Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins

Authors
Stanley L Schrier, MD
Wendell F Rosse, MD

Section Editor
William C Mentzer, MD

Deputy Editor
Stephen A Landaw, MD, PhD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Feb 2015. | **This topic last updated:** Nov 24, 2014.

INTRODUCTION — Autoimmune hemolytic anemia (AIHA) due to the presence of warm agglutinins is almost always due to the presence of IgG antibodies that react with protein antigens on the red blood cell (RBC) surface at body temperature. For this reason, they are called "warm agglutinins" even though they seldom directly agglutinate the RBCs.

This topic review will discuss the clinical features and diagnosis of AIHA due to warm agglutinins [1,2]. Treatment of this disorder is discussed separately. (See "Treatment of autoimmune hemolytic anemia: Warm agglutinins".)

- AIHA is a frequent problem in patients with systemic lupus erythematosus, occurring in up to 10 percent of patients. This subject is discussed separately. (See "Hematologic manifestations of systemic lupus erythematosus in adults", section on 'Autoimmune hemolytic anemia'.)
- The pathogenesis, diagnosis, and treatment of AIHA associated with the presence of cold agglutinins is discussed separately. (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease" and "Clinical features and treatment of autoimmune hemolytic anemia: Cold agglutinins" and "Paroxysmal cold hemoglobinuria".)

ETIOLOGY — A variety of factors may initiate the antibody production in warm agglutinin AIHA. This issue is discussed in detail separately. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Genesis of antibody production'.) Reviewed briefly, most cases are idiopathic, in that no underlying disorder or direct cause can be found.

Underlying causes — Underlying causes or conditions that may be associated with AIHA include the following:

- Preceding viral infections (usually in children). Typical AIHA due to the presence of warm agglutinins has been described in patients with HIV infection. (See "Hematologic manifestations of HIV infection: Anemia", section on 'Antibody-mediated'.)
- Autoimmune and connective tissue diseases (eg, systemic lupus erythematosus, autoimmune lymphoproliferative syndrome). (See "Hematologic manifestations of systemic lupus erythematosus in adults", section on 'Autoimmune hemolytic anemia' and "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis", section on 'Autoimmunity'.)
- Immune deficiency diseases, such as common variable immunodeficiency. (See "Clinical manifestations, epidemiology, and diagnosis of common variable immunodeficiency in adults", section on 'Autoimmune disease'.)
- Malignancies of the immune system (eg, non-Hodgkin lymphoma, chronic lymphocytic leukemia [CLL], with a higher incidence in those treated with purine analogs). (See "Overview of the complications of chronic lymphocytic leukemia", section on 'Autoimmune hemolytic anemia' and "Autoimmune complications following purine analog therapy", section on 'Autoimmune hemolytic anemia'.)
- Prior allogeneic blood transfusion, hematopoietic cell transplantation, or solid organ transplantation [3,4]. (See "Donor selection for hematopoietic cell transplantation", section on 'ABO and Rh status'.)

CLL may be a particular problem. It has been estimated that as many as 11 percent of patients with this disorder develop AIHA. The incidence is even higher in patients with CLL who are treated with purine analogs such as fludarabine [5,6], pentostatin (2-deoxycoformycin) [7], or cladribine (2-chlorodeoxyadenosine) [8]. Anemia has been severe in some cases, resulting in death [7,9]. Why purine analogs appear to predispose to AIHA in patients with CLL is not clear. One possibility is immune deregulation, which is a common complication when purine analogs are used in this setting [10,11]. (See "Overview of the complications of chronic lymphocytic leukemia", section on 'Autoimmune hemolytic anemia' and "Autoimmune complications following purine analog therapy", section on 'Autoimmune hemolytic anemia'.)

Drugs — A large number of drugs have been implicated as the cause of immune hemolytic anemia. This subject is discussed in depth separately. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Drug-related immune hemolysis'.)

CLINICAL MANIFESTATIONS — The signs and symptoms of AIHA are nonspecific and common to all types of anemia. The clinical syndrome seen with AIHA of the warm-antibody type varies greatly with the amount and effectiveness of the causative antibody. When the amount is small or the antibody is inefficient at effecting hemolysis, the patient may be asymptomatic even if slightly anemic. More commonly, the patient is moderately to severely anemic.

The likelihood of a patient with AIHA developing symptoms due to anemia is determined by the severity of the disease, whether the patient is at rest or during exertion, the rapidity with which the anemia develops, and whether there is concurrent illness (eg, underlying cardiac disease). In healthy resting humans, normal oxygen delivery can be maintained by enhanced extraction alone down to a hemoglobin concentration of 8 to 9 g/dL [12]; when the added compensation of increases in stroke volume and heart rate (and therefore cardiac output) are included, oxygen delivery can be maintained at a hemoglobin concentration as low as 5 g/dL (equivalent to a hematocrit of 15 percent) [13]. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult", section on 'Role of blood in oxygen delivery'.)

Symptoms will occur when the hemoglobin concentration falls below this level at rest, at higher hemoglobin concentrations during exertion, or when the cardiac compensation does not occur due to underlying heart disease. The primary symptoms include exertional dyspnea, dyspnea at rest, varying degrees of fatigue, and signs and symptoms of the hyperdynamic state, such as bounding pulses, palpitations, and "roaring in the ears." (See "Approach to the adult patient with anemia", section on 'Clinical consequences'.)

