# Treatment of autoimmune hemolytic anemia: Warm agglutinins

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**Literature review current through:** Feb 2015. | **This topic last updated:** Feb 13, 2015.

**INTRODUCTION** — Autoimmune hemolytic anemia (AIHA) due to the presence of **warm** agglutinins is almost always due to 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 condition differs from AIHA due to the presence of **cold** agglutinins, which are usually due to IgM antibodies that react with polysaccharide antigens on the RBC surface at temperatures below the core temperature of the body and can be associated with both RBC agglutination and hemolytic anemia.

This topic review will discuss the treatment of AIHA in the adult due to warm agglutinins [1,2]. The pathogenesis, clinical features, and diagnosis of AIHA due to warm agglutinins are discussed separately. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs" and "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins".)

- Treatment of warm agglutinin AIHA in children is discussed separately. (See "Autoimmune hemolytic anemia in children and adolescents".)
- Treatment of warm AIHA in patients with systemic lupus erythematosus is discussed separately, although the treatment approach is quite similar. (See "Hematologic manifestations of systemic lupus erythematosus in adults", section on 'Autoimmune hemolytic anemia'.)
- The pathogenesis and treatment of hemolytic anemia due to 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".)

**TREATMENT OVERVIEW** — The course of warm agglutinin AIHA varies with age.

- **Children** – In children, AIHA is usually a self-limited disease, arising one to three weeks after a viral infection and disappearing within one to three months [3,4]. (See "Autoimmune hemolytic anemia in children and adolescents", section on 'Clinical presentation'.)
- **Adults** – In adults, the disease is usually chronic and may be variably manifest for months to years. The patient should be told of the chronic nature of this disease at the time of diagnosis, since the subsequent course may be complex and protracted. (See "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins", section on 'Clinical manifestations'.)

Two semi-independent approaches to the treatment of warm agglutinin AIHA are employed, namely reduction in the production of the autoantibody and reduction in the effectiveness of the autoantibody in destroying red cells [5].

- **Reduction in autoantibody production** – Two means of reduction of antibody production are available in warm agglutinin AIHA: glucocorticoids and cytotoxic drugs, with most clinicians favoring initial treatment with glucocorticoids [6,7]. Rituximab, an antibody that targets B cell lymphocytes, has also been shown to be very effective in reducing antibody production in a large number of autoimmune disorders [8]. In addition, since the spleen represents approximately 25 percent of total lymphoid tissue in the body, its removal also helps to remove the source of the antibody. (See "Approach to the adult patient with splenomegaly and other splenic

disorders", section on 'Normal splenic function'.)

- **Reduction in autoantibody effectiveness** – Antibody in AIHA destroys the red cells primarily by binding to Fc receptors on effector cells (phagocytes) of the immune system; this occurs most efficiently in the spleen due to close contact of the blood with these cells during the slow circulation through the cords of Billroth (picture 1). Binding results in phagocytosis (partial or complete) or membrane rupture. When complement is fixed, phagocytic cells in sites other than the spleen are able to bind to the target red cells efficiently. The hemolytic process can be reversed either by removing the primary site of destruction via splenectomy, or by reducing the interaction between splenic macrophages and the antibody-coated RBCs utilizing intravenous immune globulin.

**Initial management**

**Stabilization of the patient** — The clinical syndrome of AIHA may become life-threatening when severe anemia is present. If the hemoglobin falls below a level able to sustain sufficient oxygenation, the patient may become lethargic, confused, and dyspneic with tachycardia. This presentation constitutes a medical emergency, especially in those with underlying cardiac disease. If not corrected, death from pulmonary edema, myocardial infarction, or terminal cardiac arrhythmia is inevitable. Accordingly, corrective measures must be taken at once (eg, institution of glucocorticoids with or without high-dose intravenous immunoglobulin). Immediate transfusion of blood, which almost always requires urgent discussion with blood bank personnel, can be life-saving. Conversely, delay of transfusion because of blood matching issues can be fatal. (See 'Red blood cell transfusion' below.)

**Glucocorticoids as first-line agents** — Aside from the need for blood transfusion, most experts consider the use of single agent glucocorticoids to be the initial treatment of choice. However, this is based on experience rather than prospective, randomized trials. (See 'Glucocorticoids' below.) Since chronic hemolysis can lead to folate deficiency, the use of low doses of folic acid has been suggested as long as hemolysis persists. (See "Etiology and clinical manifestations of vitamin B12 and folate deficiency", section on 'Increased requirements'.)

**Search for secondary causes** — Initial management should also include cessation of any possible offending drug (eg, penicillin, fludarabine) and investigation for a contributing disorder (eg, systemic lupus erythematosus, chronic lymphocytic leukemia, autoimmune lymphoproliferative syndrome). An extensive list of drugs associated with immune hemolytic anemia and/or a positive direct Coombs test is available (table 1) [9]. (See "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins", section on 'Etiology' and "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Drug-related immune hemolysis'.)

