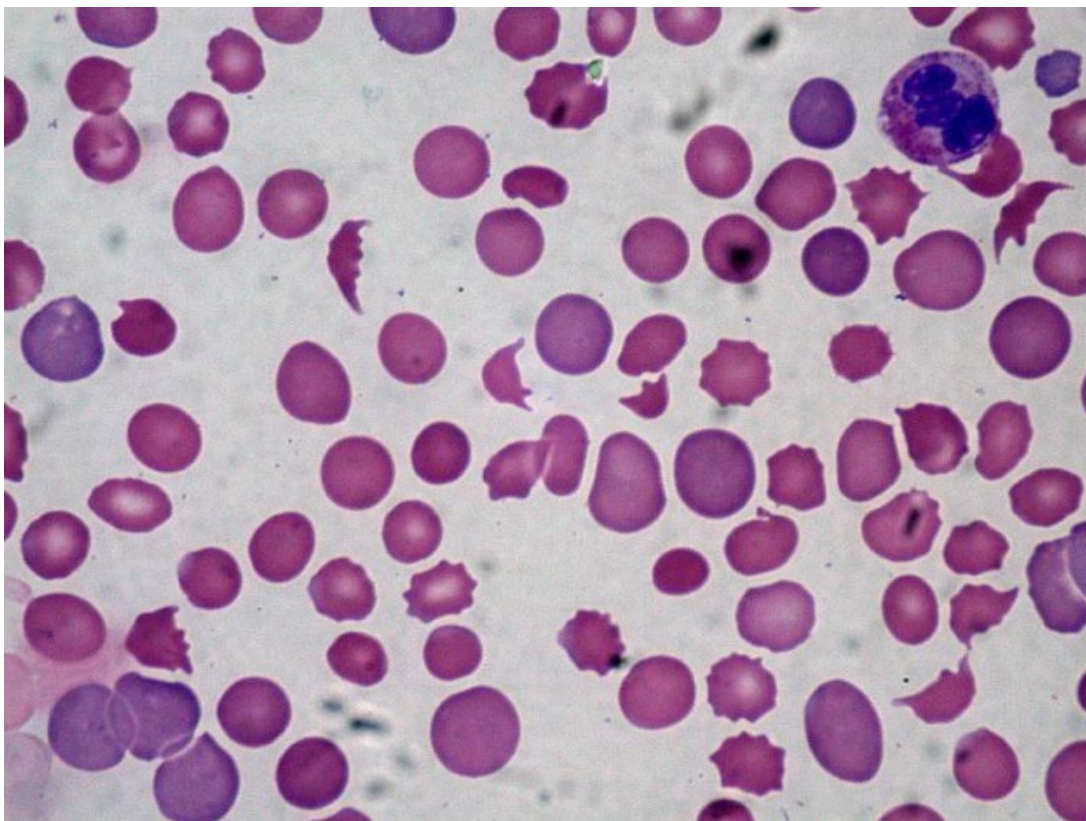


## Normocytic Anemia: Autoimmune Hemolytic Anemia (AIHA), Drug-Induced Hemolytic Anemia, and Rh Disease

[See online here](#)

**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

#### Definition

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

# Etiology

Different antibodies (IgM, IgG) can be the cause of AIHA. AIHA is classified into forms with warm autoantibodies and those with cold autoantibodies. Approx. 50% of AIHA cases are **idiopathic**. The remaining 50% develop from infections, drugs, or in the context of proliferative and rheumatoid diseases.

## Diagnostic: coombs test

### Direct coombs test

The Coombs test is positive despite the form of AIHA, which is why it is the most important test for the general determination of AIHA. This test is also referred to as a **direct antiglobulin test (DAT)**.

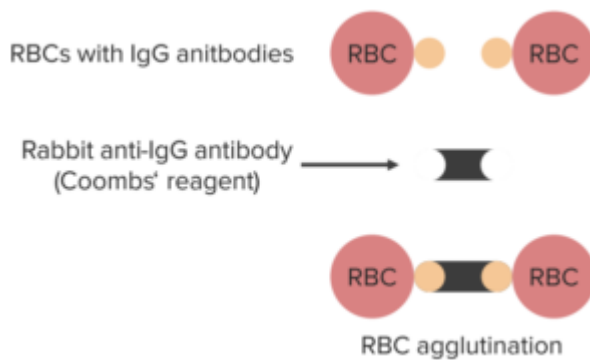


Image: Direct Coombs Test: Looking for antibody and/or C3 on the surface of patient RBCs. By Lecturio

Generally, there are 2 possibilities for the Coombs test - the direct Coombs test and the indirect Coombs test. However, for the determination of AIHA, only the direct test is used, in 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

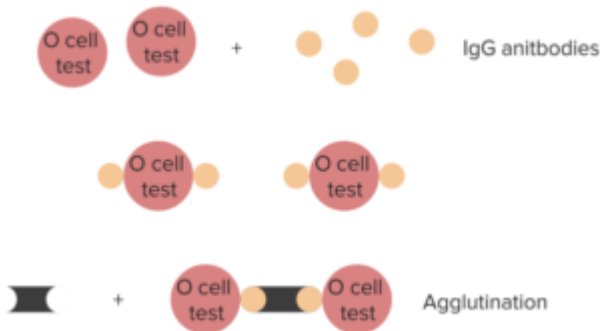


Image: Indirect Coombs Test - Antibody Screen: Looking for antibodies in the patient's serum. By Lecturio