The clinical syndrome of AIHA may become life-threatening with more severe anemia. If the hemoglobin falls below a level able to sustain sufficient oxygenation, the patient may become lethargic, confused, and dyspneic with tachycardia. In such patients, corrective measures must be taken at once (eg, glucocorticoids, intravenous immunoglobulin, transfusion). It is important to remember that wholly compatible blood for transfusion will not be available, but that transfusion with the most compatible, quickly found unit(s) may be life-saving. If not corrected, death from pulmonary edema, myocardial infarction, or fatal cardiac arrhythmia is inevitable.

Physical examination may show varying degrees of pallor and jaundice. The spleen is commonly enlarged to a moderate degree. Signs and symptoms of cardiac decompensation may be present in those with severe anemia and/or underlying cardiac disease (eg, resting sinus tachycardia, narrow pulse pressure, diaphoresis, pulmonary congestion, peripheral edema, elevated jugular venous pressure). (See "Evaluation of the patient with suspected heart failure", section on 'Physical examination'.)

LABORATORY FINDINGS — Laboratory findings in patients with warm agglutinin AIHA include hemolytic anemia of varying severity, a reticulocytosis in response to the anemia, the presence of spherocytic red cells on the peripheral blood smear, and a positive direct antiglobulin (Coombs) test. These findings are discussed in detail below. An example of the baseline characteristics of 60 patients with warm agglutinin AIHA, seen in a French tertiary-care national referral center for adult autoimmune cytopenias is shown in the table (table 1) [14].

Hemolytic anemia — The laboratory findings in patients with warm agglutinin AIHA are those of hemolytic

anemia, with a hemoglobin usually in the range of 7 to 10 g/dL (equivalent to a hematocrit of 21 to 30 percent). As examples of typical values:

- In one series of 109 patients, the mean hematocrit at presentation was 24 percent, with 30 percent of patients having values below this level [15].
- Serum levels of lactate dehydrogenase (normal: 140 to 280 International Units/L) were elevated in 93 percent of patients in one series [14], with median levels of 511 Units/L in a second series [16]. Those presenting with severe anemia (ie, hemoglobin levels <8 g/dL) may have levels of LDH of 1000 or more [17].
- Serum haptoglobin levels were reduced in 93 percent of patients, often to unmeasurable levels [14].
- Serum levels of indirect bilirubin (normal range: 0.2 to 0.7 mg/dL; 3 to 12 micromol/L) were elevated in 87 percent of patients in one series [14], with median levels in the range of 35 to 51 micromoles/L (2.0 to 3.0 mg/dL [16].

The combination of an increased serum LDH and reduced haptoglobin is 90 percent specific for diagnosing hemolysis, while the combination of a normal serum LDH and a serum haptoglobin greater than 25 mg/dL is 92 percent sensitive for ruling out hemolysis [18,19]. (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Diagnostic approach'.)

Spherocytosis — The peripheral blood smear usually shows the presence of spherocytosis (picture 1 and picture 2), most often single but rarely in doublets [20], although spherocytes might not be obvious in milder cases [14]. Red blood cell (RBC) indices may show an elevated mean corpuscular hemoglobin concentration (MCHC), consistent with the presence of spherocytes and/or an increase in the mean corpuscular volume (MCV) indicative of an increase in the percent of reticulocytes. (See "Approach to the adult patient with anemia", section on 'Mean corpuscular hemoglobin concentration' and "Macrocytosis", section on 'Reticulocytosis'.)

Positive antiglobulin (Coombs) test — The diagnosis of warm agglutinin AIHA is based upon detection of antibody and/or complement components on the surface of the RBC (ie, a positive direct antiglobulin [Coombs] test), or, less commonly, in the circulation (ie, a positive indirect antiglobulin [Coombs] test). These are described below.

The direct Coombs test — In this test, the RBCs of the patient are washed free of adherent proteins and reacted with antiserum or monoclonal antibodies prepared against the various immunoglobulins, particularly IgG and a fragment of the third component of complement, C3d. When these tests are accurately and specifically performed, 97 to 99 percent of patients with warm agglutinin AIHA will exhibit a positive result with anti-IgG, anti-C3, or both, compared with less than 1 percent of the normal population (table 2) [21-23].

The Coombs test can be quantitated by an estimate of the degree of agglutination, or by more quantitative methods such as ELISA, immunoassay techniques, or flow cytometry [24-27]. The specificity of the antibody can be identified by eluting it from the red cells and testing it against a panel of red cells of known antigenic composition. In most cases, the antigen with which the antibody reacts is not polymorphic and occurs on the cells of almost all donors.

- In some instances, the antibody may have specificity for a known blood group antigen. This may be tested using serum in an indirect antiglobulin test or, preferably, using an eluate of the patient's red cells. Often, test cells of rare phenotype (eg, Rh_{null}) are necessary to establish a specificity.
- Antibodies of IgA or IgM isotype are rare causes of warm AIHA and can be detected with specific anti-IgA or anti-IgM antisera, respectively [28-33].

The indirect Coombs test — The indirect antiglobulin (Coombs) test, in which the patient's serum is incubated with normal red cells in order to test for the presence of circulating antibodies, is generally of little value for making the diagnosis in patients with warm AIHA. Exceptions include the following circumstances:

- When testing blood for compatibility for transfusion. (See "The incompatible crossmatch", section on 'Autoantibodies' and "Treatment of autoimmune hemolytic anemia: Warm agglutinins", section on 'Red blood cell transfusion'.)

- Antibodies of low affinity may sometimes be detected by enzymatically digesting the normal red cells used in an indirect antiglobulin test; this procedure increases the affinity between antigen and antibody. Sometimes the specificity of the antibody may be identified by the indirect Coombs alone.

