HEMOLYTIC ANEMIA

In a healthy person, a red blood cell survives 90 to 120 days in the circulation, so about 1% of human red blood cells break down each day. The spleen (part of the reticulo-endothelial system) is the main organ that removes old and damaged RBCs from the circulation. In healthy individuals, the breakdown and removal of RBCs from the circulation is matched by the production of new RBCs in the bone marrow. Extravascular hemolysis occurs when RBCs are phagocytized by macrophages in the spleen, liver and bone marrow. During the normal aging of red cells in the circulation, effete red cells are destroyed by macrophages, i.e. extravascular hemolysis is always occurring to some degree. However, this is a physiologic process and does not result in anemia or excessive unconjugated bilirubin production. 

Hypoxia-inducible factor (HIF) - erythropoietin receptor (EpoR) - Erythropoietin, also known as erythropoetin or erthropoyetin or EPO

Ref.: http://coppermine-gallery.net/
Hemolytic anemia (or haemolytic anaemia) is a form of anemia due to abnormal hemolysis, the **excessivel breakdown** of red blood cells (RBCs), either in the blood vessels (**intravascular hemolysis**) or elsewhere in the human body (**extravascular**). It has numerous possible causes, ranging from relatively harmless to life-threatening. Hemolytic anemias (intravascular or extravascular) are usually regenerative (if sufficient time is given for the marrow to regenerate and if there are no additional factors suppressing erythropoiesis).

### Diagnosis of the Hemolytic Anemia

#### History and Physical Examination

Anemia most often is discovered through laboratory tests, but the history and physical examination can provide important clues about the presence of hemolysis and its underlying cause.

1. The patient may complain of **dyspnea** or **fatigue** (caused by anemia).
2. **Dark urine** may be present.
3. Occasionally, **back pain** may be reported by patients with intravascular hemolysis.
4. The **skin may appear jaundiced** or **pale**.
5. A **resting tachycardia** with a **flow murmur** may be present if the anemia is pronounced.
6. **Lymphadenopathy** or **hepatosplenomegaly** suggest an underlying lymphoproliferative disorder or malignancy.
7. Alternatively, an **enlarged spleen** may reflect hypersplenism causing hemolysis.
8. **Leg ulcers** occur in some chronic hemolytic states, such as sickle cell anemia.

#### Paraclinical Testing

**Workup:** Standard blood studies for the workup of suspected hemolytic anemia include the following:

1. **Complete blood cell count**
2. **Peripheral blood smear** (PBS)
3. **Serum lactate dehydrogenase** (LDH) study
4. **Serum haptoglobin**
5. **Indirect bilirubin**

In detail, the tests and the results are the:

**HEMATOLOGIC TESTS**

Along with anemia, a characteristic laboratory feature of hemolysis is **reticulocytosis**, the normal response of the bone marrow to the peripheral loss of red blood cells. In the absence of concomitant bone marrow disease, a brisk reticulocytosis should be observed within three to five days after a decline in hemoglobin. In a minority of patients, the bone marrow is able to chronically compensate, leading to a normal and stable hemoglobin concentration. The anemia of hemolysis usually is **normocytic**, although a marked reticulocytosis can lead to an elevated measurement of mean corpuscular volume, because the average mean corpuscular volume of a reticulocyte is 150 fL. Review of the **peripheral blood smear** is a critical step in the evaluation of any anemia. Along with an assessment for pathognomonic red blood cell morphologies, such as **spherocytes** or
**CHEMISTRY TESTS**

The destruction of red blood cells is characterized by

1. **Increased unconjugated bilirubin.**
2. **Increased lactate dehydrogenase.**
3. **Decreased haptoglobin levels.**

Lactate dehydrogenase and hemoglobin are released into the circulation when red blood cells are destroyed. Liberated hemoglobin is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The hemoglobin-haptoglobin complex is cleared quickly by the liver, leading to low or undetectable haptoglobin.

**URINARY TESTS**

In cases of severe intravascular hemolysis, the binding capacity of haptoglobin is exceeded rapidly, and free hemoglobin is filtered by the glomeruli. The renal tubule cells may absorb the hemoglobin and store the iron as hemosiderin;

1. **Hemosiderinuria** is detected by **Prussian blue staining** of sloughed tubular cells in the urinary sediment approximately one week after the onset of hemolysis.
2. **Hemoglobinuria**, which causes **red-brown urine**, is indicated by a **positive urine dipstick reaction** for heme in the absence of red blood cells.

**IMMUNOLOGIC TESTS**

The **direct Coombs’ test** (the direct antiglobulin test) is the hallmark of autoimmune hemolysis. **Red blood cell agglutination with anti-IgG serum reflects warm AIHA** or **warm agglutinins**; while a **positive anti-C3 DAT occurs with cold agglutinins**; Warm AIHA also is associated with autoimmune diseases (e.g., systemic lupus erythematosus), while cold AIHA may occur following infections, particularly infectious mononucleosis and Mycoplasma pneumoniae infection. Human immunodeficiency virus infection can induce both warm and cold AIHA. Lymphoproliferative disorders (e.g., chronic lymphocytic leukemia, non-Hodgkin’s lymphoma) may produce warm or cold autoantibodies. A number of commonly prescribed drugs can induce production of both types of antibodies


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**The general classification of hemolytic anemia takes in account either inherited or acquired causes:**

**A) Intrinsic causes**

1. **Hereditary** (inherited) hemolytic anemia can be due to:
   a) Defects of red blood cell membrane production
      - as in hereditary spherocytosis
      - and hereditary elliptocytosis
   b) Hereditary (inherited) hemolytic anemia can be due to defects in hemoglobin:
      - Defects in hemoglobin production as in
        - thalassemia,
        - sickle-cell disease and congenital dyserythropoietic anemia
   c) Hereditary (inherited) hemolytic anemia can be due to enzyme defects: Defective red cell metabolism
      - as in glucose-6-phosphate dehydrogenase deficiency
      - and pyruvate kinase deficiency

2. **Acquired**
a) Paroxysmal nocturnal hemoglobinuria (PNH), sometimes referred to as Marchiafava-Micheli syndrome, is a rare, acquired, potentially life-threatening disease of the blood characterized by complement-induced intravascular hemolytic anemia.

- **Acute transfusion reactions** may be divided into at least 8 distinct entities. Acute hemolytic transfusion reactions may be either immune mediated or non–immune mediated.
  - Immune-mediated hemolytic transfusion reactions caused by immunoglobulin M (IgM) anti-A, anti-B, or anti-A,B typically result in severe, potentially fatal complement-mediated intravascular hemolysis. Immune-mediated hemolytic reactions caused by immunoglobulin G (IgG), Rh, Kell, Kidd, or other non-ABO antibodies typically result in extravascular sequestration, shortened survival of transfused red cells, and relatively mild clinical reactions.
  - Nonimmune hemolytic transfusion reactions occur when RBCs are damaged prior to transfusion, resulting in hemoglobinemia and hemoglobinuria without significant clinical symptoms.
  - Nonhemolytic febrile transfusion reactions usually are caused by cytokines from leukocytes in transfused red cell or platelet components, causing significant clinical symptoms such as fever, chills, or rigors.

B) **Extrinsic causes**

Acquired hemolytic anemia may be caused by immune-mediated causes, drugs and other miscellaneous causes.

a) **Immune-mediated causes** could include

1) transient factors as in Mycoplasma pneumoniae infection (cold agglutinin disease)
2) or permanent factors
   - as in autoimmune diseases like autoimmune hemolytic anemia (itself more common in diseases such as systemic lupus erythematosus and chronic lymphocytic leukemia)

a) Any of the causes of hypersplenism (increased activity of the spleen where the red blood cells are normally destroyed) such as portal hypertension

b) Acquired hemolytic anemia is also encountered

- in burns
- and as a result of certain infections. Bacterial contamination during blood transfusion and endotoxemia may result from
  - inadequate sterile preparation of the phlebotomy site.
  - opening the blood container in a nonsterile environment.
  - or the presence of bacteria in the donor's circulation at the time of blood collection.

c) **Lead poisoning** resulting from the environment causes non-immune hemolytic anemia.

d) **Runners** can suffer hemolytic anemia due to "footstrike hemolysis", owing to the destruction of red blood cells in feet at foot impact.

e) Low-grade hemolytic anemia occurs in 70% of prosthetic heart valve recipients, and severe hemolytic anemia occurs in 3%

f) March hemoglobinuria

**Table of Classification of the Hemolytic Disorders**

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<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
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<tbody>
<tr>
<td>Intrinsic</td>
<td>1. as above</td>
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<tr>
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<td>2. Rarer hereditary abnormalities</td>
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<table>
<thead>
<tr>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physical agents: Burns, cold exposure</td>
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<tr>
<td>2. Chemical agents: Drugs and venoms</td>
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<tr>
<td>3. Infectious agents:</td>
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<td>• Malaria,</td>
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• toxoplasmosis,
• mononucleosis,
• hepatitis,
• primary atypical pneumonia,
• clostridial infections,
• bartonellosis,
• leishmaniasis

4. Traumatic: Prosthetic heart valves, march hemoglobinemia, DIC (disseminated intravascular coagulation), graft rejection

5. Diseases:
• Hepatic and renal disease
• Collagen vascular disease
• Malignancies: Particularly hematologic neoplasia

6. Immune-mediated causes
• Transfusion of incompatible blood
• Hemolytic disease of the newborn
• Cold hemagglutinin disease
• Autoimmune hemolytic anemia
• TTP (Thrombotic Thrombocytopenic Purpura) and HUS (hemolytic uremic syndrome)

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**Chronic Intravascular Hemolysis occurs after Aortic Valve Replacement - Case Studies:**

To **assess the severity of hemolysis** and to **determine whether severity of hemolysis was related to type of prosthesis**, the following tests were performed at the **New York Cornell University Hospital** on 54 patients who had three different types of aortic ball-valve prostheses:

1. hematocrit readings (Hct),
2. schistocyte counts (S),
3. reticulocyte counts (R),
4. and determinations of haptoglobin (Hp),
5. lactic acid dehydrogenase (LDH),
6. bilirubin,
7. urinary hemoglobin,
8. and urinary hemosiderin (Hs).