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

**Step II:** Add Coombs reagent

<b>Direct Coombs test</b>	<b>Indirect Coombs test</b>
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<ul style="list-style-type: none"> <li>• Incubate patient RBCs with anti-IgG or IgM (Coombs reagent) <ul style="list-style-type: none"> <li>• If RBCs agglutinate → positive <ul style="list-style-type: none"> <li>◦ IgG = 'warm'</li> <li>◦ IgM = 'cold'</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Maternal prenatal testing</li> <li>• Prior to a blood transfusion</li> <li>• Detects unbound anti-RBC antibodies that are in the patient's serum</li> <li>• Patient serum is incubated with RBCs of known antigenicity</li> <li>• Agglutination → positive</li> </ul>
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## Autoimmune hemolytic anemia via warm antibodies

The optimal temperature for the warm antibodies belonging to the IgG class is **37.0°C (98.6°F)**. After the antibodies bind to the surface of the erythrocytes, they are not only recognized by the macrophages of the MMS (monocyte-macrophage system) but also destroyed. The patient shows non-specific 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. Apart from the treatment of the underlying disease and the avoidance of AIHA-triggering factors, high-dose immunosuppressive corticoids can be administered. If the spleen, and not the liver, is the main location of erythrocyte degradation in the MMS, a splenectomy can be considered.

## Autoimmune hemolytic anemia via cold antibodies

The optimal temperature of the cold antibodies, mainly belonging to the IgM class, is **4°C (39.2°F)**; thus, the risk of the antibodies binding to the surface of the erythrocytes is increased when the blood temperature is low, i.e. in the periphery. Chronic hemolytic anemia, which worsens with cold exposure, can develop.

Clinically, mild jaundice and splenomegaly can occur. Moreover, acrocyanosis in the nose, ears, fingers, and toes may be observed. The primary goal of therapy is to avoid exposure to cold. Since hemolysis can also be intravascular, the necessity of splenectomy must be examined thoroughly before it is performed. Splenectomy should only be performed for a severely enlarged spleen.

## Drug-Induced Hemolytic Anemia

### Etiology

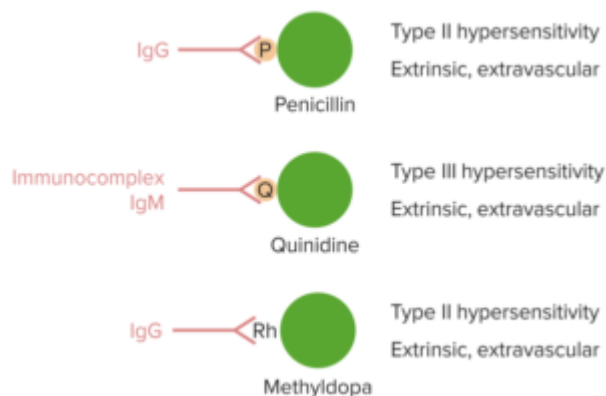


Image: Drugimmune-hemolytic. By Lecturio

Generally, drug-induced hemolytic anemia is based on 3 different mechanisms, which is

why different reactions between antibodies and complements occur.

1. **Autoimmune type:** Antibodies do not activate complement and persist after the termination of medication (e.g. methyldopa, fludarabine).
2. **Immune-complex type:** Antibodies activate complement and disappear with the termination of medication (e.g. NSAR, cephalosporins).
3. **Hapten-type:** Antibodies react against a drug-erythrocyte-complex (e.g. penicillin, ampicillin).

For all 3 mechanisms, opsonized erythrocytes are degraded in the MMS and the resulting hemolytic anemia does not regress until the medication is terminated. One should consider that, for the autoimmune type, antibodies persist for several months even if the medication is terminated.

## Rhesus-Incompatibility of Newborns

### Etiology and pathogenesis

**Rhesus incompatibility** between the blood of the fetus and the blood of the mother results 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. As these antibodies are capable of passing the placenta during the next pregnancy, they lead to hemolysis of the fetal erythrocytes if the fetus is Rh-D positive.

### Clinical features

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. Moreover, paleness, tachycardia, and edema can be present.

### Diagnostics

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 to the mother when the indirect Coombs test is performed.

### Therapy

With 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 large amounts of unconjugated bilirubin residue in the basal ganglia, the risk of kernicterus, with accompanying damage to 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

- RBC damage 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

Anemia, Hemolytic Autoimmune. (n.d.). *SpringerReference*.  
doi:10.1007/springerreference\_109167

Bowman, Z. S. (2005). *Primaquine-induced hemolytic anemia: Hemotoxicity of 5-hydroxyprimaquine (5-HPQ)*.

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.

Petz, L. D., & Garratty, G. (2004). Drug-Induced Immune Hemolytic Anemia. *Immune Hemolytic Anemias*, 261-317. doi:10.1016/b978-0-443-08559-8.50012-1

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