Coombs negative AIHA — In less than 3 percent of patients with warm agglutinin AIHA, the direct Coombs test (the customary agglutination test used to diagnose AIHA) is negative. If Coombs negative AIHA is suspected, tests more sensitive and quantitative than this agglutination test may be needed in order to demonstrate the presence of increased numbers of bound immunoglobulin and/or complement molecules on the red cell surface [24,25]. Such tests (ie, the "super" Coombs) may not be generally available, but may be offered by specialized reference laboratories.

As an example, in one specialized laboratory employing a radioimmunoassay, the following observations were made concerning the number of IgG molecules per red blood cell in these various scenarios [34,35]:

- Normal subjects – 33 ± 13
- Average level in patients with Coombs negative AIHA – 179 ± 288
- Minimal level required for direct Coombs test positivity – 335 ± 72
- Average level in patients with Coombs positive AIHA – 1397 ± 1934

Reticulocyte response — The increase in erythropoietin production induced by anemia should raise the reticulocyte percentage above 4 to 5 percent; in one series of patients with AIHA, the median reticulocyte percentage at diagnosis was 9 percent [15]. The absolute reticulocyte count or the reticulocyte production index are preferred methods to measure the reticulocyte response. (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Reticulocyte response'.)

Some patients (20 to 37 percent in one series) with acute hemolysis do not have the expected degree of reticulocytosis [15], and a few may actually have reticulocytopenia [36]. This is most often due to a lag in marrow responsiveness to hemolytic stress [15]. Alternatively, the antibody may also be directed against Rh receptors that appear on late orthochromic normoblasts and lead to their recognition and removal by bone marrow macrophages, thus preventing reticulocytes from being formed. Other patients may have direct or indirect bone marrow suppression (eg, parvovirus B19 or other infection). (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Hemolysis without reticulocytosis'.)

Other findings — Thrombocytopenia due to immune destruction of the platelets is occasionally seen, especially in children (Evans-Duane syndrome). Signs of intravascular hemolysis (elevated plasma hemoglobin, hemoglobinuria, and hemosiderinuria) are not typical of warm AIHA, but may be present in severe cases.

DIAGNOSIS — The diagnosis of warm agglutinin AIHA is suspected in a patient who presents with the sudden onset of anemia, with laboratory evidence for hemolysis (ie, increased lactate dehydrogenase (LDH), increased indirect bilirubin, reduced to absent haptoglobin). The workup for such patients should include the following:

- Complete blood count with red blood cell indices (eg, MCV, MCH, MCHC), reticulocyte percentage, and examination of the peripheral blood smear
- Tests for hemolysis, including indirect bilirubin, lactate dehydrogenase, and haptoglobin
- Direct and Coombs testing, including testing for both IgG and C3 on the red cell surface
- Testing for specificity of the antibody for antigens identified on red blood cells

The diagnosis of warm agglutinin AIHA is made when all of the following are present (see 'Laboratory findings' above):

- Hemolytic anemia (anemia, high LDH, low haptoglobin, high indirect bilirubin)

- Presence of spherocytic red blood cells on the peripheral blood smear
- Positive direct or indirect antiglobulin (Coombs) test for the presence of IgG or C3d (after ruling out cold agglutinin disease) or both

While in most cases there will also be an absolute increase in reticulocytes, such reticulocytosis is a non-specific erythropoietic response to anemia of any cause, and may not be seen initially in some patients. (See 'Reticulocyte response' above.)

Evans syndrome — Evans syndrome (ES), the occurrence of two or more hematologic immune cytopenias, most often autoimmune hemolytic anemia and immune thrombocytopenia, is recognized as a special variant of AIHA [37]. Although usually described in children, adults may also have ES. In approximately half of the patients, no other immune disorder is recognized, but in half it may be a manifestation of systemic lupus erythematosus, common variable immune deficiency [38], autoimmune lymphoproliferative disorder [39,40], or another immune disorder [41]. (See "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis", section on 'Autoimmunity'.)

It is important to recognize ES and to test for these various underlying immune disorders [40], as ES is more difficult to treat and has a higher mortality than AIHA presenting alone. (See "Apoptosis and autoimmune disease", section on 'Autoimmune lymphoproliferative syndrome' and "Treatment of autoimmune hemolytic anemia: Warm agglutinins", section on 'Evans syndrome' and "Autoimmune lymphoproliferative syndrome (ALPS): Management and prognosis".)

DIFFERENTIAL DIAGNOSIS — The major differential diagnosis of warm AIHA includes hemolytic anemia due to drugs and AIHA due to the presence of cold agglutinins. Accordingly, a complete drug history is required as well as a history of the relationship, if any, between the onset of hemolysis and exposure to a drug known to be associated with warm AIHA or exposure to cold.

- **AIHA due to drugs** – A number of drugs can cause hemolytic anemia through an immune mechanism (table 3), resulting in a positive direct antiglobulin (Coombs) test (table 2). (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Drug-related immune hemolysis'.)

The immunosuppressive modalities used in warm agglutinin AIHA are generally not effective in cold agglutinin AIHA, which is generally due to the presence of IgM autoantibodies. Thus, distinction between warm and cold agglutinin AIHA is important for the selection of the proper treatment (table 2). The two most common conditions causing cold agglutinin AIHA are listed below:

- **AIHA due to cold agglutinins** – Symptoms of acral cyanosis upon exposure to cold temperatures and a direct Coombs test that is positive for C3 but not IgG are suggestive features; the diagnosis is confirmed by documenting the presence of high titers of cold agglutinins in the serum. (See "Clinical features and treatment of autoimmune hemolytic anemia: Cold agglutinins".)

