Hemolytic Anemia in children

Hematology-Oncology Division
Child Health Departement
Sumatera Utara University
Hemolytic anemia

- Premature destruction of erythrocyte or red blood cells (RBC)

- Anemia: rate of destruction exceeds the capacity of the marrow to produce RBC

- RBC survival is shortened, RBC count falls, erythropoietin is increased
Classification

1. Cellular:
   - Intrinsic abnormalities of the membrane
   - Enzymes
   - Hemoglobin

Virtually: *Inherited*

There are four main types of Inherited Hemolytic anemia:

1. Hemoglobinopathies
2. Thalassemia
3. Enzyme defects
4. Membrane defects
2. Extracellular
   - antibodies
   - mechanical factors
   - plasma factors

Virtually: **Acquired**

Acquired hemolytic anemia

**Immune:**
- Direct complement mediated
- Autoimmune HA → Warm ab → IgG
  Cold ab → IgM
2. Non-Immune:

1. Mechanical trauma: HUS, TTP, DIC
2. Thermal injury
3. Acanthocytosis
4. Severe hypophosphatemia
5. Wilson’s disease, Copper poisoning
6. Oxidative drugs or chemical
7. Severe burns
8. Venom
9. Infection: Malaria, babesiosis, bartonellosis, Trypanosomiasis, gram negative/positive
Table 3. Some common drugs and chemicals that can induce hemolytic anemia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetanilide</td>
<td>Niridazole</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>Phenazopyridine</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Primaquine</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Sulfamethoxazole</td>
</tr>
</tbody>
</table>

N Eng J Med 1991; 324;171
1. Immune mediated (alloimmune or autoimmune)
2. Membrane defects (spherocytosis, elliptocytosis)
3. Enzym defects (G6PD deficiency, pyruvate kinase deficiency)
4. Hemoglobin defects (sickle cell disease, thalassemia)
Approach to diagnosis

- 1. Clinical features suggesting hemolytic disease
- 2. Laboratory
- 3. Special hematologic investigation
Clinical features suggest a hemolytic process

1. Ethnic factors
2. Age factors
3. History of anemia, jaundice, gallstones in family
4. Persistent or recurrent anemia associated reticulocytosis
5. Anemia unresponsive to hematins
6. Intermittent or persistent indirect hyperbilirubinemia
7. Splenomegaly
8. Hemoglobinuria
9. Multiple gallstones
10. Chronic leg ulcers
11. Exposure to certain drugs
History
Physical examination
Low hemoglobin
Increased reticulocyte count
Peripheral blood smear examination

Coombs' test

Negative
Morphologic characteristics of red cells

Positive
Immune mediated
Coagulation studies
ANA
Identification of antibody

Red cell fragmentation
Microangiopathic

Consider:
DIC
Coagulation screen (fibrinogen, PT, aPTT, FDP)
Platelet count, blood cultures, antibiotics
HUS
Blood pressure
BUN, Cr
Urine analysis
Platelet count
Cardiac prosthesis

Spherocytes
Elliptocytes
Pyropoikilocytosis

Consider:
Family studies
Osmotic fragility or karyometrology
Thermal reactivity

Hereditary spherocytosis
Hereditary elliptocytosis
Hereditary pyropoikilocytosis
Hypersplenism
Coombs negative
Autoimmune hemolysis

Target cells
Sickle cells

Hemoglobin electrophoresis
Hgb SS
Hgb SC
Hgb CC
Hgb S/β-Thalassemia

Normal or nonspecific abnormalities
Enzyme deficiencies
G6PD
PK
Others

BUN=blood urea nitrogen; Cr=creatinine; EMP=Emden-Meyerhof pathway; FDP=fibrin degradation products; G6PD=glucose-6-phosphate dehydrogenase; Hgb=hemoglobin; HK=hexokinase;
HMS=hexose monophosphate shunt; PK=pyruvinate kinase; PT=prothrombin time;
aPTT=partial prothrombin time. HUS=hemolytic uremic syndrome.
Inherited Hemolytic Anemia

A. Red cell membrane defect
   A.1. Hereditary Spherocytosis
       Essentials of diagnosis & typical features
       - Anemia and jaundice
       - Splenomegaly
       - Positive family history of anemia, jaundice or gallstones.
       - Spherocytosis with ↑ reticulocytes
       - ↑ Osmotic fragility
       - Negative coombs test
A.2. Hereditary Elliptocytosis

- Autosomal dominant inheritance
- Most are asymptomatic
- Elevated reticulosityte
- Jaundice and splenomegaly

No treatment is indicated:
  - folate suplementation
  - splenectomy
B. Enzyme Deficiencies

B.1. Glucose-6-phosphate Dehydrogenase (G6PD) Deficiency

Essentials of diagnosis & typical features
- Symptoms develop 24-48 hr after ingested a substances→has oxidant properties, such as aspirin, sulfonamides, and antimalarias
- African, Mediterranean or Asian ancestry
- Neonatal hyperbilirubinemia
- Sporadic hemolysis → infection, oxidant drugs fava beans
- X- linked inheritance.
- Acute : precipitous fall Hb + Ht
- Heinz bodies in RBCs’ unstained/supravital
- Polychromatophilic cells, reticulocytosis
- Enzymes activity < 10% normal
- Reduction of enzymes activity more extreme in Americans of European descent and in Asians than Americans of Africans descent
- Screening tests: decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH.
- After hemolytic episode → reticulocytes and young RBCs predominate
- Dx suspected: G6PD activity is within low normal range in the presence of a high reticulocyte count
# List of Drugs Usually Associated with Clinically Significant Hemolysis in G6PD Deficiency

<table>
<thead>
<tr>
<th>Antimalarials</th>
<th>Sulfa Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamaquine</td>
<td>Salicylazosulfapyridine</td>
<td>Fava beans</td>
</tr>
<tr>
<td>Pentaquine</td>
<td>N-Acetylsulfanilamide</td>
<td>Nalidixic acid</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Sulfapyridine</td>
<td>Naphthalene</td>
</tr>
<tr>
<td>Quinocide</td>
<td>Sulfamethoxypyridazine</td>
<td>Phenylhydrazine</td>
</tr>
<tr>
<td>Antipyretics/Analgesics</td>
<td>Thiazolsulfone</td>
<td>Toluidine blue</td>
</tr>
<tr>
<td>Acetanilid</td>
<td></td>
<td>Acetylphenylhydrazine</td>
</tr>
<tr>
<td>Aminopyrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipyrine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIG. 11.33 Peripheral smear of patient with G_6PD deficiency in the midst of a hemolytic episode. Note blister cells with hemoglobin condensed in the remaining (nonblistered) portion of the cell.
Acquired Hemolytic Anemia

1. Microangiopathic Hemolytic Anemia

**Hallmark**: - schistocytes (red cell fragments) on peripheral blood smear analysis.

Infection and sepsis $\rightarrow$ microangiopathy, uncontrolled fibrinogenesis $\rightarrow$ RBC destruction

Severe RBC destruction, thrombocytopenia, coagulation factor consumption, $\rightarrow$ DIC
Hemolytic Uremic Syndrome (HUS)
- Microangiopathic
- Decreased von Willebrand protease
- Infection with enteric bacteria: Escherichia coli O157:H7

Thrombotic thrombocytopenic purpura
- Decreased von Willebrand protease
- HUS + neurologic symptoms, inherited or acquired
2. Immune-Mediated Hemolytic Anemias

- Antibody against one or more antigens on the surface of RBC → opsonization → premature destruction: - erythocytes → RES
  - complement-mediated lysis of RBC in the bloodstream
- Antibodies come from patients: AIHA
- Antibodies come from another source: Alloimmune hemolytic anemia → Hemolytic disease of the newborn
2.1. Autoimmune Hemolytic Anemia (AIHA)

- History: previous viral or viral like illness, fatigue, pallor
- Usually sudden, severe anemia
- Dark urine: acute intravascular hemolysis → complement mediated red cell lysis
- Jaundice, sclerae, pruritus
- Mild splenomegaly
Autoimmune Hemolytic Anemia
2.1.1. Intravascular hemolysis

- Complement mediated, IgM, complement-fixing IgG direct against RBC antigen → jaundice (hyperbilirubinemia), LDH ↑↑, low haptoglobin
2.1.2. Extravascular hemolysis

- Mediated by IgG
- NO increase LDH, bilirubin
- RBC destroyed in RES, plasma

- **Laboratory evaluation**
  - Moderate to severe anemia
  - Brisk reticulocytosis
  - Spherocytosis, polychromasia, RBC clumping
- Hemoglobinuria
- Direct Coombs test (antibody bound to the patient’s RBC): (+)
- Indirect Coombs test (test for free antierythrocyte antibody in the patient’s serum)
Primary AIHA:

1. Warm-reactive AIHA
   Usually: IgG binds RBC antigen at 37°C
2. Paroxysmal Cold Hemoglobinuria
3. Cold Agglutinin Disease:
   Usually IgM binds erythrocyte antigens
   (typically red cell surface polysaccharide)
   and fixes complement at temp. below 37°C
# Classification of autoimmune hemolytic anemia

<table>
<thead>
<tr>
<th>Warm-reactive autoantibodies</th>
<th>Paroxysmal cold hemoglobinuria (PCH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td>Lymphoproliferative disorders</td>
<td>Tertiary syphilis</td>
</tr>
<tr>
<td>Autoimmune disorders (SLE)</td>
<td>Post-viral infection</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td></td>
</tr>
<tr>
<td>Evan’s syndrome</td>
<td>Drug induced hemolytic anemia</td>
</tr>
<tr>
<td>HIV associated</td>
<td>Hapten mediated (PCN)</td>
</tr>
<tr>
<td></td>
<td>Immune complex type</td>
</tr>
<tr>
<td></td>
<td>(quinidine, quinine)</td>
</tr>
<tr>
<td></td>
<td>True autoimmune anti-RBC</td>
</tr>
<tr>
<td></td>
<td>type (methyldopa)</td>
</tr>
<tr>
<td></td>
<td>Metabolite driven</td>
</tr>
</tbody>
</table>

| Cold-reactive antibodies    |                                      |
|-----------------------------|                                      |
| Idiopathic (cold aglutinin disease) |                                      |
| secondary                   |                                      |
| Atypical or mycoplasma pneumonia |                                      |
| Infectious mononucleosis    |                                      |
| Lymphoproliferative disorders |                                      |
Treatment of Acquired Hemolytic Anemia

- Methyl-prednisolone 1 to 2 mg/Kg/day/iv every 6 hours should be initiated promptly. Response (+): increasingly stable Hb, decreasing reticulocytosis, diminishing transfusion. After stabilization, prednisone 1 to 2 mg/Kg/day can be substituted for methylprednisolone → gradually tapered over several weeks to months.
- IV Immunoglobulin
- Exchange transfusion/Plasmapheresis: limited efficacy, effective for IgM
- Splenectomy: refractory IgG dependent chronic extravascular hemolysis
- Immunosuppressive drugs: cyclophosphamide, 6-mercaptopurine, 6-thioguanine, azathioprine, cyclosporine A
Thank you