Clinical features and treatment of autoimmune hemolytic anemia: Cold agglutinins

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INTRODUCTION — Cold agglutinin disease (ie, cold agglutinin associated autoimmune hemolytic anemia) is typically characterized by the presence of clinical symptoms related to exposure to cold, hemolytic anemia, and antibodies (most commonly IgM, rarely IgA or IgG) directed against polysaccharide antigens on the red blood cell surface that are responsible for the agglutination of red cells at low temperatures [1]. (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease".)

This topic will review the clinical manifestations, diagnosis, and treatment of autoimmune hemolytic anemia (AIHA) due to cold agglutinins [2]. Paroxysmal cold hemoglobinuria, another form of cold-related hemolysis, as well as the clinical features and treatment of AIHA due to warm agglutinins are discussed separately. (See "Paroxysmal cold hemoglobinuria" and "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins" and "Treatment of autoimmune hemolytic anemia: Warm agglutinins".)

EPIDEMIOLOGY — Cold agglutinin disease is rare, most often affecting females in the seventh decade of life, with an incidence of one case per million people per year [3]. As an example, in a single institutional experience with 43,000 patients having a monoclonal gammopathy, less than 1 percent had cold-reactive autoantibodies [4].

In the largest reported series to date, covering 89 patients, the median age at diagnosis was 72 years (range: 43 to 91), while the median age at the onset of symptoms was 65 years (range: 41 to 83). Sixty-one percent of the subjects were females [4]. In two series the median survival following diagnosis was 10.6 and 12.5 years, being similar to that of an age- and sex-matched normal population [3,4].

CLINICAL MANIFESTATIONS — Pathologic cold agglutinins are produced either in response to infection or by paraneoplastic or neoplastic growth of a single immunocyte clone. In either case, they generally share the same immunochemical characteristics and polysaccharide specificities, and result in the same clinical manifestations.

Symptoms — Patients with cold agglutinin AIHA may have symptoms related to both the anemia and the agglutination of red blood cells. In the series noted above, the following chief concerns were present at the time of diagnosis [4]:

- Anemia – 35 percent
- Acrocyanosis – 24 percent
- Fatigue – 21 percent
- Weakness or dyspnea on exertion – 7 percent
- Hemoglobinuria – 3 percent

In other series, cold-induced symptoms ranging from moderate acrocyanosis to disabling Raynaud phenomena triggered by slight cold exposure have been noted in more than 90 percent of unselected patients [3], along with characteristic seasonal variations in which hemolysis is worsened or improved when ambient temperatures are lower or higher, respectively [5]. Other cold-induced changes have included livedo reticularis, urticaria, and, rarely, cutaneous necrosis [6-9].

Approximately two-thirds of the patients also experience "paradoxical" exacerbations of hemolysis precipitated by febrile illnesses, trauma, or surgery, thought to be due to transient increases in complement levels. (See

'Complement levels' below.)

Anemia — In general, the symptoms of anemia include exertional dyspnea, dyspnea at rest, varying degrees of fatigue, and signs and symptoms of the hyperdynamic state; the intensity of these symptoms varies with both the degree and rapidity of the fall in hematocrit. (See 'Laboratory findings' below and "Approach to the adult patient with anemia", section on 'Clinical consequences'.)

While anemia in this disorder is usually considered to be mild to moderate in severity, in two series it was of sufficient severity to require transfusion in more than 50 percent of patients, and therapy was considered necessary in 70 percent [3,10]. Levels as low as 4.5 to 6.2 g/dL have been reported [4,11].

Signs and symptoms on exposure to cold — Patients with cold agglutinin syndrome may also have symptoms related to the agglutination of red cells in vivo upon exposure to cold ambient temperatures. The most common manifestations of this process are livedo reticularis (picture 1) and acrocyanosis, a dark, purple to gray discoloration of the skin on the most acral parts: finger tips, toes, nose, and ears. These changes disappear upon warming of the part, and there is little or no reactive hyperemia, as occurs in the Raynaud phenomenon. This process may be sufficiently severe to cause ulceration of the skin. Patients may also complain of pain and discomfort on swallowing cold food or liquids.

Other physical findings — Patients with cold agglutinin disease also may have scleral icterus from the resulting hemolysis, although splenomegaly, if present, is not prominent. If enlarged lymph nodes are present, an underlying systemic lymphoma should be suspected.