- **Paroxysmal cold hemoglobinuria** – Patients with paroxysmal cold hemoglobinuria (PCH) typically present with intravascular hemolysis and darkly colored urine (hemoglobinuria), beginning a few minutes to several hours after exposure to cold along with the presence of an IgG antibody that reacts with the red cell at reduced temperature but not at 37°C and causes hemolysis on rewarming (ie, a positive Donath-Landsteiner antibody test). The direct antiglobulin (Coombs) test is positive for the presence of complement, but not IgG, during the acute hemolytic episode. (See "Paroxysmal cold hemoglobinuria".)

Patients with inherited causes of anemia often have evidence for hemolysis along with the presence of spherocytes on the peripheral blood smear and may not be easily distinguished from those with warm AIHA. Examples include:

- **Congenital spherocytosis** – Patients with congenital spherocytosis (CS) with life-long mild to moderate degrees of spherocytic hemolytic anemia may not be diagnosed until they become symptomatic following a concurrent illness or episode of transient aplasia due to parvovirus infection. A negative Coombs test and a positive personal and/or family history of anemia help to distinguish CS from warm AIHA. (See "Hereditary

spherocytosis: Clinical features, diagnosis, and treatment", section on 'Diagnosis'.)

- **Glucose 6-phosphate dehydrogenase deficiency** – Patients with this disorder (G6PD deficiency) are most often asymptomatic until they are exposed to a food or medication with oxidant potential, or following an acute infection. During such exacerbations, spherocytic hemolytic anemia is found. The presence of oxidized hemoglobin in circulating red cells (Heinz bodies) and a negative Coombs test help to distinguish G6PD deficiency from warm AIHA. (See "Diagnosis and treatment of glucose-6-phosphate dehydrogenase deficiency", section on 'Diagnosis'.)

DISEASE COMPLICATIONS — Two potential complications of warm AIHA are the development of a lymphoproliferative disorder and venous thromboembolic disease.

Lymphoproliferative disorder — The onset of idiopathic warm or cold AIHA may either precede or follow the diagnosis of a lymphoproliferative disorder (LPD) [42]. A LPD is suspected when the patient with a new or prior diagnosis of warm AIHA develops systemic symptoms (eg, weight loss, night sweats, fever), lymphadenopathy, and/or the presence of abnormal white blood cells on the peripheral blood smear. (See "Clinical presentation and diagnosis of non-Hodgkin lymphoma", section on 'Patient history'.)

In one series of 107 patients with idiopathic AIHA, 18 percent developed a malignant lymphoproliferative disorder (LPD) after a median time of approximately two years (range: 9 to 76 months) [43]. The following were risk factors for development of LPD in this group of patients:

- Advanced age
- Underlying autoimmune disease
- The presence of a monoclonal IgM gammopathy

AIHA may also follow the use of purine analog therapy in patients with chronic lymphocytic leukemia or other indolent non-Hodgkin lymphoma variants. (See "Autoimmune complications following purine analog therapy".)

Venous thromboembolism — An increased risk for venous thromboembolism (VTE), occasionally fatal, has been described in adults with idiopathic AIHA [14,44-46] as well as in those with AIHA and underlying HIV infection [47]. VTE may be especially common following splenectomy for inherited and acquired hemolytic anemias, including AIHA. In one study, for example, of nine patients with warm AIHA who underwent splenectomy, four developed post-operative portal vein thrombosis and a fifth developed pulmonary embolism [14]. (See "Approach to the adult patient with splenomegaly and other splenic disorders", section on 'Splenectomy'.)

While the presence of antiphospholipid antibodies or a "lupus anticoagulant" in 19 patients with AIHA was found to be a significant risk factor for the development of VTE in one study [48], this was not confirmed in a second report of 16 such patients [49]. Whether patients with warm AIHA and antiphospholipid antibodies or a lupus anticoagulant should receive prophylactic anticoagulation to prevent or reduce the risk of VTE is therefore an open question. (See "Clinical manifestations of the antiphospholipid syndrome", section on 'Thrombosis' and "Clinical manifestations of the antiphospholipid syndrome", section on 'Lupus anticoagulant'.)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient information: Autoimmune hemolytic anemia (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Etiology** – The cause in most cases of warm agglutinin autoimmune hemolytic anemia (AIHA) is unknown. In a minority of cases, an associated disorder may be present. These include (see 'Etiology' above):
  - Preceding viral infection, usually in children
  - Autoimmune disorders, especially systemic lupus erythematosus
  - Lymphoproliferative diseases (eg, chronic lymphocytic leukemia)
  - Disorders of immune deficiency/regulation (eg, common variable immunodeficiency)
  - Drugs (eg, penicillin, methyldopa)
  - Allogeneic blood transfusion or ABO-incompatible hematopoietic cell transplantation
- **Clinical manifestations** – The clinical syndrome seen with AIHA of the warm-antibody type varies greatly with the amount and effectiveness of the causative antibody (see 'Clinical manifestations' above).
  - When the amount is small or the antibody is inefficient at effecting hemolysis, the patient may be asymptomatic even if slightly anemic.
  - More commonly, the patient may complain of shortness of breath and dyspnea on exertion. If the hemolysis is severe and of sudden onset, symptoms may be those of severe degrees of cardiac decompensation, including heart failure, arrhythmia, and/or chest pain, constituting a medical emergency.
  - Physical examination usually reveals pallor, jaundice, and moderate splenomegaly.
- **Laboratory testing** – Recommended laboratory tests to document the presence and extent of AIHA include the following (see 'Laboratory findings' above):
  - Complete blood count with red blood cell indices (eg, MCV, MCH, MCHC), reticulocyte percentage, and examination of the peripheral blood smear
  - Tests for hemolysis, including indirect bilirubin, lactate dehydrogenase, and haptoglobin
  - Direct and indirect Coombs testing, including testing for both IgG and C3 on the red cell surface
  - Testing for specificity of the antibody for antigens identified on red blood cells
- **Diagnosis** – Accurate diagnosis requires documentation of the following features (see 'Diagnosis' above):
  - Anemia is usually present and may be severe. The mean corpuscular hemoglobin concentrations (MCHC) is increased, reflecting spherocytosis. If anemia has been present long enough, the absolute reticulocyte count and the mean corpuscular volume (MCV) will be elevated, reflecting the bone marrow's response to anemia.
  - Laboratory findings indicating the presence of hemolysis include elevated levels of indirect bilirubin and lactate dehydrogenase, along with reduced levels of haptoglobin. (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Diagnostic approach'.)
  - The peripheral blood smear shows the presence of spherocytes, usually with an increased number of polychromatophilic red cells (reticulocytes) (picture 1).
  - The diagnosis of warm agglutinin AIHA is based upon detection of antibody and/or complement components on the surface of the RBC, usually by the direct antiglobulin (Coombs) test. Ninety-seven to 99 percent of patients with warm agglutinin AIHA will exhibit a positive result with anti-IgG, anti-C3, or both. (See 'Positive antiglobulin (Coombs) test' above.)
- **Treatment** – Treatment of warm agglutinin AIHA is discussed separately. (See "Treatment of autoimmune

