Normocytic Anemia: Autoimmune Hemolytic Anemia (AIHA), Drug-Induced Hemolytic Anemia and Rh Disease

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Hemolytic anemia is characterized by intravascular and extravascular destruction of erythrocytes. It manifests if the production of the erythrocytes in the bone marrow is slower than their degradation. A first good differentiation of the several forms of hemolytic anemia can be made between ‘hereditary’ and ‘acquired’. In this article, the most important forms of acquired hemolytic anemia are presented, emphasizing on their etiology, clinic and therapy.

Autoimmune Hemolytic Anemia (AIHA)

Definition

Autoimmune hemolytic anemia is characterized by premature intra- and extravascular lysis of erythrocytes due to antibodies.
Etiology

Different antibodies can be the cause of AIHA (IgM, IgG). Depending on the antibody, they are classified into forms with warmth autoantibodies and those with cold autoantibodies. Ca. 50 % of the diseases are idiopathic. The remaining 50 % develop on the basis of infections, the intake of medicaments, or in the context of proliferative and rheumatoid diseases.

Diagnostic: Coombs Test

**Direct Coombs´ Test**

Independent of the respective form of AIHA, the Coombs test is positive, which is why it is the most important test for general determination of an autoimmune hemolytic anemia. It is also referred to as *direct antiglobulin test (DAT)*.

![Diagram of Direct Coombs Test](image)

Generally, there are two possibilities for the performance of the Coombs test – the direct Coombs test and the indirect Coombs test. However, for determination of AIHA, only the first, direct test is used, at which the examined erythrocytes are mixed with *rabbit serum (Coombs serum)*. If an agglutination of the erythrocytes occurs, this is proof of an AIHA.

**Indirect Coombs´ Test**

![Diagram of Indirect Coombs Test](image)

**Step I:** Add test blood group 0 RBCs to the test tube to bind with IgG antibodies

**Step II:** Add Coombs´ reagent
### Direct Coombs´ test
- Incubate patient RBCs with anti-IgG or IgM (Coombs´ reagent)
- If RBCs agglutinate → positive
  - IgG = “warm”
  - IgM = “cold”

### Indirect Coombs´ test
- Maternal prenatal testing
- Prior to a blood transfusion
- Detects unbound anti-RBC antibodies that are in the patient´s serum
- Patient serum is incubated with RBCs of known antigenicity
- Agglutination → positive

## Autoimmune Hemolytic Anemia via Warmth Antibodies
The temperature optimum of the warmth antibodies belonging to the IgG class is **37 °C**. After the antibodies bind the surface of the erythrocytes, they are not only recognized by the macrophages of the MMS, but also destroyed. The patient shows unspecific symptoms like fatigue, tiredness, tachycardia and tachypnea.

In the context of a hemolytic crisis, fever occurs, which can be accompanied by jaundice and beer-brown urine. Besides treatment of the underlying disease and the avoidance of AIHA triggering factors, high-dose application of immunosuppressive corticoids can be performed. If not the liver, but the spleen is the main location of degradation of the erythrocytes in the MMS, splenectomy can be considered.

## Autoimmune Hemolytic Anemia via Cold Antibodies
The temperature optimum of the cold antibodies mainly belonging to the IgM class is **4 °C**; thus the risk for the antibodies binding with the surface of the erythrocytes is increased where blood temperature is low, that is in the periphery. A chronic hemolytic anemia, with worsening at cold exposure, can develop.

Clinically, mild jaundice and splenomegaly can occur. Also, acrocyanosis at nose, ears, fingers and toes can be observed. The primary goal of therapy is to avoid every form of exposure to cold. Since hemolysis can also be of intravascular nature, the necessity of splenectomy must be examined thoroughly before it is performed. It should only be conducted at a severely enlarged spleen.

## Drug-Induced Hemolytic Anemia

### Etiology
Generally, drug-induced hemolytic anemia is based on three different mechanisms, which is why different reactions between antibodies and complements occur.
Antibodies do not activate complement and persist after the termination of medication (e.g. methyldopa, fludarabin).

2. **Immune-complex type**: Antibodies activate complement and disappear with termination of medication (e.g. NSAR, cephalosporins).

3. **Hapten-type**: Antibodies react against a medicament-erythrocyte-complex (e.g. penicillin, ampicillin).

For all three mechanisms, opsonized erythrocytes are degraded in the MMS and the resulting hemolytic anemia does not regress until medication is terminated. One should consider that, for the autoimmune type, antibodies persist for several months even if medication was terminated.

### Rhesus-Incompatibility of Newborns

#### Etiology and Pathogenesis

As the name states, the cause is a **Rhesus incompatibility** between the blood of the fetus and the blood of the mother. If an Rh-D-negative mother gives birth to an Rh-D-positive child, she is Rh-D sensitized and produces anti-D-antibodies of the IgG class, which can pass the placenta. These antibodies are capable to pass the placenta during the next pregnancy, which leads to hemolysis of the fetal erythrocytes if the fetus is Rh factor D-positive.

#### Clinic

In severe cases, rhesus incompatibility leads to the death of the fetus (hydrops fetalis). In milder cases, the newborn shows jaundice with hepatosplenomegaly at birth. Also, paleness, tachycardia and edemas can be present.

#### Diagnostic

In the navel vein blood of the newborn, distinct anemia with increased reticulocytes can be observed and bilirubin levels are also elevated. The direct Coombs test is positive for the child; this also applies for the mother when the indirect Coombs test is performed.

#### Therapy

At distinct signs of anemia, jaundice, possible heart insufficiency, and a positive direct Coombs test of the newborn, exchange transfusion can become necessary. For degradation of the bilirubin in the skin, the child can undergo phototherapy.

#### Complications

Due to the great amounts of residue of unconjugated bilirubin in the basal ganglia, the risk for kernicterus, with accompanying damages of the central nervous system, is present after birth of the child (and only then!). Deafness, epilepsy and mental retardation can be irreversible consequences.

### Further Possible Causes of Acquired Hemolytic
Anemia

- Damages of the erythrocytes after long foot marches and long-distance runs (march hemoglobinuria)
- **Infections (Malaria)**: Quotidian: variable; Falciparum; Tertian: vivax, every 48 hours; Quartan: malariae, every 72 hours
- Intoxication (lead intoxication)
- Severely increased copper levels (Wilson’s disease)
- Hemolytic anemia via iso-antibodies (blood transfusion)
- Paroxysmal nocturnal hemoglobinuria (PNH)

References


Lim, Young Ae, Kim, Moon Kyu, Hyun, & Bong Hak. (n.d.). Autoimmune hemolytic anemia predominantly associated with IgA anti-E and anti-c. Korean Academy of Medical Sciences.


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