Disease spectrum from benign to malignant — Conditions associated with the presence of cold agglutinins appear to be part of a spectrum that ranges from "benign" cold agglutinin disease to high-grade malignant lymphoma [12-17]. In two series, an underlying hematologic malignancy was noted in over 75 percent of patients with cold agglutinin disease, whereas monoclonal $CD20^+$ $kappa^+$ lymphocytes were detected in bone marrow aspirates from 90 percent of patients in whom flow cytometric immunophenotyping had been performed [2,4]. (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease", section on 'Association with malignancy'.)

In a review of bone marrow histology in 66 patients otherwise classified as having primary cold agglutinin disease, the following histologic findings were observed [3]:

- Normal or reactive: 11 percent
- Irregular lymphoid hyperplasia: 13 percent
- Lymphoplasmacytic lymphoma: 50 percent
- Marginal zone lymphoma: 8 percent
- Small lymphocytic B cell lymphoma: 6 percent
- Clonal lymphocytosis/other small B cell lymphoma: 12 percent

Cold agglutinin-associated lymphoproliferative disorder may constitute a distinct entity, different from lymphocytoplasmic lymphoma. In one study, the responsible cells had neither the characteristics of plasma cells nor of the cells typical of lymphocytoplasmic lymphoma [18].

Association with infection — Cold agglutinins regularly occur during the course of two infections, Mycoplasma pneumoniae (primary atypical pneumonia) [19] and infectious mononucleosis [20]. In the former, they are usually specific for the I antigen and in the latter, the i antigen (table 1). Although low titers of these antibodies are frequently encountered in patients with these disorders, clinical manifestations of cold agglutinin syndrome occur only in those unusual cases in which the antibody titer is greatly elevated. (See "Infectious mononucleosis in adults and adolescents" and "Mycoplasma pneumoniae infection in adults", section on 'Hemolysis'.)

Less commonly, cold agglutinins are associated with other bacterial and viral diseases, such as cytomegalovirus, Epstein-Barr virus, legionella, Citrobacter, influenza, and varicella [4,21]. One bacterial infection, a particular strain

of Listeria monocytogenes, may also cause the production of anti-I antibodies because of shared epitopes on its surface.

When cold agglutinin production is secondary to Mycoplasma infection or infectious mononucleosis, it usually occurs approximately two weeks after the onset of the primary disease. Peak antibody titers are quickly reached and diminish as soon as the illness begins to resolve. The titer is usually back to normal three to four months after the initial occurrence. The manifestations of the primary disease often predominate, although hemolysis can be significant in some cases. (See "Mycoplasma pneumoniae infection in adults", section on 'Laboratory abnormalities'.)

Benign monoclonal variant — The benign variant (chronic cold agglutinin syndrome) is due to a monoclonal IgM gammopathy, which usually occurs in persons >60 years of age. The antibody is nearly always of anti-I in specificity and characterized by bearing kappa light chains (ie, IgM kappa). In many patients it persists without change for a number of years. However, in 5 to 10 percent of patients who present with chronic cold agglutinin syndrome, a malignant clone arises that also expresses the cold agglutinin. This may be heralded by an increasing titer of the antibody, even before the other manifestations of the disease (eg, enlarged lymph nodes, circulating malignant lymphocytes) may be manifest. The presence of trisomy 3 on chromosomal analysis of the lymphocytes may predict for this transformation [22,23]. (See "Recognition of monoclonal proteins", section on 'Clonal size' and "Diagnosis of monoclonal gammopathy of undetermined significance", section on 'IgM MGUS'.)

Lymphoid malignancies — Among patients with lymphoid malignancy, those with the most indolent variants (chronic lymphocytic leukemia, small lymphocytic lymphoma) may have antibodies with specificity for the I antigen, whereas those with the more aggressive forms are more likely to have antibodies with specificity for the i antigen. There are exceptions to this rule, but the finding of an anti-i antibody in the absence of viral disease is usually a clear indication that the patient is harboring a lymphoma.

Whenever the cold agglutinin is the result of malignant proliferation, its concentration in the plasma may be used as a tumor marker. The antibody may disappear with appropriate treatment and reappear with relapse of the tumor.

Non-lymphoid malignancies — Monoclonal cold agglutinins, usually anti-I in specificity and bearing kappa light chains, may occur in patients with nonlymphocytic tumors, particularly adenocarcinomas [24]. The age of the patients with such tumors usually corresponds to the time of highest natural incidence of cold agglutinins (age >60); it is therefore likely that the two conditions are coincidental, rather than related [19,20].