hemolytic anemia: Warm agglutinins".)

REFERENCES

1. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002; 69:258.
2. Petz LD. Treatment of autoimmune hemolytic anemias. Curr Opin Hematol 2001; 8:411.
3. Young PP, Uzieblo A, Trulock E, et al. Autoantibody formation after alloimmunization: are blood transfusions a risk factor for autoimmune hemolytic anemia? Transfusion 2004; 44:67.
4. Hoffman PC. Immune hemolytic anemia--selected topics. Hematology Am Soc Hematol Educ Program 2009; :80.
5. Gonzalez H, Leblond V, Azar N, et al. Severe autoimmune hemolytic anemia in eight patients treated with fludarabine. Hematol Cell Ther 1998; 40:113.
6. Myint H, Copplestone JA, Orchard J, et al. Fludarabine-related autoimmune haemolytic anaemia in patients with chronic lymphocytic leukaemia. Br J Haematol 1995; 91:341.
7. Byrd JC, Hertler AA, Weiss RB, et al. Fatal recurrence of autoimmune hemolytic anemia following pentostatin therapy in a patient with a history of fludarabine-associated hemolytic anemia. Ann Oncol 1995; 6:300.
8. Fleischman RA, Croy D. Acute onset of severe autoimmune hemolytic anemia after treatment with 2-chlorodeoxyadenosine for chronic lymphocytic leukemia. Am J Hematol 1995; 48:293.
9. Tertian G, Cartron J, Bayle C, et al. Fatal intravascular autoimmune hemolytic anemia after fludarabine treatment for chronic lymphocytic leukemia. Hematol Cell Ther 1996; 38:359.
10. Juliusson G. Complications in the treatment of CLL with purine analogues. Hematol Cell Ther 1997; 39 Suppl 1:S41.
11. Beyer M, Kochanek M, Darabi K, et al. Reduced frequencies and suppressive function of CD4+CD25hi regulatory T cells in patients with chronic lymphocytic leukemia after therapy with fludarabine. Blood 2005; 106:2018.
12. Jones J. Transfusion in oligemia. In: Blood Transfusion in Clinical Medicine, 8th ed, Mollison PL, Engelfriet CP, Contreras M (Eds), Blackwell, Oxford 1987. p.41.
13. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 1998; 279:217.
14. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients. Am J Hematol 2014; 89:E150.
15. Liesveld JL, Rowe JM, Lichtman MA. Variability of the erythropoietic response in autoimmune hemolytic anemia: analysis of 109 cases. Blood 1987; 69:820.
16. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia. Br J Haematol 2013; 163:393.
17. Barcellini W, Fattizzo B, Zaninoni A, et al. Clinical heterogeneity and predictors of outcome in primary autoimmune hemolytic anemia: a GIMEMA study of 308 patients. Blood 2014; 124:2930.
18. Marchand A, Galen RS, Van Lente F. The predictive value of serum haptoglobin in hemolytic disease. JAMA 1980; 243:1909.
19. Galen RS. Application of the predictive value model in the analysis of test effectiveness. Clin Lab Med 1982; 2:685.
20. Mantripragada K, Quesenberry PJ. Doublet spherocytes. Blood 2014; 124:12.
21. Chaplin H Jr. Clinical usefulness of specific antiglobulin reagents in autoimmune hemolytic anemias. Prog

Hematol 1973; 8:25.