**Second-line agents for poorly responsive or relapsed disease** — For patients not responding to initial treatment with glucocorticoids, those relapsing following their discontinuation, and/or those who require high doses of glucocorticoids to maintain response (eg, >15 mg/day), there are a number of agents available (eg, splenectomy, rituximab, cytotoxic agents, danazol, immunosuppressive agents). However, there are no prospective, randomized trials comparing second-line agents to guide the clinician in this matter. While the classically preferred second-line agent for such patients had been splenectomy, the use of rituximab as a second-line agent has been gaining favor in the last decade [10].

Given the absence of randomized trials, the choice of splenectomy versus rituximab is particularly difficult and may ultimately be decided by the patient, rather than the clinician, taking into account the age of the patient, performance status, suitability for surgery, and acuity of the illness, as well as the potential risks and benefits of each modality [11]. A similar issue (ie, splenectomy versus rituximab) arises in patients with immune thrombocytopenia who have failed first-line therapy with glucocorticoids. As is also true in patients with immune thrombocytopenia, the main factor for the selection of agent(s) employed in warm AIHA should be safety, as the curative potential of currently available modalities is low and such treatment may be more dangerous for the patient than the disease being treated [1]. (See "Immune thrombocytopenia (ITP) in adults: Second- and third-line therapies", section on 'Choice and sequence of therapy'.)

**Third-line agents for resistant disease** — An appreciable number of patients with warm AIHA may fail to respond

to sequential treatment with glucocorticoids followed by splenectomy or rituximab. The choice of further therapy is not supported by any prospective trials and may be influenced by the clinician's prior experience as well as the values and preferences of the patient. Options include the following [1,11-13]:

- Those not responding to splenectomy may respond to treatment with rituximab, and vice versa.
- Patients may respond to lower doses of glucocorticoids (with or without danazol) following treatment with splenectomy or rituximab.
- For those with long remission durations after their first treatment with rituximab, retreatment with this agent is a reasonable option.
- Those relapsing following splenectomy with evidence for the return of splenic function (eg, loss of previously noted Howell-Jolly bodies) may respond to removal of an accessory spleen. (See "Approach to the adult patient with splenomegaly and other splenic disorders", section on 'Hyposplenism and asplenia'.)
- The successful use of immunosuppressive or cytotoxic agents (eg, azathioprine, cyclophosphamide, alemtuzumab, cyclosporine, mycophenolate mofetil) has been reported, although their risk/benefit ratios are unclear and their curative potentials are low.
- There is limited anecdotal information on the success of allogeneic hematopoietic cell transplantation. The use of therapeutic plasma exchange in warm AIHA is considered as a Category III intervention (ie, disorders for which the optimum role of apheresis therapy is not established). (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology".)

**Long-term treatment** — A report on the single-center experience with the treatment of warm AIHA is instructive concerning the natural history of this disorder. For the 55 subjects in whom long-term data were available, the following observations were made [14]:

- Two (4 percent) with compensated hemolysis were treated only with folic acid.
- Twenty-two (40 percent) obtained complete or partial remission with glucocorticoids alone.
- Thirty-one (56 percent) required two or more lines of treatment.
  - Thirteen required third-line treatment.
  - Seven required four or more lines of treatment.
- Status at last follow-up (mean 3.6 years):
  - Complete remission off treatment: 44 percent
  - Complete or partial remission with <10 mg/day glucocorticoids: 25 percent
  - Active disease: 31 percent

Success in the treatment of warm agglutinin AIHA depends upon balancing of the several means available. Success does not mean cure, since there is usually evidence of persistent activity of the underlying process. Rather, it means control of the degree of anemia sufficient for most activities without excessive compromise of immunologic responsiveness [1].

**Monitoring disease response** — The magnitude of hemolysis and response to treatment can be serially monitored by use of those laboratory tests initially employed for establishing the presence of hemolytic anemia (eg, hemoglobin, reticulocyte count, serum lactate dehydrogenase [LDH], haptoglobin, indirect bilirubin, Coombs test). (See "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins", section on 'Laboratory findings' and "Approach to the diagnosis of hemolytic anemia in the adult", section on 'Diagnostic approach'.)

## GLUCOCORTICOIDS

**Initial dosing** — Glucocorticoids are the most commonly employed agents as initial therapy for warm AIHA, as they result in initial clinical responses in 50 to 90 percent of patients [6,7,15]. However, only approximately one-third of patients remain in long-term remission once the drug is discontinued. A further 50 to 60 percent require

maintenance doses, and approximately 20 to 30 percent require second-line therapies [11,14]. It has been estimated that less than 20 percent of adults with warm AIHA are cured by steroids alone [1].

The recommended initial doses are quite high (1 to 1.5 mg/kg per day of prednisone or its equivalent in adults). Doses in children are generally similar. However, the minimal prednisone dose capable of inducing remission has never been established. The use of intravenous methylprednisolone (eg, 250 to 1000 mg/day for one to three days) has been suggested for those with rapidly evolving, severe hemolysis [11-13]. (See "Autoimmune hemolytic anemia in children and adolescents", section on 'Glucocorticoids'.)

When successful, the effect on decreasing antibody production, manifest by a rising hemoglobin concentration, is usually seen within one to three weeks. How glucocorticoids act in this setting is not clear; some have suggested that the simultaneous presence of steroid in its receptor and the antigen in its receptor induces apoptosis of specifically-programmed T cells.

**Subsequent dosing** — Once remission has been achieved, the steroid dose must be tapered. In children, this can be done quite rapidly since the disease process is often self-limited [3,4]. In adults, tapering should be more gradual in an attempt to **find the lowest dose that will maintain an adequate remission** [6]. This process must take into account the fact that evidence of an insufficient dose will not be apparent for three to four weeks [16]. Based on our experience, we have found the following schedule to be useful:

- After a sufficient hemoglobin concentration (usually >10 g/dL) has been achieved, maintain the prednisone dose at 60 mg/day for one week.
- Rapidly taper the dose to 20 mg/day over a period of two weeks. This is the largest dose that will be tolerable over time. Maintain this dose for one month.
- If remission persists, further reduce the dosing to 20 mg/day alternating with 10 mg/day. Maintain this regimen for one month.
- If remission persists, omit the dose on alternate days while maintaining the dose at 20 mg every other day.
- If remission persists, reduce the dose to 10 mg/day on alternate days. Tapering of glucocorticoids should be continued as long as the hemoglobin and haptoglobin levels remain improved and stable, lactate dehydrogenase levels stay low, and the absolute reticulocyte count remains below 100,000/microL.
- Glucocorticoids can be stopped when there is normalization of the hemoglobin, haptoglobin, LDH, and absolute reticulocyte count, although the Coombs test may remain positive. The patient should be monitored for recurrence for a number of months following cessation of treatment.

If, at any time during this dose tapering process, the remission is not maintained, and especially if the prednisone dose needed to maintain remission exceeds 15 mg/day, other measures (eg, addition of cytotoxic therapy, addition of danazol, splenectomy, rituximab) must be instituted [1,6]. This approach is also warranted in patients who show no response to prednisone after two to three weeks. Other treatment measures may not be required for patients who can be kept in a satisfactory remission using low doses of prednisone (eg, ≤0.1 mg/kg per day) [1].

**Adverse events** — In one series of patients with warm AIHA, glucocorticoids had been employed for a mean duration of 15±3 months, at a mean dose of 15 mg of prednisone per day [14]. Such dosing has been associated with a host of long-term complications, including weight gain, diabetes mellitus, osteoporosis with fractures, osteonecrosis of the femoral head, and cataracts. These side effects are not seen when steroids are given every other day, even for long periods of time. (See "Major side effects of systemic glucocorticoids".)

Since glucocorticoid-induced osteoporosis is a potentially preventable complication, it has been suggested that patients receiving long-term treatment with glucocorticoids should be given bisphosphonates, vitamin D, and calcium [1,12]. (See "Prevention and treatment of glucocorticoid-induced osteoporosis".)

We recommend that steroids be given on alternate days if possible and that they be stopped as other therapy is

introduced if they are not effective.

**SPLENECTOMY** — Splenectomy has been advised as the most effective second-line treatment for warm AIHA following the use of glucocorticoids, although its efficacy has never been compared with other available second-line agents in randomized, prospective studies. Splenectomy should be considered in patients who have not had a satisfactory response to initial treatment with glucocorticoids, who relapse after having responded to glucocorticoids, or who require the equivalent of more than 15 mg/day of prednisone to maintain an acceptable hemoglobin level [12]. It is also an option for those who have not responded satisfactorily to, or have relapse following, other second-line treatments such as rituximab or immunosuppressive or cytotoxic agents.

Splenectomy is nearly as efficient as glucocorticoids in reducing hemolysis in patients with AIHA, and is likely only the curative regimen [6]. Two-thirds to three-quarters of patients will show a short-term improvement in the anemia following splenectomy, usually evident within two weeks [17-19]. In approximately one-half of those that achieve remission, glucocorticoids in lower doses than necessary before splenectomy will be required to maintain the remission, one-third will relapse, and approximately 20 percent will be "cured", remaining in remission for years without medication [1,12,13,19,20].

- Splenectomy can be performed safely by a laparoscopic procedure, with less expense and a lower complication rate than via an open laparotomy, and an estimated mortality of approximately 0.5 percent [18,21]. (See "Approach to the adult patient with splenomegaly and other splenic disorders", section on 'Splenectomy'.)
- Splenectomy is **not recommended** in patients with warm AIHA associated with the autoimmune lymphoproliferative syndrome (ALPS), due to the reported lack of sustained therapeutic benefit together with the increased risk of postsplenectomy sepsis in both children and adults. (See "Autoimmune lymphoproliferative syndrome (ALPS): Management and prognosis", section on 'Autoimmune manifestations'.)
- Complications of splenectomy include postsplenectomy sepsis as well as postoperative thrombosis (eg, intraabdominal vein thrombosis, deep vein thrombosis, pulmonary embolism).
    - It has been suggested that all patients should receive thromboprophylaxis with low molecular weight heparin in the immediate postoperative period, although the need for longer-term prophylaxis is unknown [1].
    - All patients being considered for splenectomy should undergo preoperative immunization against pneumococci, meningococci, and hemophilus, preferably at least two to three weeks before the procedure, and should be advised to take antibiotics in case of fever [1,12]. (See "Prevention of sepsis in the asplenic patient".)

**RITUXIMAB** — The monoclonal anti-CD20 antibody rituximab has been successfully employed in patients with warm AIHA, with or without glucocorticoids as first-line therapy, or following failure of treatment with glucocorticoids or second-line agents such as splenectomy, immunosuppressive, or cytotoxic agents. While splenectomy has been considered the classical second-line agent for patients failing treatment with glucocorticoids, more recent experience with rituximab and patient preference have elevated this treatment modality in the eyes of many investigators [11,13,14,19].

**Single agent rituximab** — Multiple case studies and retrospective reports have indicated success with use of rituximab in both adults and children with resistant AIHA and/or Evans syndrome, with estimated median overall and complete response rates of 83 to 87 percent and 54 to 60 percent, respectively [12,22-32], and disease-free survivals at one and two years of 72 and 56 percent, respectively [30].

Although long-term responses to this agent are not expected, patients have been retreated with this agent with new responses comparable to the previous response, both in quality as well as duration of response [1,13,30]. While this use of rituximab for warm AIHA is off-label and there are no prospective, randomized studies comparing rituximab with splenectomy, most experts believe that rituximab is the second-line agent of choice for those who

are not eligible for, or refuse, splenectomy.

A retrospective report described the response to treatment with standard doses of rituximab (375 mg/m$^2$ intravenously once weekly for four doses in most patients) in 36 rituximab-naïve patients with refractory AIHA who had received a median of four (range: one to eight) previous treatments, 13 of whom had undergone splenectomy. Results included the following [31]:

- Overall and complete response rates were 77 and 61 percent, respectively.
- For the 22 patients achieving complete remission, treatment response was maintained at 6 and 12 months in 100 and 73 percent, respectively.

In a small study with limited follow-up, single agent rituximab in reduced doses (100 mg/week for four doses) has been successfully employed in 12 older adults with newly diagnosed AIHA who were not eligible for treatment with glucocorticoids, with complete and partial remissions in eight and three patients, respectively [33].

**Rituximab plus glucocorticoids** — Two small studies have evaluated the efficacy and toxicity of rituximab (standard or reduced dosage) plus a glucocorticoid (prednisone or prednisolone) as primary or secondary therapy in patients with AIHA.

A prospective, non-randomized 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 therapy in 18 patients with warm AIHA [34,35]. The following results were noted:

- In their initial report in 14 patients, complete responses (ie, hemoglobin >12 g/dL with normalization of all hemolytic markers) and partial responses (ie, hemoglobin 10 to 12 g/dL or at least a 2 g/dL increase from baseline with no transfusion requirement) were noted after two months of treatment in 79 and 21 percent, respectively.
- Complete plus partial responses were seen in 94 percent at six months (18 patients) and in 100 percent at 12 months (14 patients), 24 months (12 patients), and 36 months (seven patients). Nine of the initial 14 patients completely stopped prednisone treatment at a median time of 89 days (range: 58 to 150 days).
- Relapse-free survivals were 89 percent at 6 and 12 months, and 76 percent at 24 and 36 months.
- Treatment was well tolerated; no patient experienced the most frequently described infusion-related reactions from rituximab, and no infectious, hematologic, or extra-hematologic complications were seen during a median follow-up period of 15 months.

A Danish multicenter, randomized, open-label, phase III trial compared the use of prednisolone (1.5 mg/kg per day for two weeks, with a slow taper thereafter) with or without rituximab (375 mg/m$^2$ intravenously once weekly for four weeks) in 64 patients with **newly diagnosed** warm AIHA. Results included the following [36]:

- For the group receiving prednisolone alone, complete remission (CR) rates at 3, 6, and 12 months were 18, 39, and 36 percent, respectively. The corresponding CR rates for those receiving prednisolone plus rituximab were 10, 63, and 75 percent, respectively.
- The cumulative relapse-free survival at 36 months for all patients who had achieved either a complete or partial remission was significantly greater in the group receiving combined treatment (70 versus 45 percent, HR 0.33; 95% CI 0.12-0.88).
- There were no significant differences between the two treatment arms in terms of red blood cell transfusions given, patients undergoing splenectomy during the study, deaths, serious adverse events, or overall side effects.

**Side effects** — Although the above results showed high initial response rates, long relapse-free survival, and

generally low toxicity of rituximab with or without glucocorticoids, cost issues and side effects of infusional rituximab are a concern. As examples, the wholesale cost for four doses of rituximab (375 mg/$m^2$) is approximately $22,000 US dollars, with "Boxed Warnings" in the United States of first infusion-related reactions, reactivation of hepatitis B infection, severe mucocutaneous reactions, as well as progressive multifocal leukoencephalopathy, any one of which may be fatal. Longer-term follow-up will be needed before this treatment can be routinely recommended as initial therapy for patients with warm AIHA [6,17,18].

**IMMUNOSUPPRESSIVE AND CYTOTOXIC AGENTS** — Treatment with other immunosuppressive or cytotoxic drugs (primarily azathioprine or cyclophosphamide) also reduces the production of antibody and raises the hemoglobin concentration in patients with warm agglutinin AIHA [6,7,37]. General indications for their use are lack of response to or inability to tolerate prednisone, or the necessity for a maintenance prednisone dose >15 to 20 mg/day in adults [6].

These drugs are usually given orally in daily doses, although intravenous pulse dosing has been used [6,37]. They generally take at least one month to be effective; if no effect is seen in four months, further therapy is unlikely to be effective. A common error is to use and persist with a fixed, inadequate dose of these agents. The dose should be adjusted to produce a fall in the total white blood cell count to approximately 3000/microL. If the dose is reduced after remission to insufficient levels, a falling hematocrit and increased reticulocytes, due to recrudescence of hemolysis, may not be seen for three to four months.

**Cyclophosphamide** — Cyclophosphamide is given in initial doses of 100 mg/day by mouth or 500 to 700 mg intravenously every three to four weeks [7,15,38,39]. Although cyclophosphamide may be more effective than azathioprine, it has numerous side effects including hair loss, gonadal toxicity, bone marrow suppression, bladder irritation with hematuria, and development of myelodysplastic syndrome or leukemia. Bladder irritation can be minimized by giving the medication as a single dose in the morning, increasing urinary output during the day, and voiding before retiring to bed at night, or by intravenous pulse therapy. (See "General toxicity of cyclophosphamide in inflammatory diseases".)

High dose cyclophosphamide, in doses that have been used to treat refractory aplastic anemia (ie, 50 mg/kg per day IV for four days along with Mesna and G-CSF), produced the anticipated severe and prolonged neutropenia, but produced remissions in six of nine patients with refractory disease [40].

**Azathioprine** — Azathioprine has fewer side effects but may be somewhat less effective than cyclophosphamide [6,37]. It is given in an initial oral dose of 100 to 150 mg/day (reduced appropriately for children), which generally does not reduce the reticulocyte count or other blood cell counts by direct toxicity.

**Danazol** — There is a limited experience with danazol, primarily in patients with warm agglutinin AIHA that is either refractory to or has relapsed after treatment with prednisone [41,42]. Its main value may be to minimize the prednisone exposure, thereby reducing the incidence of splenectomy. In the limited trials reported, danazol appeared most effective when given in combination with prednisone as initial treatment, and was less effective when given at later times.

In one series of 17 patients, danazol (initial dose 600 to 800 mg/day by mouth) was added to previous regimens or given initially in conjunction with high-dose prednisone treatment [42]. Twelve patients showed a rise in hematocrit within one to three weeks. Glucocorticoid therapy was then tapered to a minimum requirement or stopped and, once remission was sustained, the maintenance dose of danazol was reduced to 400 to 600 mg/day.

**Cyclosporine and mycophenolate mofetil** — Cyclosporine (Cyclosporin A, starting oral dose 5 to 10 mg/kg per day in two divided doses, with subsequent dose adjustment depending on hematologic response, blood pressure, BUN, creatinine, and electrolytes) and mycophenolate mofetil (MMF, starting dose 500 to 1000 mg/day in two divided oral doses, increasing to 1000 to 2000 mg/day) are immunosuppressive agents that have been used in some cases of resistant autoimmune disease. Their successful use in patients with AIHA resistant to standard therapy, including those with accompanying immune thrombocytopenia (Evans syndrome), has been reported [43-45].

**Alemtuzumab** — Less experience is available with use of the monoclonal anti-CD52 antibody alemtuzumab (Campath-1H), alone or in combination with low-dose rituximab, which may be associated with disease response but also with profound immunosuppression and development of opportunistic infections [46-48]. (See "Overview of the complications of chronic lymphocytic leukemia", section on 'Autoimmune hemolytic anemia'.)

**Other cytotoxic agents** — Other cytotoxic drugs have been used to suppress antibody production but are without wide experience. Intravenous vinca alkaloids (particularly vincristine) may induce a rapid but evanescent remission and may be used while waiting for azathioprine or cyclophosphamide to become effective. Vincristine has been delivered attached to platelets, based upon the theory that such "poison bait" would be ingested by macrophages; however, there is no clear-cut advantage to this approach.

**INTRAVENOUS GAMMA GLOBULIN** — Unlike its efficacy in the related disorder immune thrombocytopenia (ITP), intravenous immune globulin (IVIG) is only occasionally effective in the treatment of autoimmune hemolytic anemia refractory to conventional therapy with prednisone and splenectomy [5]; it can also be used as part of the initial regimen to establish control in patients with very severe disease [49,50]. However, very high doses may be required (1000 mg/kg per day intravenously for five days, which is more than twice the usual dose) [51,52]. Only approximately 40 percent of patients respond [49], and in those who do the effect is usually transient unless repeated courses of IVIG are given every three weeks [53]. (See "General principles in the use of immune globulin".)

**RED BLOOD CELL TRANSFUSION** — Red cell transfusion may be required when the hemoglobin falls below a level tolerated by the physiology of the patient. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult".) Special care must be taken in the testing for compatibility because of the presence of a pan-reacting antibody [54,55]. It is unlikely that fully compatible blood can be found, since the autoantibody usually reacts with antigens present on the cells of almost all individuals in the donor population. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Characteristics of the antigens'.)

**Presence of alloantibodies** — Of greatest importance, the patient with AIHA should be tested for the presence of co-existing alloantibodies, which may have developed following pregnancies or prior transfusions [56,57]. Alloantibodies, rather than autoantibodies, may cause major transfusion reactions in such patients if not discovered [58,59]. (See "The incompatible crossmatch", section on 'Alloantibodies'.)

However, the process of sorting out the presence and specificity of an alloantibody in the presence of an autoantibody takes additional time. Thus, if the patient needs to be transfused emergently, transfusion should be given prior to the availability of the results. **No patient with AIHA should die because of difficulties in finding blood for transfusion**.

Experience indicates that most patients will tolerate even serologically incompatible blood [58,60]. One report, for example, described 53 patients who received blood transfusions because of decompensated AIHA [60]. No patient had transfusion-related alloimmunization or a definite increase in hemolysis, even when the transfused red cells were serologically incompatible because of free serum autoantibodies.

**Blood bank liaison** — Discussion of the above-noted issues should be initiated **immediately** with blood bank personnel in order to minimize delays in providing blood, and to minimize potential misunderstandings concerning the degree to which available blood units are compatible with the patient [61]. Nevertheless, the blood bank should always be able to find blood for the patient, with the degree of compatibility increasing as the amount of time given to the blood bank for such testing is increased [55,62,63]. (See "The incompatible crossmatch", section on 'Autoantibodies' and "The incompatible crossmatch", section on 'Immediate management'.)

**WARM AIHA IN LYMPHOMA** — Coombs-positive warm AIHA has been found in up to one-third percent of patients with chronic lymphocytic leukemia (CLL) during the course of their disease while Coombs positivity, with or without hemolysis, has been found in up to 30 percent of patients with angioimmunoblastic T cell lymphoma. AIHA, with or without Coombs positivity, may also be seen in a variable percent of lymphoma patients who have been treated with purine analogs (eg, fludarabine, cladribine, pentostatin). (See "Overview of the complications of chronic lymphocytic leukemia", section on 'Autoimmune hemolytic anemia' and "Clinical manifestations, pathologic features, and

diagnosis of angioimmunoblastic T cell lymphoma", section on 'Clinical features' and "Autoimmune complications following purine analog therapy", section on 'Autoimmune hemolytic anemia'.)

Treatment of secondary symptomatic warm AIHA in patients with lymphoma is generally similar to that of primary warm AIHA, although these patients generally have a worse prognosis due to older age, higher comorbidity, and increased risk of infection. The use of chemotherapy and/or monoclonal antibodies for the underlying lymphoma may be required in those with poorly responsive AIHA [1,64-66]. Success has been reported following the use of rituximab and bendamustine in patients with CLL and AIHA [67].

- Purine analogs should be discontinued immediately on recognition of AIHA in lymphoma patients treated with these agents.
- Splenectomy may be particularly effective in patients with splenic marginal zone lymphoma complicated by the presence of warm AIHA. (See "Treatment of marginal zone (MALT) lymphoma", section on 'Splenic marginal zone lymphoma'.)
- Cold, rather than warm, AIHA may be a complication of some lymphoproliferative disorders (eg, Waldenström macroglobulinemia). Such patients respond poorly to glucocorticoids and splenectomy and are most effectively treated with rituximab alone or in combination with other chemotherapeutic agents. (See "Clinical features and treatment of autoimmune hemolytic anemia: Cold agglutinins", section on 'Treatment'.)

**AIHA IN LUPUS** — Treatment of warm AIHA in patients with systemic lupus erythematosus is discussed separately, although the treatments used are generally quite similar to those presented here. (See "Hematologic manifestations of systemic lupus erythematosus in adults", section on 'Autoimmune hemolytic anemia'.)

**EVANS SYNDROME** — Evans syndrome (ES) refers to the combination of Coombs-positive warm AIHA and immune thrombocytopenia (ITP), although, less commonly, some patients will also have autoimmune neutropenia (15 percent in one series) [68]. The antibodies that cause hemolysis are different from those that cause platelet destruction. Those causing red blood cell (RBC) destruction are directed against a base protein portion of the Rh blood group, while those that destroy platelets are frequently directed against platelet GPIIb/IIIa.

Although many cases are idiopathic in origin, ES has been associated with a number of other conditions in approximately one-half of the cases, including infections (eg, HCV, HIV), systemic lupus erythematosus, lymphoproliferative disorders, common variable immunodeficiency, and autoimmune lymphoproliferative syndrome, and may be seen following allogeneic hematopoietic cell transplantation [68-70]. (See "Hematologic manifestations of systemic lupus erythematosus in adults", section on 'Autoimmune hemolytic anemia' and "Apoptosis and autoimmune disease", section on 'Autoimmune lymphoproliferative syndrome' and "Autoimmune lymphoproliferative syndrome (ALPS): Epidemiology and pathogenesis" and "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis".)

ES is common in both children and adults, and is often either resistant to standard treatment for AIHA or ITP (eg, glucocorticoids, IVIG, splenectomy), or follows a chronic, relapsing course [68,71-75]. In one report of 68 patients with this condition, only 32 percent were in remission off treatment at a median follow-up of 4.8 years, and 24 percent had died [68]. In this series, treatment was as follows:

- First-line treatment – All 68 patients received at least one course of treatment with a glucocorticoid (initial dose: 1 to 2 mg/kg per day), with an initial response in over 80 percent. The short-term response to IVIG was 60 percent.
- Second-line treatment – Almost three-quarters of the patients received second-line therapy (eg, danazol, cyclophosphamide, vinca alkaloids, azathioprine). Eleven patients received treatment with rituximab, with initial and long-term responses in nine and seven patients, respectively.
- Splenectomy – Splenectomy was performed in 19 patients (28 percent), with initial and long-term responses in 15 and 10 patients, respectively. One patient died of sepsis on day 21 post-splenectomy.

There have been no systematic or randomized studies of the treatment of ES; the available literature consists almost entirely of anecdotal case reports and retrospective series [68,73]. The following treatments (in addition to glucocorticoids, IVIG, and splenectomy) have been reported as successful in some, but not all, patients with ES:

- Rituximab [25,26,68,75-77]
- Cyclophosphamide [78]
- Mycophenolate mofetil [79]
- Cyclosporine [44,80]
- Vincristine [81,82]
- Danazol [83]
- Hematopoietic cell transplantation [72,84]
- Azathioprine [68,73,85]

There is not sufficient information to choose one of these agents over another, although in the current literature there have been more reports of success following the use of rituximab [2].

**Autoimmune lymphoproliferative syndrome** — Management of autoimmune lymphoproliferative syndrome (ALPS), which may be present in some patients with ES, is discussed separately. Of the available treatment options in patients with ALPS, splenectomy is **not** recommended, due to the reported lack of sustained therapeutic benefit and increased incidence of postsplenectomy sepsis in both children and adults. (See "Autoimmune lymphoproliferative syndrome (ALPS): Management and prognosis".)

**POST-TRANSPLANT AIHA** — A review of the literature found 18 reports of the treatment of immune hemolytic anemia developing after allogeneic hematopoietic cell transplantation in patients with hematologic disease. Results of treatment included the following [86]:

- Reported mortality for 70 of these subjects was 54 percent.
- Treatment with oral prednisone or intravenous methylprednisolone was administered as first-line therapy in almost all cases. Hemolytic anemia resolved following the use of glucocorticoids alone in only 12 of 92 cases.
- Reported second-line therapy included IVIG and rituximab in most cases. Rituximab was successful in achieving complete remission in only 19 of 32 patients.
- Three or more different agents were employed in 51 subjects, with 15 deaths and 36 survivors. Bortezomib, an agent with activity against malignant B and plasma cells, was employed as third-line therapy in four subjects, with two responses.

**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 5$^{th}$ to 6$^{th}$ 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 10$^{th}$ to 12$^{th}$ 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**

- **Diagnosis** – Accurate diagnosis of warm agglutinin autoimmune hemolytic anemia (AIHA) requires

documentation of the presence of red cell destruction (hemolysis) along with demonstration of the presence of an autoantibody or complement on the surface of the patient's red cells. (See "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins", section on 'Diagnosis'.)

- **Indications for treatment** – Most patients with AIHA present with an acute onset of severe hemolysis with symptomatic anemia, requiring immediate treatment. In patients with underlying cardiac disease, AIHA can present as a medical emergency, requiring immediate packed red cell transfusion. (See 'Red blood cell transfusion' above and "Clinical features and diagnosis of autoimmune hemolytic anemia: Warm agglutinins", section on 'Clinical manifestations'.)

- **Initial treatment** – Once the diagnosis of **symptomatic** warm agglutinin AIHA is confirmed, we recommend immediate institution of treatment with glucocorticoids over splenectomy, rituximab, or other immunosuppressive agents (**Grade 1B**). (See 'Glucocorticoids as first-line agents' above and 'Glucocorticoids' above.)

- **Poorly responsive, severe, or resistant disease**

  - **Second-line treatment** – For symptomatic patients not responding to glucocorticoids, or for those who require large doses to maintain their response (eg, >15 mg/day), we suggest either elective splenectomy or rituximab over the use of immunosuppressive or cytotoxic agents (**Grade 2B**). (See 'Second-line agents for poorly responsive or relapsed disease' above and 'Splenectomy' above and 'Rituximab' above.)

    For adults, we prefer splenectomy over rituximab as it is the only modality with potential for long-term cure, while rituximab is the treatment of choice for adults who either are not surgical candidates or refuse surgery. For children, rituximab has become the preferred treatment for those who do not respond to treatment with glucocorticoids, and is generally suggested before resorting to splenectomy. (See "Autoimmune hemolytic anemia in children and adolescents", section on 'Rituximab'.)

  - **Third-line treatment** – For those who have failed treatment with both splenectomy and rituximab, we suggest the institution of immunosuppressive or cytotoxic agents (eg, azathioprine, cyclophosphamide, cyclosporine) (**Grade 2C**). There is insufficient information to choose one of these agents over another. (See 'Third-line agents for resistant disease' above and 'Immunosuppressive and cytotoxic agents' above.)



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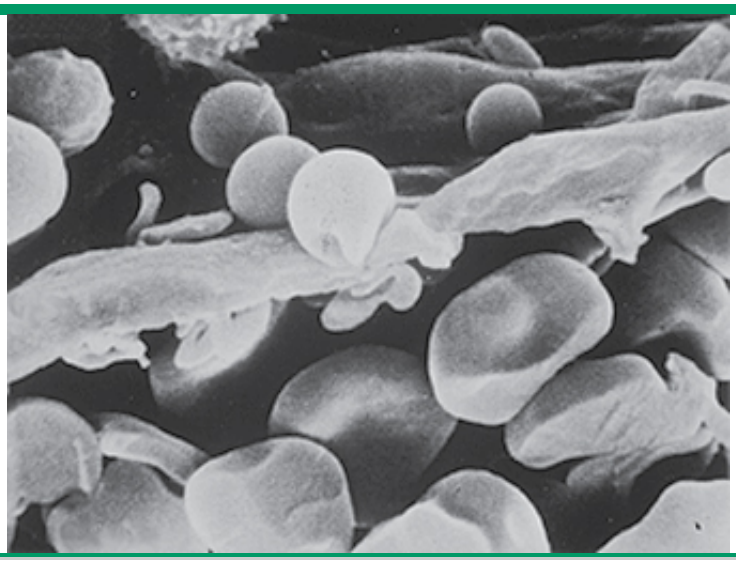
Topic 7138 Version 30.0

## GRAPHICS

### Red blood cell deformation in splenic cords



Scanning electron microphotograph of normal murine red blood cell passing from a splenic cord (below) through the sinusoidal barrier and into the splenic sinusoid (above). Note the deformation necessary to squeeze through the slit in the sinusoidal wall and how a surface area depleted spherocyte would be incapable of transversing the barrier.

*Courtesy of Mohandas Narla, ScD.*

Graphic 53105 Version 3.0

## 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.



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**