LABORATORY FINDINGS

Anemia — The anemia of cold agglutinin disease is highly variable but is usually only of moderate severity and is mainly due to extravascular hemolysis. In some cases, however, an IgG antibody accompanies the cold agglutinin (so-called "mixed" autoimmune hemolytic anemia), in which case the hemolytic anemia may be more severe and may also be intravascular [11,25]. (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease", section on 'Pathophysiology of RBC destruction'.)

Great care must be taken in analyzing the blood on flow cytometry. Cold agglutinins, activated by a fall in temperature either in the sample prior to counting or during cooling of the sample within the apparatus itself, will cause red blood cells (RBCs) to pass through the counter in small groups, rather than one by one, and will be counted as macrocytic cells [26]. This problem is sufficiently common that spurious macrocytosis should be considered a clue to the possible presence of cold agglutinins. (See "Macrocytosis", section on 'Spurious macrocytosis'.)

There are two general ways to determine that these sorts of cold-induced artifact have occurred:

- Examination of the peripheral smear (or alternatively of a cooled RBC suspension) may confirm the presence of RBC agglutination (picture 2).
- Examination of the erythrocyte volume histograms as printed out by the automated counter may show that

populations of RBCs are present with a mean corpuscular volume (MCV) two to three times that of the patient's normal RBC [27]. These abnormal populations should disappear on warming of the sample to 37°C before analysis if cold agglutinins are present.

Reticulocyte count — The reticulocyte count is most often elevated in response to the patient's anemia. On occasion, the increase may be less than one would expect for the degree of anemia, suggesting the presence of immune-mediated destruction or apoptosis of red cell precursors, marrow suppression (eg, infection, malignancy, chemotherapy), or concomitant nutrient deficiency (eg, iron, folate, B12). (See "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Hemolysis without reticulocytosis'.)

In particular, reticulocytopenia in a patient with severe anemia appears to be a feature indicating a worse prognosis, and may be an indication for the use of erythropoietin to overcome the inadequate bone marrow response [11,28-30].

Bone marrow — The bone marrow usually shows erythroid hyperplasia and may show the presence of lymphoplasmacytic aggregates. The latter are often nearly monoclonal (light chain restricted) on analysis and consist of cells that are making the antibody. When lymphoma supervenes, the aggregates may become larger and confluent.

Antiglobulin (Coombs) test — In the antiglobulin (Coombs) test, the RBCs of the patient are washed free of adherent proteins and reacted with antiserum or monoclonal antibodies prepared against the various immunoglobulins and a fragment of the third component of complement, C3d. This test is invariably positive using anti-C3 and is usually negative with anti-IgG (table 2). However, when an IgG antibody accompanies the cold agglutinin, the test may be positive with anti-IgG as well.

Cold agglutinins — Great care must be taken in collecting blood for cold agglutinin titration; the specimen must be maintained at 37 to 40°C until the clot has formed and retracted and the serum has been removed.

The titer of cold agglutinin in the serum (ie, the highest dilution of the serum sample at which agglutination of red cells in the cold is still seen) is highly variable among affected patients, but is usually quite constant for a given patient. Cold agglutinins are typically present in virtually all normal individuals in low titer (less than 1 in 64, and usually less than 1 in 10), with no age or seasonal variation [31]. On the other hand, the titer in patients with cold agglutinin syndrome may reach or exceed 1 in 50,000, and is typically higher than 1 in 2000 [3]. Hemolysis is seldom seen if the titer is less than 1 in 512, although exceptions exist [4].

In addition to the concentration of antibody, the amount of hemolysis also depends upon other factors, including the thermal amplitude of the interaction (ie, the highest temperature at which antibody and antigen are able to interact), inhibition of antibody binding by cell bound C3, and the presence of hexameric IgM antibodies. Some cold agglutinins are cryoprecipitable (ie, cryoglobulins); these antibodies generally fix C1 poorly. When cryoglobulins are present acral necrosis is sometimes seen, but hemolysis is often less than expected for the titer of antibody. Rare cold agglutinins are IgA and do not fix C1 at all.

Complement levels — Because of constant consumption, serum levels of complement proteins C3 and C4 are low in most patients with cold agglutinin disease, which may limit further extra- and intravascular hemolysis [2]. Complement levels may rise during acute phase responses in these patients, resulting in "paradoxical" exacerbations of the anemia following febrile disease, trauma, or surgery [32].