22. Wheeler CA, Calhoun L, Blackall DP. Warm reactive autoantibodies: clinical and serologic correlations. Am J Clin Pathol 2004; 122:680.
23. Sachs UJ, Röder L, Santoso S, Bein G. Does a negative direct antiglobulin test exclude warm autoimmune haemolytic anaemia? A prospective study of 504 cases. Br J Haematol 2006; 132:655.
24. Podberezin M, Levina A, Romanova L, et al. Quantitation of red cell-bound immunoglobulins and complement in lymphoma patients. Immunohematology 2000; 16:147.
25. Bencomo AA, Diaz M, Alfonso Y, et al. Quantitation of red cell-bound IgG, IgA, and IgM in patients with autoimmune hemolytic anemia and blood donors by enzyme-linked immunosorbent assay. Immunohematology 2003; 19:47.
26. Nathalang O, Chuansumrit A, Prayoonwiwat W, et al. Comparison between the conventional tube technique and the gel technique in direct antiglobulin tests. Vox Sang 1997; 72:169.
27. Lin JS, Hao TC, Lyou JY, et al. Clinical application of a flow cytometric direct antiglobulin test. Transfusion 2009; 49:1335.
28. Garratty G, Arndt P, Domen R, et al. Severe autoimmune hemolytic anemia associated with IgM warm autoantibodies directed against determinants on or associated with glycophorin A. Vox Sang 1997; 72:124.
29. Reusser P, Osterwalder B, Burri H, Speck B. Autoimmune hemolytic anemia associated with IgA--diagnostic and therapeutic aspects in a case with long-term follow-up. Acta Haematol 1987; 77:53.
30. Janvier D, Sellami F, Missud F, et al. Severe autoimmune hemolytic anemia caused by a warm IgA autoantibody directed against the third loop of band 3 (RBC anion-exchange protein 1). Transfusion 2002; 42:1547.
31. Bardill B, Mengis C, Tschopp M, Wuillemin WA. Severe IgA-mediated auto-immune haemolytic anaemia in a 48-yr-old woman. Eur J Haematol 2003; 70:60.
32. Arndt PA, Leger RM, Garratty G. Serologic findings in autoimmune hemolytic anemia associated with immunoglobulin M warm autoantibodies. Transfusion 2009; 49:235.
33. Bartolmäs T, Salama A. A dual antiglobulin test for the detection of weak or nonagglutinating immunoglobulin M warm autoantibodies. Transfusion 2010; 50:1131.
34. Kamesaki T, Oyamada T, Omine M, et al. Cut-off value of red-blood-cell-bound IgG for the diagnosis of Coombs-negative autoimmune hemolytic anemia. Am J Hematol 2009; 84:98.
35. Kamesaki T, Toyotsuji T, Kajii E. Characterization of direct antiglobulin test-negative autoimmune hemolytic anemia: a study of 154 cases. Am J Hematol 2013; 88:93.
36. Conley CL, Lippman SM, Ness P. Autoimmune hemolytic anemia with reticulocytopenia. A medical emergency. JAMA 1980; 244:1688.
37. Michel M, Chanet V, Dechartres A, et al. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood 2009; 114:3167.
38. Savaşan S, Warrier I, Buck S, et al. Increased lymphocyte Fas expression and high incidence of common variable immunodeficiency disorder in childhood Evans' syndrome. Clin Immunol 2007; 125:224.
39. Teachey DT, Manno CS, Axsom KM, et al. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). Blood 2005; 105:2443.
40. Seif AE, Manno CS, Sheen C, et al. Identifying autoimmune lymphoproliferative syndrome in children with Evans syndrome: a multi-institutional study. Blood 2010; 115:2142.
41. Stepensky P, Rensing-Ehl A, Gather R, et al. Early-onset Evans syndrome, immunodeficiency, and premature immunosenescence associated with tripeptidyl-peptidase II deficiency. Blood 2015; 125:753.
42. Genty I, Michel M, Hermine O, et al. [Characteristics of autoimmune hemolytic anemia in adults: retrospective analysis of 83 cases]. Rev Med Interne 2002; 23:901.
43. Sallah S, Wan JY, Hanrahan LR. Future development of lymphoproliferative disorders in patients with autoimmune hemolytic anemia. Clin Cancer Res 2001; 7:791.
44. Allgood JW, Chaplin H Jr. Idiopathic acquired autoimmune hemolytic anemia. A review of forty-seven cases

treated from 1955 through 1965. Am J Med 1967; 43:254.

45. Hendrick AM. Auto-immune haemolytic anaemia--a high-risk disorder for thromboembolism? Hematology 2003; 8:53.
46. Yusuf HR, Hooper WC, Beckman MG, et al. Risk of venous thromboembolism among hospitalizations of adults with selected autoimmune diseases. J Thromb Thrombolysis 2014; 38:306.
47. Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. AIDS Patient Care STDS 2001; 15:311.
48. Pullarkat V, Ngo M, Iqbal S, et al. Detection of lupus anticoagulant identifies patients with autoimmune haemolytic anaemia at increased risk for venous thromboembolism. Br J Haematol 2002; 118:1166.
49. Comellas-Kirkerup L, Hernández-Molina G, Cabral AR. Antiphospholipid-associated thrombocytopenia or autoimmune hemolytic anemia in patients with or without definite primary antiphospholipid syndrome according to the Sapporo revised classification criteria: a 6-year follow-up study. Blood 2010; 116:3058.

Topic 7078 Version 21.0

GRAPHICS

Baseline characteristics of 60 patients with warm agglutinin autoimmune hemolytic anemia (AIHA)