**Results:** They can be found at the online version located on the World Wide Web at: http://circ.ahajournals.org/content/44/4/657

**Conclusion:** At the end of the study, it has been concluded that hemolysis is more severe in the presence of **Starr-Edwards** valves than **Magovern** or **Cutter** valves. Based on these observations, the following criteria for rapid clinical evaluation of cardiac hemolysis are suggested to **determine the severity of hemolysis**:

1. **Mild:**
   a) Hs (presence of urinary hemosiderin)
   b) or absence of Hp (haptoglobin)
   c) but S (schistocyte counts) < 10,
   d) R (3. reticulocyte counts) < 5,
   e) LDH < 500;

1. **Moderate:**
   a) Hs
b) or absence of Hp
c) but S > 10,
d) R > 5,
e) LDH > 500;

1. **Severe**: all of above i.e.,
a) Hs
b) or absence of Hp
c) but S > 10,
d) R > 5,
e) LDH > 500;
f) plus hemoglobinuria.

**Pathophysiology of anemia due heart valve prostheesis**

The red cell has a critical tolerance to **shearing stress**. High shearing stresses cause stretching of the membrane with tearing and cell fragmentation.

**Fragmented cells** or **schistocytes** are not specific for heart valve hemolysis since fragmentation is an important final common pathway for red cell destruction in a variety of hemolytic states. However, the number of fragmented cells in the peripheral blood of patients with artificial heart valves appears to bear a direct relationship to the severity of the hemolysis.

In the present study, **schistocyte counts** were significantly higher in patients without haptoglobins than in those with haptoglobins. Moreover, the magnitude of the counts correlated well with other measurements of red cell destruction such as **reticulocyte counts**, **serum LDH** and **bilirubin** (primarily unconjugated) determinations.

**Explanation of the variations in serum LDH levels**: Since the red cell is rich in LDH fractions, hemolysis results in elevated serum levels, and **increased concentrations of both total LDH and the isoenzyme LDH 1** have been reported in patients with **aortic prostheses**. In the present study elevation of total LDH was a constant finding, and **good correlation was noted between LDH levels, schistocyte counts, reticulocyte counts, and serum bilirubin levels** (table 1)

a) The significantly higher levels found in the group without haptoglobins compared to the group with haptoglobins were due largely to more severe hemolysis in the former group.
b) Extremely high values for LDH above 800 mU were seen only in those patients with hemoglobinuria.

**Explanation of the variations of serum haptoglobin**: Red cell fragmentation results in loss of a piece of membrane which may or may not contain hemoglobin.

a) Free hemoglobin dissociates into half molecules which are rapidly bound to plasma haptoglobin.
b) The **hemoglobin-haptoglobin complex** is too large to pass through the glomerulus and is cleared from the circulation by the reticuloendothelial system.

**Explanation of the hemoglobinuria and hemosideruria**: After plasma haptoglobin has been depleted, the half molecules (molecular weight, 34,000) pass through the glomerular filter into the proximal tubule, and the free hemoglobin remaining in the circulation is oxidized to **methemoglobin**.

a) When large quantities of hemoglobin are presented to the tubule, the transport mechanism is exceeded and **hemoglobinuria occurs**.
b) When smaller quantities are filtered, hemoglobin is absorbed by the cells of the proximal tubule where it is converted to ferritin and **hemosiderin**.
c) Later, when the tubule cells desquamate, hemosiderin granules may be seen by light microscopy in the sediment stained for iron. Thus **hemoglobinuria occurs acutely with massive hemolysis** while **hemosiderinuria is found in chronic intravascular hemolysis**. Since haptoglobin can be regenerated within several days following cessation of hemolysis while iron appears in the urine at a very slow rate, the simultaneous presence of haptoglobin and hemosiderin is probably indicative of intermittent rather than continuous hemolysis. In most reported cases of chronic intravascular hemolysis **renal function has not been significantly impaired**.20 21

TREATMENT OF HEMOLYTIC ANEMIAS - LE TRAITEMENT DES ANEMIES HEMOLYTIQUES


Ref.:  
- ELAINE EYSTER, JOHN ROTHCHILD and OLGA MYCHAJLIW; Chronic Intravascular Hemolysis after Aortic Valve Replacement: Long-Term Study Comparing Different Types of Ball-Valve Prostheses; Circulation. 1971;44:657-665; Copyright © 1971 American Heart Association, Inc. All rights reserved
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- Hemolytic Anemia GURPREET DHALIWAL, M.D., PATRICIA A. CORNETT, M.D., and LAWRENCE M. TIERNEY, JR., M.D., San Francisco Veterans Affairs Medical Center/University of California–San Francisco School of Medicine, San Francisco, California