DIAGNOSIS — The diagnosis of cold agglutinin disease is suspected in the patient complaining of pain and discomfort on exposure to cold as well as on swallowing cold food or liquids (see 'Signs and symptoms on exposure to cold' above).

The diagnosis is confirmed when all of the following are present:

- A peripheral blood smear showing red blood cell aggregates (picture 2).
- Presence of a high titer of cold agglutinins. While the upper limit of normal is 1 in 40, hemolysis is not usually

seen unless titers are above 1 in 512. The typical patient with cold agglutinin disease has a titer in excess of 1 in 2000. (See 'Cold agglutinins' above.)

- Positive direct antiglobulin (Coombs) test for the presence of bound complement on red cells. The test is usually negative for bound IgG. (See 'Antiglobulin (Coombs) test' above.)
- The additional diagnosis of mycoplasma infection, infectious mononucleosis, or lymphoma should be made under appropriate clinical circumstances. (See 'Clinical manifestations' above.)

After a diagnosis is made, patients should be evaluated for infection, lymphoma, or an autoimmune disorder (eg, rheumatoid arthritis, systemic lupus erythematosus), as more than 70 percent of such patients will have one of these associated conditions [4]. Because of the high incidence of lymphoma in patients with cold agglutinin disease, it has been suggested that all patients undergo the following additional tests [2]:

- Measurement of serum immunoglobulin classes
- Serum protein electrophoresis, including immunofixation
- Flow cytometry of a bone marrow aspirate sample
- Bone marrow aspirate/biopsy examination by an experienced hematopathologist

As mentioned above, an IgM Kappa monoclonal immunoglobulin is likely to be present in 90 percent of these patients and a frank lymphoma in about 76 percent, with the most common being lymphoplasmacytic lymphoma/Waldenström macroglobulinemia and marginal zone lymphoma. (See 'Disease spectrum from benign to malignant' above.)

DIFFERENTIAL DIAGNOSIS — If all of the following three features are present (symptoms on exposure to cold, a high titer of cold agglutinins, and a positive direct antiglobulin [Coombs] test for bound complement), the diagnosis of cold agglutinin disease should be made. If only one or two are present, the differential is limited to the following three disorders:

- **Paroxysmal cold hemoglobinuria –** This disorder is associated with an IgG antibody, usually with anti-P specificity; a positive Donath-Landsteiner test; and, frequently, a recent history of a viral infection. The Coombs test may be positive for bound complement, but the cold agglutinin titer is, at most, only moderately elevated (ie, <1:160). (See "Paroxysmal cold hemoglobinuria".)
- **Drug-induced autoimmune hemolytic anemia –** This condition may be associated with a positive Coombs test for bound complement. A positive drug history and lack of elevated cold agglutinins should help to make this diagnosis. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs".)
- **Cryoglobulinemia/Raynaud phenomenon** – A history of symptoms induced by exposure to cold may be present in patients with cryoglobulinemia or the Raynaud phenomenon. However, the Coombs test is usually negative and cold agglutinins are not increased. (See "Overview of cryoglobulins and cryoglobulinemia" and "Clinical manifestations and diagnosis of the Raynaud phenomenon".)

TREATMENT

Indications for treatment — Some patients with cold agglutinin disease have mild disease, with minimal anemia and modest or absent circulatory symptoms. Such patients do not require treatment and only need to avoid exposure to cold [33]. Despite these precautions, transfusions may be needed during the winter months in some patients with otherwise mild to minimal disease [2,11].

In general, indications for treatment include symptomatic anemia, transfusion-dependence, and/or disabling circulatory symptoms. While no randomized studies comparing the various available treatment regimens have been performed, the best results to date have been obtained using rituximab, alone or in combination.

Avoidance of cold — The most useful single therapy in cold agglutinin disease is avoidance of cold. This means that the patient must dress warmly even in the summer. Warm shoes, stockings, and gloves are essential, and

many patients use a face scarf, ear muffs, warm hats, and other clothing to maintain warmth. If possible, patients living in northern climes should try to live the coldest months in more temperate regions. Avoidance of cold demands constant vigilance (eg, avoiding cold rooms or environments, immersion of hands and other body parts in cold water, drinking of cold liquids).

Rituximab-containing regimens — A number of reports have indicated the usefulness of the monoclonal anti-CD20 antibody rituximab, alone or in combination, in those with severe hemolysis, with response rates as high as 76 to 83 percent [2-4,34-42]. While durations of remission using this agent are often short, patients may respond to successive courses of treatment following relapse [2].

- Rituximab **with or without interferon** – In an uncontrolled prospective study, 14 of 27 patients with cold agglutinin disease, 15 of whom had been previously treated, responded to a single course of rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22), and 6 of 10 responded to re-treatment with this agent plus interferon (rituximab as per first course plus interferon 5 million units SQ three times per week starting two weeks before retreatment with rituximab) [39]. The overall response rate was 54 percent. The median increase in hemoglobin levels in responders was 4.0 g/dL, with median times to response and duration of response of 1.5 and 11 months, respectively. Treatment was well-tolerated; response could not be predicted using pretreatment hematologic, immunologic, or histologic parameters.

- **Low-dose** rituximab **plus** prednisone – A small prospective study investigated the efficacy, safety, and response duration of **reduced** doses of rituximab (100 mg fixed dose weekly for four doses) along with a short course of prednisone (initial dose 1 mg/kg/day for 30 days, with a slow taper thereafter) as primary or secondary treatment in 13 patients with cold AIHA [41,42]. Complete plus partial response rates were 85 percent at six months, with relapse-free survival rates of 85, 67, and 57 percent at 6, 12, and 24 months, respectively.

- Rituximab **plus** fludarabine – Excellent results in have been obtained from the combination of rituximab and fludarabine in an uncontrolled prospective study in 29 patients with symptomatic disease, 10 of whom were previously unresponsive to treatment with single agent rituximab. Treatment was a combination of intravenous rituximab at regular doses (375 mg/m^2 on days 1, 29, 57, and 85) plus oral fludarabine (40 mg/m^2 on days 1 through 5, 29 through 34, 57 through 61, and 85 through 89) [40]. Complete and overall response rates were noted in 21 and 76 percent, respectively, with an estimated median response duration in excess of 66 months. Grade 4 hematologic toxicity (absolute neutrophil count <500/microL) occurred in four patients. Dose reduction or discontinuation of fludarabine occurred in 13 patients (45 percent).

Cytotoxic agents — Cytotoxic agents, particularly cyclophosphamide and chlorambucil, have been given to reduce the production of antibody. While sometimes successful in combination with corticosteroids [4,43], this modality is not generally useful, since the therapeutic index is too narrow. However, when the patient has an underlying lymphoma, appropriately aggressive chemotherapy is indicated, which will treat the cold agglutinin disease, as well. (See 'Disease spectrum from benign to malignant' above.)

In this regard, the combination of rituximab plus bendamustine has been successfully employed in the treatment of patients with low-grade lymphoma, including those most often associated with cold agglutinin disease (eg, Waldenström macroglobulinemia) [44]. It is therefore of interest to note a long-term response to this treatment combination in two older patients not responding to multiple courses of treatment with other chemotherapeutic agents [45,46].

Other agents — Other therapies are less useful. Those interventions that are effective in IgG-mediated warm agglutinin disease are generally of little value in cold agglutinin disease [10]. (See "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins".)

- **Glucocorticoids** – The use of glucocorticoids (eg, prednisone) does not diminish antibody production, and any benefit is mediated by downregulation of phagocytosis, which typically requires unacceptably high doses [3,11,47], with response rates as low as 14 percent [2]. There are, however, occasional exceptions to

glucocorticoid resistance:

- Patients with low titer of antibodies of high thermal amplitude (ie, antibodies that produce some hemolysis at 37°C) [47,48].
- The rare patient with accompanying IgG cold-reacting antibodies. Such patients may respond to prednisone and splenectomy in a fashion similar to those with IgG warm agglutinins [1].
- The patient with concurrent IgG warm agglutinins (eg, induced by ampicillin therapy in a patient with Mycoplasma pneumonia) [25].

- **Intravenous immunoglobulin (IVIG)** – IVIG may be of benefit for the treatment of the polyclonal cold hemolysis seen with Mycoplasma pneumonia, pending spontaneous clearing of the antibody [49].
- **Recombinant interferon alpha** – This agent has been used successfully to treat cold agglutinin disease in a small number of patients [50,51].
- **Erythropoietin** – Some patients with severe anemia and reticulocytopenia benefit from modest doses of erythropoietin (40,000 units SQ once or twice a week) in order to support an increased rate of RBC production by the bone marrow. (See 'Reticulocyte count' above.)
- **Splenectomy** – The liver, not the spleen, is the organ of red cell destruction in cold agglutinin disease; as a result, splenectomy is generally of no value [3]. Splenectomy may be of value in the rare patient with cold agglutinin disease in whom the autoantibody is IgG, rather than IgM [1].
- **Complement inhibitors** – Eculizumab, a humanized monoclonal antibody that binds to the C5 component of complement and inhibits terminal complement activation, has shown efficacy in three transfusion-dependent patients refractory to treatment with rituximab [52-54]. Early studies have suggested that a mouse monoclonal antibody targeting the classical pathway-specific serine protease C1s prevented cold agglutinin-mediated deposition of complement opsonins that promote red cell phagocytosis in vivo [55]. A 15 amino acid long peptide has been identified that inhibits C1q and may be useful in treatment [56]. More experience is needed to determine the role of these modalities. (See "Treatment and prognosis of paroxysmal nocturnal hemoglobinuria", section on 'Eculizumab'.)

Plasmapheresis — Plasmapheresis can be used as adjunctive treatment to physically remove the IgM antibody from the plasma, leading to a reduction in the rate of hemolysis [57]. This procedure is effective when whole-body exchange techniques are performed, since the antibody, being IgM, is confined to the intravascular space. Plasmapheresis should be performed in as warm an environment as possible. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology", section on 'ASFA therapeutic categories'.)

The effect of plasmapheresis is relatively short lived as the half-life for replacement of the protein is only five days. It is therefore difficult to use successfully for chronic treatment. There are, however, several indications for plasmapheresis in the treatment of cold agglutinin disease:

- It can be used to reduce severe hemolysis, particularly at initial presentation when the syndrome is due to an infection. In these cases, the thermal amplitude of the agglutinin (ie, the highest temperature at which antibody and antigen are able to interact) may be high, approaching room and/or body temperature, and special precautions may be needed to successfully accomplish the treatment [58].
- It can be used to prepare the patient for surgery. In this setting, plasmapheresis should be performed no more than one to two days prior to the surgery [59].
- In some patients, the symptoms of acrocyanosis are sufficiently severe to require acute relief by plasmapheresis [60].
- The neuropathic symptoms of those patients with anti-Pr antibodies and polyneuropathy can be relieved by plasmapheresis [61].

Special precautions — Special precautions need to be taken for the patient with cold agglutinin disease in order to avoid the consequences of exposure to cold temperatures.

- Ideally, all patients in whom hypothermic surgical procedures are contemplated should be routinely tested preoperatively for the presence of cold agglutinins. Exposure of large blood-containing areas to cold temperatures may result in marked hemolysis and other complications unless precautions are taken [62]. Appropriate changes in cardiopulmonary bypass and myocardial management plans should be made in patients who test positive [63]. As examples, the patient may undergo plasmapheresis just prior to surgery (carefully performed to avoid exposure to cold), and forced warm air may be used on the operative field [64]. (See 'Plasmapheresis' above.)
- Space heaters may be necessary to keep room temperature at adequate levels.
- Intravenous solutions and previously refrigerated blood products must have their temperature raised before infusion. Warming coils for such use are commercially available. Red cell preparations should not be heated above 40°C, as thermal hemolysis may ensue. (See "Transfusion reactions caused by chemical and physical agents", section on 'Blood warmers'.)
- Use of cooling blankets to reduce fever in patients with cold agglutinins may result in worsening of hemolysis as well as peripheral gangrene [65].

With these precautions, patients can undergo these procedures with relative little morbidity [66].

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

- Cold agglutinin disease may arise secondary to infection (eg, Mycoplasma pneumonia, infectious mononucleosis), or may reflect the presence of an underlying lymphoproliferative disorder ranging from benign monoclonal gammopathy to malignant lymphoma. Symptoms are related to the presence of anemia secondary to hemolysis, and/or to in vivo red blood cell agglutination secondary to exposure to cold (see 'Clinical manifestations' above).
- The diagnosis of cold agglutinin disease is suspected in the patient complaining of symptoms on exposure to cold and is made by demonstrating the presence of significant titers of a cold agglutinin in adequately prepared blood specimens along with a positive Coombs test for bound complement. The cold agglutinin is most often an IgM antibody with specificity for the I or i red blood cell antigen (see 'Diagnosis' above).
- Treatment of mildly symptomatic cold agglutinin disease (eg, mild degrees of acrocyanosis or anemia) is mainly supportive and consists of avoidance of exposure to cold and additional sources of complement (see 'Special precautions' above and 'Avoidance of cold' above). When there is evidence for its presence, treatment of an underlying lymphoma is often successful in reducing signs and symptoms of cold agglutinin disease.
- In the presence of severe signs and symptoms, we suggest treatment with rituximab with or without

fludarabine (with attention to the toxicity of the combined regimen) (**Grade 2C**). (See 'Rituximab-containing regimens' above.)

Low-dose alkylating agents (eg, cyclophosphamide, chlorambucil) or interferon may also be used but are usually less effective. Only highly selected patients are expected to respond to prednisone and/or splenectomy (see 'Other agents' above).

- When signs and symptoms of cold agglutinin disease are severe, especially in the setting of an acute infection or prior to a surgical procedure, we recommend the adjunctive use of plasmapheresis to remove the cold agglutinin (**Grade 1C**). (See 'Special precautions' above and 'Plasmapheresis' above.)

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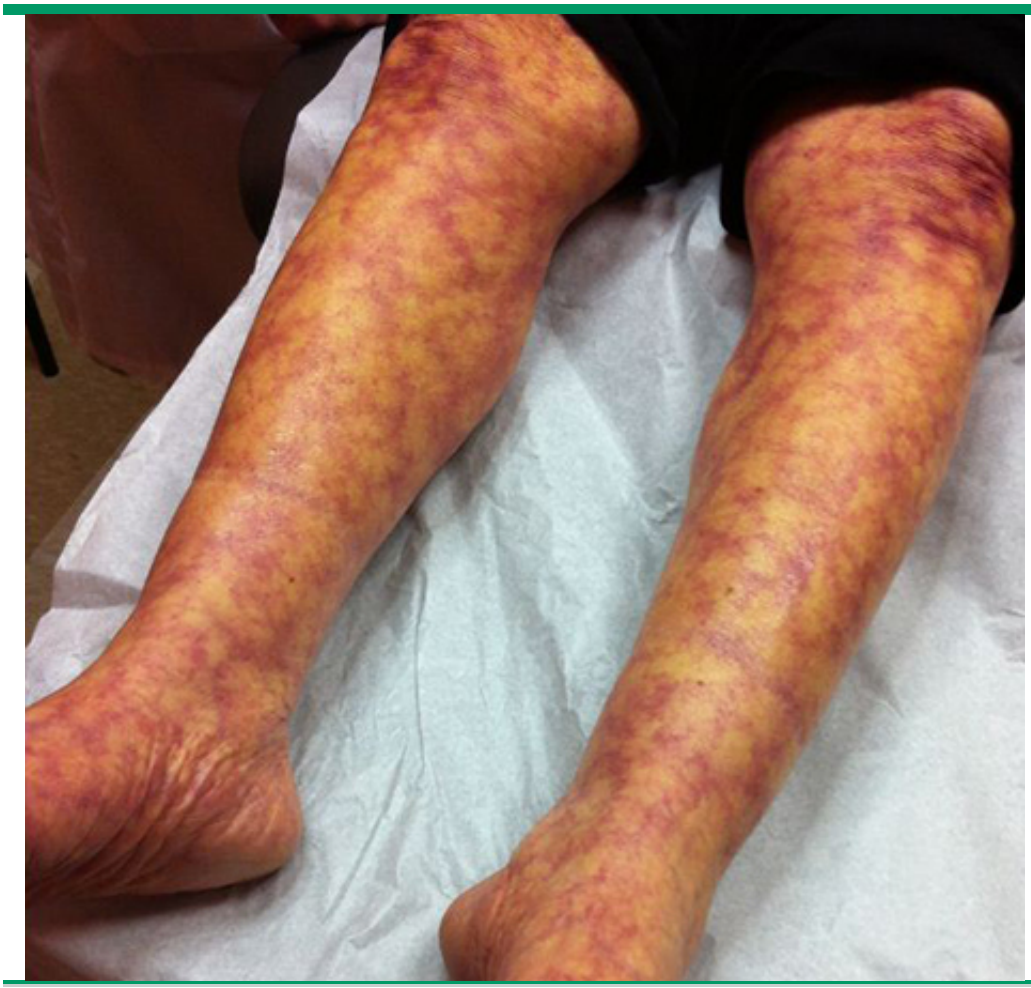
Topic 7084 Version 15.0

GRAPHICS

Livedo reticularis in cold agglutinin disease



This photograph demonstrates a severe degree of livedo reticularis in a patient with cold agglutinin disease following exposure to cold. The patient's skin changes disappear completely without residua within several minutes following warming.

Photo courtesy of Dr. Jason Gotlib, Stanford University School of Medicine.

Graphic 61212 Version 3.0

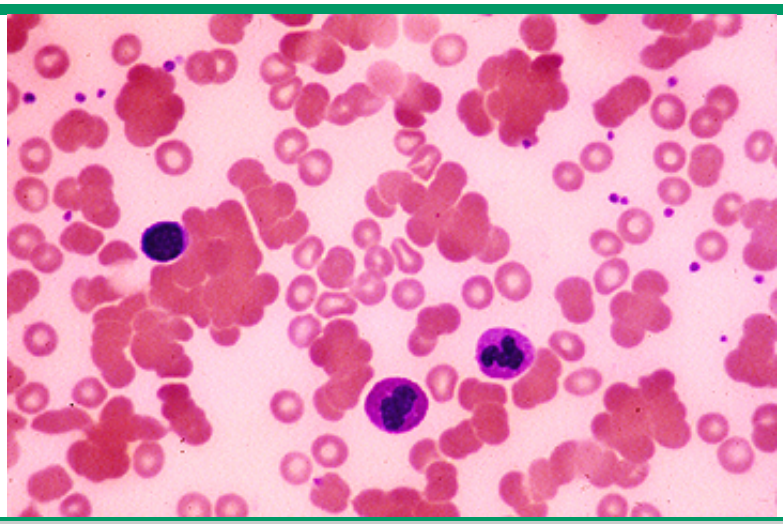
Reactions of the cold agglutinins and their occurrence in clinical settings

Specificity	Antigen	Reaction to:				Antibody	Clinical presentation
		Adult RBC	Fetal RBC	Pro-T RBC	Sial-T RBC		
Anti-I	Branched aminyllactose polymers	++++	+	++++	++++	IgM mono	Benign chronic cold agglutin, non-aggressive lymphoma
						IgM oligo	M. pneneumoniae infection, other viruses
Anti-i	Linear aminyllactose polymers	+	++++	++++	+++++	IgM mono	Aggressive lymphoma
						IgM oligo	Infectious mononucleosis
Anti-Pr	Polysaccharides on glycoproteins	++++	++++	0	0 to ++++	IgM mono	Benign or malignant lymphocytic proliferation
Various	Polysaccharides containing sialic acid	+++	+++	+++	0	IgM mono	Benign or malignant lymphocytic proliferation

Pro-T: protease-treated; Sial-T: sialidase-treated; mono: monoclonal; oligo: oligoclonal.

Graphic 61974 Version 1.0

Red blood cell agglutination due to a cold agglutinin

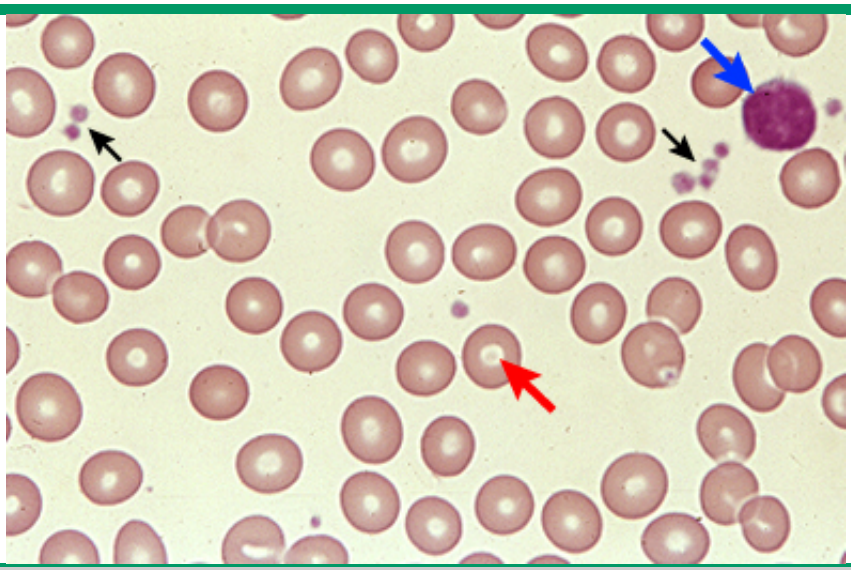


Peripheral blood smear from a patient with cold agglutinin hemolytic anemia shows marked red blood cell agglutination into irregular clumps.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50522 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

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

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).

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