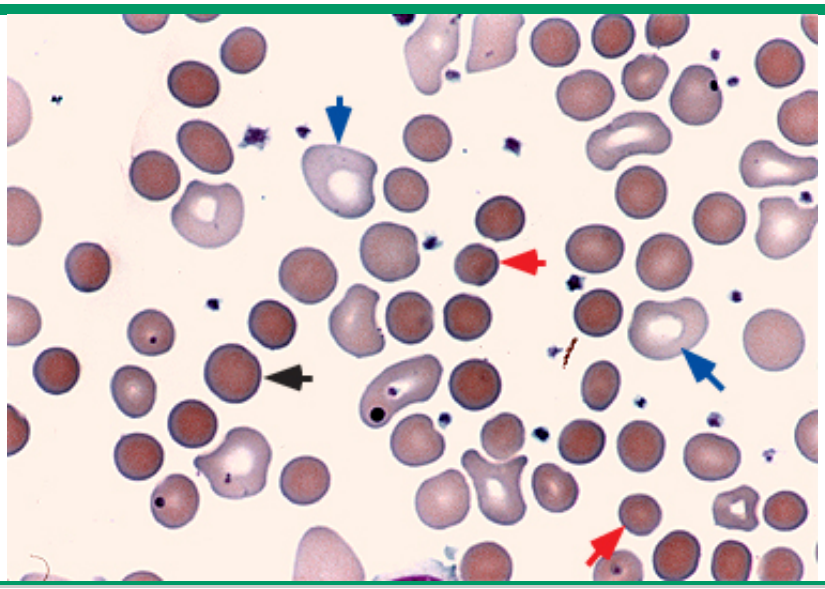
Mean age at AIHA onset	53.6 ± 22.8 years (mean ± SD)
Percent females	50%
Clinical symptoms at onset	87%
Anemia-related symptoms	75%
Jaundice/dark urine	33%
Chest pain/coronary syndrome	7%
Venous thrombosis	20%
Mean hemoglobin at onset	6.4 ± 1.7 g/dL
Mean reticulocytes at onset	285 ± 175 x 10^3/microL
MCV at onset	108 ± 14 fL
Decreased haptoglobin	93%
Increased LDH	93%
Increased bilirubin	82%
Spherocytes at onset	41%
Immune thrombocytopenia	5%
Hypergammaglobulinemia	31%
Hypogammaglobulinemia	20%
Monoclonal immunoglobulin	30%
Antinuclear antibodies	30%
Direct antiglobulin test positivity	100% (eligibility requirement)
IgG only	40%
IgG plus C3d	57%
Other	3% (one each of C3d only and IgA only)
Secondary cause present	62%
Lymphoproliferative disorder	33%
Autoimmune disorder	14%
Miscellaneous disorders	14% (ulcerative colitis, immunodeficiency, HCV, carcinoma, drug)

AIHA: autoimmune hemolytic anemia; MCV: mean corpuscular volume; LDH: lactate dehydrogenase; HCV: hepatitis C virus.

Data from: Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients. Am J Hematol 2014; 89:E150.

Graphic 97136 Version 1.0

Peripheral blood smear in autoimmune hemolytic anemia (AIHA)

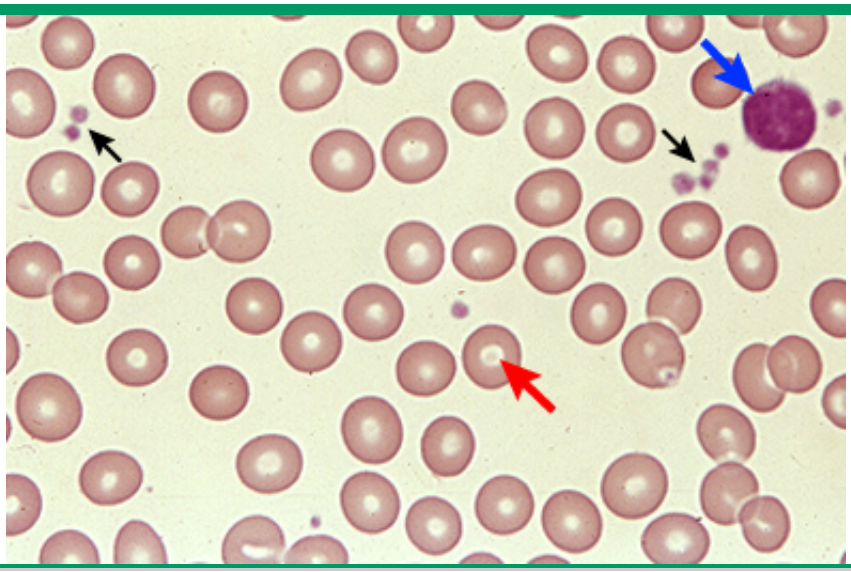


This peripheral blood smear from a patient with autoimmune hemolytic anemia (AIHA) due to a warm-reactive IgG antibody demonstrates the presence of many dark red small microspherocytes (red arrows) and larger spherocytes (black arrow) (x1000). Many large irregular blue-tinted red cells are also present, representing reticulocytes (blue arrows).

Reproduced from: Ware RE. Autoimmune hemolytic anemia. In: Nathan and Oski's Hematology of Infancy and Childhood, 7th Ed, Orkin S, Nathan DG, Ginsburg D, et al (Eds), Saunders, Philadelphia 2009. Illustration used with the permission of Elsevier Inc.

Graphic 53523 Version 3.0

Normal peripheral blood smear



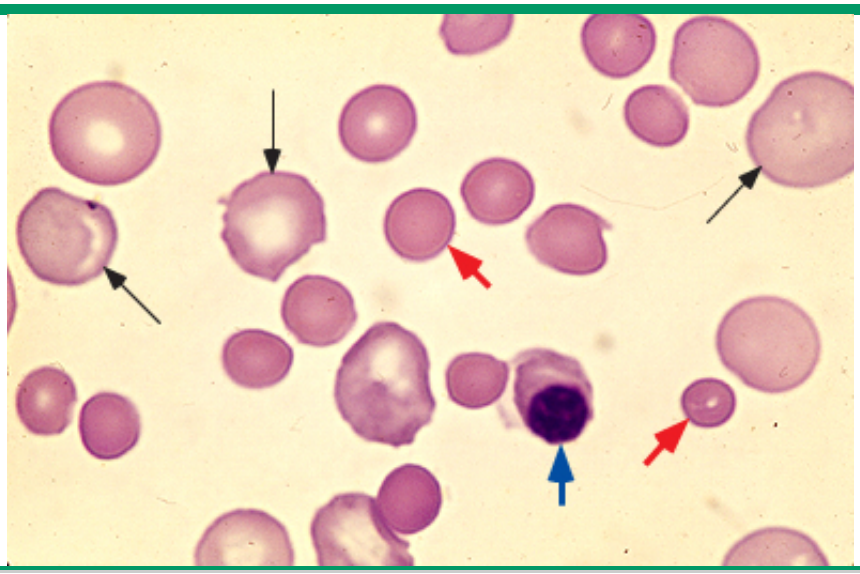
High power view of a normal peripheral blood smear. Several

platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (red arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Peripheral smear in severe autoimmune hemolytic anemia



