look at when you’re faced with a blood smear: the red cells, the white cells, and the platelets. It helps if you have a plan that you follow every time, kind of like radiologists do when they look at imaging studies. That way you’re not tempted to just start looking at the exciting stuff and forget about all the other stuff. Here’s your plan for the red cells.

1. **Estimate number** (just eyeball it; make sure there aren’t a lot of “holes” between the cells).

2. **Look for variation in size (anisocytosis).**
   - *Oval macrocytes* (B<sub>12</sub>/folate deficiency)
   - *Microcytes* (iron deficiency anemia, thalassemia)
   - The size range can often help you narrow down which type of anemia is present (for example, in iron-deficiency anemia, there is usually a big range of sizes)

3. **Look for variation in shape (poikilocytosis).**
   - *Schistocytes* (microangiopathic hemolytic anemia)
   - *Spherocytes* (hemolytic anemia, hereditary spherocytosis)
   - *Teardrop cells or dacryocytes* (myelofibrosis or myelophthisic processes)
   - *Target cells or codocytes* (hemoglobinopathies, thalassemias, liver disease)
   - *Sickle cells* (sickle cell anemia)
   - *Echinocytes and acanthocytes* (liver disease)

4. **Estimate the average amount of hemoglobin in each cell (chromasia).**
   - *Normochromic* (zone of central pallor comprises ≤ 1/3 of the cell diameter)
   - *Hypochromic* (zone of central pallor comprises >1/3 of the cell diameter)

5. **Estimate number of reticulocytes (look for polychromatophilic cells).**
   - Normal: one or two polychromatophilic cells per field.
   - The lower the Hgb, the higher the reticulocyte count should be.

6. **Look for anything else weird.**
   - Nucleated red blood cells
   - Inclusions (Howell-Jolly bodies, Pappenheimer bodies, bugs)

When looking at blood smears, it helps to **follow the same plan** every time.

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**Reticulocytes vs. polychromatrophic cells**

“Reticulocyte” and “polychromatophilic cell” are two names for the same thing – immature red cells that still contain a little ribosomal RNA. When you do a supravital stain on a blood smear, the RNA stains blue, and the cells are called “reticulocytes”. When you do a normal Wright-Giemsa stain, the cells look big and slightly basophilic, and they are called “polychromatophilic cells.” This is one of those fine points that, when casually mentioned on rounds your third or fourth year, will make you look very smart.
One. Iron-Deficiency Anemia

Pathogenesis
Blood loss (e.g., GI bleed or menses) or really bad diet (rare)

Morphology
• Hypochromic, microcytic anemia
• Increased anisocytosis (some little cells, some bigger cells)
• Increased poikilocytosis (elliptocytes are present, for some reason)
• Decreased reticulocyte number (because there’s not enough iron around!)
• Platelet count usually increased for some reason

Iron studies
• ↓ serum iron
• ↑ TIBC (total iron binding capacity)
• ↓ ferritin

Treatment
Figure out why patient is iron deficient (don’t just treat the anemia, or you might miss something really important, like a GI bleed due to colon cancer). Then give iron (orally).
Two. Megaloblastic Anemia

Pathogenesis
Vitamin B\textsubscript{12} and/or folate deficiency (from bad diet, absorption problems, folate-antagonist drugs) makes it hard to make DNA (you need both B\textsubscript{12} and folate to make DNA). RNA production runs smoothly though. So the nucleus (full of DNA) lags behind the cytoplasm (full of RNA) in development, and the cell divides more slowly (because it’s waiting for signals from the slow-moving nucleus).

Morphology

Blood
- Macrocytic anemia (MCV >100)
- Oval macrocytes.
- Hypersegmented (more than 4 lobes) neutrophils.

Bone marrow
- “Megaloblastic” cells: giant red cell or neutrophil precursors with nuclear-cytoplasmic asynchrony (mature cytoplasm, immature nucleus).

Treatment
Treatment depends on the cause of the anemia. You can’t (or shouldn’t) just replace the B\textsubscript{12} and/or folate without knowing what’s wrong with the patient.
Three. Hereditary Spherocytosis

**Pathogenesis**
Patients with HS have defective spectrin (a protein which attaches the red cell membrane to the cytoskeleton). The red cell membrane is unstable, leading to increased fragility and the formation of spherocytes, which get eaten by macrophages.

**Morphology**
- Mild normochromic, normocytic anemia.
- Numerous spherocytes.

**Treatment**
If the disease is mild, patients don’t need treatment. In severe cases, splenectomy can be useful (because that’s where the red cells get destroyed).
Four. G6PD Deficiency

**Pathogenesis**
Glucose-6-phosphate dehydrogenase (G6PD) helps reduce nasty free radicals made during cell metabolism. Patients who have a deficiency of G6PD are usually okay until they encounter some sort of oxidizing substance (like a drug, or fava beans). Without G6PD, free radicals attack the molecular bonds between heme and globin, and globin becomes denatured, forming a little blob called a Heinz body. The spleen bites out these Heinz bodies, leaving what look like actual bite marks in the cell.

**Morphology**
Without exposure to offending agents, most patients have no anemia. After exposure, though, patients get an acute hemolytic episode, with cell fragments, microspherocytes, and bite cells (caused by recent pitting of Heinz bodies). Supravital staining reveals Heinz bodies (these decrease in number as Hgb bottoms out, because younger cells have greater G6PD activity).

**Treatment**
Avoid exposure to known oxidants. Usually the hemolysis is self-limiting, with spontaneous resolution in a week or so.
Five. Sickle-Cell Anemia

Pathogenesis
Sickle cell anemia is a type of hemoglobinopathy (diseases with point mutations in one of the globin chain genes). The abnormal hemoglobin (called HbS) in sickle cell anemia changes shape when it releases oxygen. The HbS molecules then aggregate and polymerize, forming the cell into a fragile, non-deformable, sickle shape. Sickle cells bust open more easily; they also stick together in small vessels, leading to ischemia (often occurring in hands, feet, lungs, and spleen). The spleen may undergo massive enlargement (due to red cell sequestration) in early childhood. By early adulthood, however, the spleen is reduced to a small, fibrotic remnant (due to recurrent hemorrhage and fibrosis); this is called “autosplenectomy”.

Morphology
In the blood, particularly during crises, sickle cells are present. After autosplenectomy occurs, there is what’s called a "post-splenectomy blood picture": nucleated red blood cells, targets, Howell-Jolly bodies, Pappenheimer bodies, and a slightly increased platelet count (the platelets love to hang out in the spleen, so when you take away their little home, they have no choice but to hang out in the blood).

Treatment
It’s important to prevent triggers (things that makes the red cells want to give up oxygen, like infection). Vaccination against encapsulated bugs is given in patients who have undergone autosplenectomy.
Six. Thalassemia

Pathogenesis
The thalassemias are characterized by a quantitative decrease in one of the hemoglobin chains. In αthalassemia, there is a decreased amount of α chain. In β-thalassemia, there is a decreased amount of β chain. You end up with a two-fold problem:

1. Decreased hemoglobin production (because of the decrease in globin chains)
2. Excess unpaired α chains (in β thalassemia) or β, γ, and δ chains (in α thalassemia), which form tetramers and lead to premature red cell destruction.

Morphology
In mild thalassemia, patients have a mild microcytic, hypochromic anemia. Sometimes there are target cells, or cells with basophilic stippling. Patients with severe thalassemia have a whopping anemia marked anisocytosis and poikilocytosis.

Treatment
Patients with mild thalassemia don’t require treatment. Patients with severe anemia may need repeated red cell transfusions or even bone marrow transplantation.
Seven. Autoimmune Hemolytic Anemia

Pathogenesis
There are two flavors of autoimmune hemolytic anemia, warm and cold. In warm autoimmune hemolytic anemia (WAIHA), the patient makes IgG anti-red-cell antibodies which bind best at 37°C (“warm”). Macrophages think these antibody-coated red cells are yummy, and they nibble them up (or gobble them whole). In cold autoimmune hemolytic anemia (CAIHA), the patient makes IgM anti-red-cell antibodies that bind best at temperatures <37°C (“cold”). This means they bind in distal body parts but fall off in warm body parts. Because the antibodies are IgM in nature, they bind a bunch of red cells together, forming clumps. In addition, complement binds to the red cells, causing intravascular hemolysis.

Morphology
In WAIHA, the blood smear shows prominent spherocytosis. In CAIHA, if you make the blood smear at a cool temperature, you can see nice big red blood cell agglutinates (clumps)!

Important lab test
Direct antiglobulin test (DAT)
Also called the Coombs test. Mix patient’s red cells with anti-human globulin (an antibody against human immunoglobulins). If the red cells are coated with antibodies (as they are in some immune processes, see later), the anti-human globulin will attach to those antibodies, bridging the red cells and making them clump together. So, a positive result (red cell clumping) means the patient’s red cells are coated with antibodies, and the hemolysis is probably immune-related.

Treatment
Treat underlying cause, if there is one. In WAIHA, steroids can be useful, and if all else fails, splenectomy might be necessary. In CAIHA, it’s helpful to keep the patient warm.
Eight. Microangiopathic Hemolytic Anemia

Pathogenesis
Red cells are ripped apart by physical trauma (fibrin strands snag them or mechanical devices bash them). There are a ton of possible causes, including disseminated intravascular coagulation, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, and artificial heart valves.

Morphology
The blood smear shows schistocytes, which are small, pointy red cell fragments.

Treatment
The important thing is to figure out what’s causing the MAHA and then treat that.
Nine. Anemia of Chronic Disease

Pathogenesis
Anemia of chronic disease happens in a ton of different diseases, from infections, to inflammatory conditions, to malignancies. There is a complex disturbance in iron metabolism which prevents iron from making it into normoblasts.

Morphology
The blood shows a normochromic, normocytic anemia with minimal anisocytosis and poikilocytosis (it’s a “bland-looking” anemia). Some cases (about 25%) are microcytic, but the MCV rarely gets below 72 fL.

Iron studies
• ↓ serum iron
• ↓ TIBC
• ↑ ferritin (ferritin is an acute phase reactant! It goes up in the types of conditions that cause ACD)

Treatment
ACD is usually so mild that no treatment of the anemia is required. The underlying disease is the focus of the patient’s treatment.
Ten. Aplastic Anemia

Pathogenesis
In aplastic anemia, there are very few hematopoietic precursor cells in the bone marrow (and therefore, decreased numbers of red cells, white cells, and platelets in the blood). The causes are numerous (like drugs, viruses, or hereditary conditions), but in most cases, no specific cause can be identified.

Morphology
The blood is pancytopenic, meaning that the red cells, white cells, and platelets are all decreased. The bone marrow is markedly hypocellular, or "empty".

Treatment
Treatment includes transfusion of blood components as needed, drug therapy to stimulate hematopoiesis and suppress the immune system, and if necessary, bone marrow transplant.