Hemolytic Anemia

Key Points:
- Think of hemolytic anemia as intracorpuscular vs. extracorpuscular
- Coombs’ positivity = immune-mediated hemolysis; the pattern of the Coombs’ (IgG vs. C3) can be useful

I. Etiology: Many different ways of classifying (intra- v. extravascular, acquired v. hereditary) – this is probably the most common/intuitive

A. Intracorpuscular:
- Enzyme defects (pyruvate kinase, G6PD, etc)
- Hemoglobinopathies (sickle cell, thalassemia)
- Hereditary spherocytosis, elliptocytosis
- Paroxysmal nocturnal hemoglobinuria (acquired mutation causing membrane protein destabilization; causes hemolytic anemia, venous thrombosis, deficient hematopoiesis; dx by flow cytometry)
- Spur cell anemia (seen in advanced cirrhosis)

B. Extracorpuscular:
- Hypersplenism
- Antibody-mediated immune hemolysis (warm, cold or drug-induced)
- Microangiopathic hemolysis (TTP, DIC)
- Infections (bartonella, malaria, babesiosis)
- Toxins (venom, copper)
- Trauma (marching, shearing with prosthetic valves)

II. Approach to diagnosis: Once you’ve figured out that hemolysis is going on, how do you determine the cause?

Most useful tools to begin with: the peripheral smear and the Coombs’ test.

<table>
<thead>
<tr>
<th>Finding on smear</th>
<th>Seen in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherocytes</td>
<td>Hereditary spherocytosis, AIHA</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>MAHA, prosthetic valves, mechanical</td>
</tr>
<tr>
<td>Spur cells/acanthocytes</td>
<td>Liver disease (spur cell anemia)</td>
</tr>
<tr>
<td>Target cells</td>
<td>Primary hemoglobinopathy, liver disease</td>
</tr>
<tr>
<td>Agglutinated cells</td>
<td>Cold agglutinin</td>
</tr>
<tr>
<td>Heinz bodies</td>
<td>Unstable Hgb, oxidant stress</td>
</tr>
</tbody>
</table>

- Coombs’ test: positive only in antibody-mediated (i.e. autoimmune) hemolysis
  a. Direct = patient’s RBCs plus antisera against IgG and C3
     -- will be positive in almost all cases of warm autoimmune hemolysis and most cases of cold agglutinin disease (if test done properly)
     -- pattern of anti-IgG vs. anti-C3 can help determine etiology (see below)
  b. Indirect = patient’s serum plus normal RBCs
     -- mainly used to detect Rh alloimmunization in pregnant women

III. Types of Immune-mediated Hemolytic (i.e. Coombs’ positive) Anemia:

1. Warm (IgG):
   - Idiopathic
   - Lymphoma, CLL
   - SLE (IgG and C3), other CVD
   - Drugs
   - Postviral
   - Other malignancies (rare)
   - Aldomet-type (IgG)
   - Penicillin-type (IgG)
   - Quinidine-type

2. Cold (IgM):* Acute Mycoplasma EBV/infectious mono
   - Chronic Idiopathic
   - Lymphoma, paraneoplastic

3. Cold (IgG):* this is Paroxysmal Cold Hemoglobinuria
   unusual; called Donath-Landsteiner antibody
   causes: tertiary syphilis, viral, or autoimmune

* Cold antibodies usually react with anti-C3 but not anti-IgG in direct Coombs’ test