Peripheral blood smear from a patient with Coombs positive autoimmune hemolytic anemia. The smear shows the presence of many spherocytes (red arrows), one nucleated red blood cell (blue arrow), and a number of larger polychromatophilic red cells (black arrows), representing a reticulocytosis in response to the anemia.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50601 Version 2.0

Significance of the pattern of positive direct antiglobulin (Coombs) test in the diagnosis of autoimmune hemolytic anemia (AIHA)

Anti-IgG	Anti-C3	Occurrence	Antibody	Antigen	Comment
+	-	AIHA	IgG	Rh protein complex	Not seen in SLE; aldomet-induced
+	-	Drug-induced	IgG	Drug attached to Rh complex	Penicillin and aldomet
+	+	Drug-induced	IgG	?	Fludarabine and cogeners
+	+	AIHA	IgG	Glycoprotein	Antibody fixes complement
+	+	Drug-induced	IgG	Drug + protein	Drug affixed to protein; needed to detect in serum
-	+	Drug-induced	IgM or IgG	Drug + protein	Drug not firmly affixed to protein; drug needed to detect serum antibody
-	+	AIHA	IgG	?	Antibody of low affinity (may be detected with enzyme treated red cells)
-	+	AIHA	IgM or IgA	?	Warm-reacting antibody detected with specific anti-isotype antisera
-	+	Cold agglutinin disease	IgM	Polysaccharide	Cold agglutinins in high titer in serum
-	+	Paroxysmal cold hemoglobinuria	IgG	P antigen (polysaccharide)	Antibody fixes complement in the cold. Hemolysis occurs when sample/patient is warmed. Donath-Landsteiner test may be positive.

AIHA: autoimmune hemolytic anemia; SLE: systemic lupus erythematosus.

Courtesy of Wendell F Rosse, MD.

Graphic 69817 Version 4.0

Drugs associated with immune hemolytic anemia and/or a positive DAT (Coombs test)*

Aceclofenac	Diethylstilbestrol	p-aminosalicylic acid
Acetaminophen	Diphenylhydantoin	Penicillin G
Aminopyrine/pyramidon	Dipyrone	Phenacetin
Amoxicillin	Erythromycin	Piperacillin
Amphotericin B	Etodolac	Probenicid
Ampicillin	Fenoprofen	Procainamide
Antazoline	Fludarabine	Propyphenazone
Butizide	Fluorescein	Quinidine
Carbenicillin	Fluoroquinolones (eg, temafloxacin)	Quinine
Carbimazole		Ranitidine
Carboplatin	Fluorouracil	Rifampicin
Carbromal	Glafenine	Sodium pentothal/thiopental
Catergen/cyanidanol	Hydrazlazine	
Cefamandole	Hydrochlorothiazide	Stibophen
Cefazolin	9-hydroxy-methyl- ellipticinium	Streptokinase
Cefixime	Ibuprofen	Streptomycin
Cefotaxime	Indene derivatives (eg, sulindac)	Sulbactam sodium
Cefotetan	Insulin	Sulindac
Cefoxitin	Interferon	Sulfonamides
Ceftazidime	Interleukin-2	Sulfasalazide
Ceftizoxime	Isoniazid	Sulfonylurea derivatives
Ceftriaxone	Latamoxef	(eg, chlorpropamide and tolbutamide)
Cephalexin	Levodopa	Suprofen
Cephaloridine	Mefenamic acid	Tazobactam sodium
Cephalothin	Mefloquine	Teicoplanin
Chlordiazepoxide	Melphalan	Temafloxacin
Chlorinated hydrocarbons	6-mercaptopurine	Teniposide
Chlorpromazine	Methicillin	Tetracycline
Chlorpropamide	Methotrexate	Ticarcillin
Cianidanol	Methyldopa	Tolbutamide
Cisplatin	Metrizoate-based radiographic contrast media	Tolmetin
Cladribine	Nafcillin	Triamterene
Clavulanate potassium	Nomifensine	Trimetallic anhydride

Diclofenac	Norfloxacin	Zomepirac
	Oxaliplatin	

* Only drugs with serologic evidence for the presence of antibodies (indirect and/or direct) have been included in this table.

Reproduced with permission from: Arndt P, Garraty G. The changing spectrum of drug-induced immune hemolytic anemia. Seminars in Hematology 2005; 42:138. Copyright © 2005 Elsevier.

Graphic 75322 Version 3.0

Disclosures

Disclosures: **Stanley L Schrier, MD** Nothing to disclose. **Wendell F Rosse, MD** Consultant/Advisory Boards: Alexion [PNH, complement-mediated disease (eculizumab)]. **William C Mentzer, MD** Equity Ownership/Stock Options: Johnson & Johnson [Anemia (Erythropoietin)]. **Stephen A Landaw, MD, PhD** Employment (Spouse): Mass Medical Society (New England Journal of Medicine).

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy