An overview of immune hemolytic anemias

Immune processes are an often-unrecognized cause of anemia, although in their presentation, the symptoms are consistent with anemia from any cause. For the primary care physician, the key is to be vigilant to the signs and symptoms of immune hemolytic anemia, especially in patients at high risk, and to initiate treatment promptly when appropriate. Although researchers have made remarkable progress in elucidating the destructive processes at work in the various types of immune hemolytic anemia, the many different causes mirror the complexity of the human immune system. This article reviews the etiologies of different forms of immune hemolytic anemias, the tests that help make the diagnosis, and the treatments that are available.

How Red Blood Cells Are Destroyed

Autoimmune hemolytic anemia was one of the first autoimmune diseases to be recognized. In one of the earliest experiments in this area, performed in 1904, Landsteiner and Donath found that the serum of patients with paroxysmal cold hemoglobinuria lysed normal red blood cells, a finding that explained the clinical characteristics of the disease. However, there was no practical way to detect or characterize immune hemolytic anemia until Coombs, Mourant, and Race developed the direct antiglobulin test (the DAT or Coombs' test) in 1945.

There are several immune hemolytic disorders; in all of them, red blood cells are destroyed in processes mediated by antibodies.4-7

Antibody production:
Alloimmune or autoimmune

Two types of processes can give rise to antibodies against red blood cells: alloimmune and

Abstract

Often patients with immune hemolytic anemias present with symptoms that are common in anemia of any cause. In the different types of immune hemolytic anemia, red blood cells are destroyed by processes mediated by antibodies. This article reviews the pathophysiology, diagnosis, and treatment of this group of diseases.

Key Points

Antibody production can be either idiopathic or due to diseases (eg, leukemia, lymphoma, infections, autoimmune diseases) or a variety of drugs.

All age groups can be affected, and clinical signs and symptoms can be quite variable.

The type and amount of antibody or antibodies involved, and whether complement fixation occurs, can provide valuable information for diagnosis and treatment.

Corticosteroids, followed by splenectomy, are the mainstays of therapy for non-drug-related hemolysis, and other adjunctive therapies are available for refractory cases.

Corticosteroid therapy has generally not shown clinical efficacy in patients with uncomplicated cold agglutinin autoimmune hemolytic anemia, paroxysmal cold hemoglobinuria, or drug-induced immune hemolysis.
TABLE 1

Types of immune hemolytic anemia

Autoimmune hemolysis
- Warm-antibody autoimmune hemolytic anemia
- Cold-antibody (agglutinin) autoimmune hemolytic anemia
- Mixed warm and cold autoimmune hemolytic anemia
- Paroxysmal cold hemoglobinuria

Drug-induced immune hemolysis
- Immune complex mechanism
- Drug adsorption (hapten) mechanism
- Autoantibody mechanism

Alloimmune immune hemolysis
- Hemolytic disease of the newborn
- Hemolytic transfusion reaction

autoimmune (FIGURE 1). Alloantibodies are produced in response to foreign antigens such as drugs or allogeneic blood transfusions; autoantibodies react against antigens present on a person’s own red cells. Antibodies that react against antigens common to all red cells are also known as panagglutinins, as they agglutinate all red cells in vitro.

Complement activation and fixation
Once an antibody attaches to the red cell membrane, the complement system may or may not become activated, depending on the class or subclass of the antibody involved.8-10 IgM, IgA, IgG1, and IgG3 antibodies can activate the complement system and fix complement proteins to red blood cells; IgG2 and IgG4 do not.

Hemolysis:
Extravascular or intravascular
Two basic mechanisms explain the immune destruction of red blood cells.

Extravascular hemolysis. Macrophages capture and phagocytize red blood cells that are coated with antibodies or complement C3b molecules or both. Red blood cells coated with IgG are destroyed primarily in the spleen, and IgM-coated cells are destroyed primarily in the liver.8,6

Intravascular hemolysis occurs when complement proteins C5 through C9 attach to red blood cells, forming pores that allow the cell contents to leak out. Since IgM and IgA antibodies are efficient at binding and activating complement, both intravascular and extravascular hemolysis can occur when these antibodies are involved.

Hemopoiesis increases to compensate for red blood cell loss
The normal life span of red blood cells is 100 to 140 days,9 and under normal, steady-state conditions, the bone marrow produces approximately 25 mL of mature red cells daily to replace those that are lost. However, in response to blood loss or increased red blood cell destruction, the bone marrow can easily produce up to 5 times as many red blood cells for sustained periods, and up to 10 times as many for short periods. Therefore, a person can have clinical or laboratory evidence of increased red cell loss, but as long as the bone marrow can compensate with increased production, he or she will not have anemia.

- TYPES OF IMMUNE HEMOLYTIC ANEMIA

The immune hemolytic disorders can be classified in several ways (TABLE 1). One distinction is the temperature at which the antibody is most active (ie, their thermal range).8,10 “Warm” antibodies are most active at 37°C, while “cold” antibodies are generally most active at less than 32°C. Occasionally, mixtures of warm and cold antibody types are seen in the same patient.8,11,12 The type and amount of antibody or antibodies involved, and whether complement fixation occurs, can provide valuable information for diagnosis and treatment.

Warm autoimmune hemolytic anemia
Warm autoimmune hemolytic anemia occurs in 1 in 50,000 to 80,000 persons, and accounts for 60% to 70% of cases of immune hemolysis.8,13 From 50% to 70% of cases are idiopathic or primary; the remaining 30% to 50% are associated with underlying diseases present at the time the patient is first evaluated, such as lymphoproliferative disorders (eg, leukemia, lymphoma, multiple myeloma, Waldenstrom’s macroglobulinemia), autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, pernicious anemia), and solid tumors.
How red blood cells are destroyed in immune hemolytic anemia

**RED BLOOD CELLS** carry antigens such as Rh on their surface.

**IMMUNOGLOBULIN ANTIBODIES** attach to the antigens.

- **RED BLOOD CELLS**

- **Antigens**

- **Antibodies**

**MACROPHAGES**

**SPHEROCYTES**, red blood cells that have assumed a spherical shape due to loss of membrane, are more rigid than normal red blood cells and therefore more easily damaged and destroyed through normal wear and tear.

**MACROPHAGES** may destroy red blood cells by phagocytosis.

**EXTRAVASCULAR HEMOLYSIS** begins as macrophages in the liver or spleen capture red blood cells by attaching to antibodies or to complement C3b molecules or both, and damage the red blood cell membrane.

**INTRAVASCULAR HEMOLYSIS** occurs if complement proteins C5 through C9 attach to red blood cells and form pores that allow the cell contents to leak out.

**COMPLEMENT SYSTEM**

The complement system may become activated and complement molecules may attach to red blood cells if the antibody is an IgM, IgA, IgG1, or IgG3, but not IgG2 or IgG4.

**Antigens**

**Antibodies**

**Complement molecules**

**Macrophage**

**SPHEROCYTES**

**MACROPHAGES**

**EXTRAVASCULAR HEMOLYSIS**

**INTRAVASCULAR HEMOLYSIS**
Cold autoimmune hemolytic anemia

Cold autoimmune hemolytic anemia, or cold agglutinin syndrome, is less common than warm autoimmune hemolytic anemia. Classically, this disease occurs after either *Mycoplasma pneumoniae* pneumonia or infectious mononucleosis, but can also be seen as part of several malignant, nonmalignant, and infectious disorders.8,10,17–20

Usually, the antibody is an IgM autoantibody against the I blood group system,8,10,21 or against the Pr or P systems. Nonpathogenic cold agglutinins, typically polyclonal IgM, react only at very low temperatures: 0° to 4°C.8,10,22 In contrast, pathogenic cold agglutinins are almost always a monoclonal IgM paraprotein (usually of the kappa light chain type), and usually react at 30° to 32°C or higher.8,10,22 Such temperatures can occur in the peripheral circulation under normal circumstances, allowing pathogenic IgM—and usually complement as well—to attach to red blood cells. Although the IgM may elute from the red cell as it rewarms to 37°C, the complement molecules (primarily C3b) remain attached.8 Then, macrophages in the reticuloendothelial system, particularly in the liver, bind to and phagocytose the C3b-coated red cells.

Paroxysmal cold hemoglobinuria

Historically, paroxysmal cold hemoglobinuria was associated with congenital or late-stage syphilis infection, but is now more common in children with various viral infections (eg, chickenpox, measles, influenza virus, or other upper respiratory infections), or rarely coincident with a bacterial infection.2,23

The antibodies in paroxysmal cold hemoglobinuria, also termed “biphasic antibodies,” are usually IgG autoantibodies against the P system.8,22 These antibodies produce positive results in the Donath-Landsteiner test.2,24 Like cold agglutinins, biphasic antibodies typically bind to red cells and bind complement at low temperatures and cause hemolysis as the red cells rewarms to 37°C. However, the red cell destruction appears to be more intravascular than extravascular.

Drug-induced immune hemolytic anemia

Numerous drugs (TABLE 2) can induce immune hemolysis. The incidence of drug-induced

<table>
<thead>
<tr>
<th>Partial list of drugs associated with immune hemolysis</th>
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<tbody>
<tr>
<td><strong>Immune complex mechanism</strong></td>
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<tr>
<td>Acetaminophen</td>
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<tr>
<td>Antihistamines</td>
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<tr>
<td>Cefotaxime</td>
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<tr>
<td>Ceftriaxone</td>
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<tr>
<td>Cephalosporins</td>
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<tr>
<td>5-Fluorouracil</td>
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<tr>
<td>Hydrochlorothiazide</td>
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<td>Insulin</td>
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<tr>
<td>Isoniazid</td>
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<td>Melphalan</td>
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<td>Probenecid</td>
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<td>Quinidine</td>
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<tr>
<td>Streptomycin</td>
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<tr>
<td>Sulfonamides</td>
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<tr>
<td>Tetracycline</td>
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<tr>
<td>Tolmetin</td>
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<tr>
<td><strong>Drug adsorption (hapten) mechanism</strong></td>
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<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Carbenicillin</td>
</tr>
<tr>
<td>Cephaloridine</td>
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<tr>
<td>Cephalothin</td>
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<tr>
<td>Methicillin</td>
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<tr>
<td>Penicillin</td>
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<tr>
<td><strong>Autoantibody mechanism</strong></td>
</tr>
<tr>
<td>Alpha-methyldopa</td>
</tr>
<tr>
<td>Ibuprofen</td>
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<tr>
<td>Levodopa</td>
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<tr>
<td>Mefenamic acid</td>
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<tr>
<td>Procainamide</td>
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<td>Thioridazine</td>
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The autoantibody in warm autoimmune hemolytic anemia is typically an IgG specifically active against components of the Rh blood group system, which thus reacts against all red cells except those that lack Rh antigens (ie, red cells from persons with the rare Rh-null syndrome).8,10 Complement, as well as IgA or IgM, may also be present on the red cell along with IgG, and these combinations may be associated with a more clinically severe hemolytic anemia.14–16 Less commonly, only IgA or IgM is present.

**TABLE 2**

**Partial list of drugs associated with immune hemolysis**

**Immune complex mechanism**
- Acetaminophen
- Antihistamines
- Cefotaxime
- Ceftriaxone
- Cephalosporins
- 5-Fluorouracil
- Hydrochlorothiazide
- Insulin
- Isoniazid
- Melphalan
- Probenecid
- Quinidine
- Streptomycin
- Sulfonamides
- Tetracycline
- Tolmetin

**Drug adsorption (hapten) mechanism**
- Ampicillin
- Carbenicillin
- Cephaloridine
- Cephalothin
- Methicillin
- Penicillin

**Autoantibody mechanism**
- Alpha-methyldopa
- Ibuprofen
- Levodopa
- Mefenamic acid
- Procainamide
- Thioridazine

**Cold autoimmune hemolytic anemia**

Cold autoimmune hemolytic anemia occurs after *M pneumoniae* pneumonia or mononucleosis. Partial list of drugs associated with immune hemolysis. Immune complex mechanism

- Acetaminophen
- Antihistamines
- Cefotaxime
- Ceftriaxone
- Cephalosporins
- 5-Fluorouracil
- Hydrochlorothiazide
- Insulin
- Isoniazid
- Melphalan
- Probenecid
- Quinidine
- Streptomycin
- Sulfonamides
- Tetracycline
- Tolmetin

**Drug adsorption (hapten) mechanism**

- Ampicillin
- Carbenicillin
- Cephaloridine
- Cephalothin
- Methicillin
- Penicillin

**Autoantibody mechanism**

- Alpha-methyldopa
- Ibuprofen
- Levodopa
- Mefenamic acid
- Procainamide
- Thioridazine
immune hemolysis is not known, but is estimated at approximately 1 case per million persons. Likewise, the incidence of drug-induced antibody formation or a positive DAT without associated hemolysis is also not known.

There are three basic mechanisms of drug-induced immune hemolytic anemia.

1. **The immune complex mechanism.** Drugs such as quinidine form a complex with plasma proteins and IgM, which binds nonspecifically to the red cell membrane.
2. **The drug adsorption mechanism.** IgG antibodies against drugs such as penicillin and cephalosporins become adsorbed onto the red cell membrane.
3. **The autoantibody mechanism** produces clinical and laboratory features similar to warm autoimmune hemolytic anemia. Methyldopa, levodopa, mefenamic acid, and procainamide are examples of drugs that can stimulate this mechanism.

Patients with various combinations of these mechanisms have been reported. A potential fourth mechanism, membrane modification or nonimmunologic protein adsorption has so far not been shown to cause immune hemolysis.

### Alloimmune hemolysis

Two situations can give rise to alloimmune hemolytic anemia: blood component transfusion and hemolytic disease of the newborn. In both, red cell alloantibodies are formed after exposure to foreign red cell antigens. The alloantibody is usually an IgG with optimal reactivity at 37°C against a specific red cell antigen (eg, K, D, Jk<sup>α</sup>). Thus, the IgG alloantibody binds only to transfused red cells bearing the corresponding antigen.

In hemolytic disease of the newborn, the mother becomes sensitized to foreign red cell antigens either after fetal red cells gain access to her circulation, or after exposure to allogeneic red cells (eg, blood component transfusion or sharing of needles in illicit drug use). Antibodies to the fetus’s blood then cross the placenta to the fetus. The most common alloantibody in this disease is anti-D, but almost any IgG antibody against any of the dozens of red cell antigens may be implicated.

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**TABLE 3**

<table>
<thead>
<tr>
<th>Selected clinical features seen in immune hemolysis*</th>
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</thead>
<tbody>
<tr>
<td><strong>FEATURE</strong></td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Normal or low reticulocytes</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
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<tr>
<td>Jaundice</td>
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</tbody>
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*Average percentages based on reports in the literature (includes both primary and secondary cases of autoimmune hemolytic anemia)

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### CLINICAL MANIFESTATIONS

The signs and symptoms of immune hemolysis can vary considerably, depending on the rapidity of the hemolysis, the degree of anemia, and the presence of any underlying diseases. **TABLE 3** lists some of the more common clinical manifestations. Shortness of breath, fatigue, dizziness, angina, pallor, and jaundice may be present in anemia of any cause and are not unique to immune hemolysis. Some patients may be totally without symptoms, with immune hemolysis manifested solely by laboratory tests.

The history may suggest an immune cause of anemia. Things to ask about:

- Immune hemolysis or another immune cytopenia (eg, autoimmune thrombocytopenia).
- Underlying autoimmune disorders (eg, systemic lupus erythematosus).
- Lymphoproliferative disorders (eg, chronic lymphocytic leukemia).
- Pregnancy complicated by hemolytic disease of the newborn.
- Transfusions or transfusion reactions.
- Recent viral or bacterial illnesses.
- Prescription or nonprescription drug use.

The history may suggest an immune cause of anemia.
Unexplained fever is common in immune hemolysis

Since cold antibodies can cause red cell agglutination in the cooler, peripheral circulation, a patient with cold antibody autoimmune hemolytic anemia may have signs and symptoms consistent with acrocyanosis or Raynaud's phenomenon.\(^8\)\(^9\)\(^2\) Cold-induced cyanosis and mottling may be evident in the ears, cheeks, fingers, nose, toes, or any region of the skin exposed to cooler temperatures. Pain and numbness may be present with the cyanosis; dry gangrene has been reported in parts of the skin exposed to cooler temperatures. Similarly, cold may precipitate attacks of hemolysis and hemoglobinuria in paroxysmal cold hemoglobinuria.

Unexplained fever is not uncommon in immune hemolysis, and is one of the most common findings in hemolytic transfusion reactions. Hepatosplenomegaly and lymphadenopathy may be variably present in one third to two thirds of patients. Additional physical findings are not unique to immune hemolysis but may be important in identifying any associated diseases (eg, a lymphoproliferative disorder).

LABORATORY MANIFESTATIONS

The direct antiglobulin or Coombs' test
The single most important test for establishing and characterizing an immune hemolytic process is the direct antiglobulin test (DAT or Coombs' test).\(^4\)\(^-\)\(^7\)\(^5\) Originally developed to be used before transfusion to detect red cell alloantibodies to minor blood group antigens (eg, Kell, Duffy, Rh) and thus provide an increased margin of safety in crossmatching blood, the DAT has proved valuable for other purposes as well, such as detecting, characterizing, and investigating the red cell autoantibodies and drug-related antibodies associated with red cell hemolysis.

The DAT uses standardized preparations of antihuman globulin to detect IgG or complement (the C3d component) coating the red cell. It can detect as few as 100 to 200 molecules of IgG per red cell,\(^8\)\(^1\) but in rare cases of immune hemolysis the DAT can be negative if there are fewer than 100 to 150 IgG molecules per red cell.\(^8\)\(^3\)\(^5\) Conversely, a positive DAT does not always indicate clinically significant immune hemolysis: a few otherwise healthy blood donors have a positive DAT at the time of donation. In general, standardized antihuman globulin reagents for detecting IgM or IgA are not available except in research laboratories. In cases of autoimmune hemolytic anemia due to IgM or IgA, the DAT is still often positive owing to the presence of complement on the red cell.

In cases in which the DAT is positive with anti-IgG antihuman globulin, the antibody can be eluted off the red cell and its characteristics further examined.\(^8\)\(^1\)\(^0\) The eluate can be tested against reagent red cells of known antigenic phenotype to determine the specificity of the IgG antibody (eg, anti-D, anti-e, panagglutinating antibody, anti-I cold agglutinin). An elution study can also provide clinically useful information in cases of known or suspected red blood cell alloimmunization secondary to transfusion or pregnancy.

Other tests
Determination of the antibody titer and optimum temperature of reactivity may provide useful information in cases of cold agglutinin autoimmune hemolytic anemia.

A Donath-Landsteiner test should be performed in cases of suspected paroxysmal cold hemoglobinuria.

Complete blood count. Routine and automated blood cell counts indicate the degree of anemia but are otherwise nonspecific. The mean corpuscular volume may be elevated because of reticulocytosis.

The reticulocyte count is usually elevated in hemolytic anemia (sometimes as high as 30%), but it is normal or low in as many as 25% of cases.\(^3\)\(^4\)\(^3\)\(^6\)

The peripheral blood smear may demonstrate increased spherocytes, polychromatophilia, and occasionally, nucleated red cells (FIGURE 2).\(^3\)\(^5\) The spherocytosis can be high enough to be confused with hereditary spherocytosis. Red cell agglutination or rouleaux formation may be visually and grossly evident in cold antibody autoimmune hemolytic anemia, and may cause problems in obtaining accurate hemograms in automated cell counters.

Liver function tests. The serum bilirubin...
(particularly the indirect fraction) and lactate dehydrogenase (LD) levels may be elevated as part of the hemolytic process. Isoenzyme fractionation of the elevated LD in acute hemolysis may demonstrate increased LD$_1$ out of proportion to the LD$_2$ fraction (ie, a "flip" in the LD isoenzyme pattern between LD$_1$ and LD$_2$). Table 4 lists some of the common laboratory signs of hemolysis.

Examination of the bone marrow is generally helpful only as part of the workup for an underlying lymphoproliferative disorder or other malignant process.

### Differential Diagnosis

The differential diagnosis includes all causes of hereditary and acquired hemolytic anemia. Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and the hemolytic-uremic syndrome should be ruled out. Congenital causes of hemolysis (eg, the hemoglobinopathies, hereditary spherocytosis) are often eliminated by a careful history and laboratory tests. Red cell enzyme deficiency disorders (eg, glucose-6-phosphate dehydrogenase deficiency) should also be considered.

More than one hemolytic process may be present at the same time. Examples include a lymphoproliferative disorder with a cold antibody autoimmune hemolytic anemia and a transfusion-induced alloantibody causing red cell hemolysis; sickle cell anemia with a superimposed warm antibody autoimmune hemolytic anemia; and glucose-6-phosphate dehydrogenase deficiency and a drug-induced immune hemolytic process. Evan's syndrome is the association of autoimmune hemolytic anemia with autoimmune thrombocytopenia.$^{37,38}$

Consultations with subspecialists in transfusion medicine and hematology are important early in the disease for diagnostic and therapeutic reasons.

### Treatment

**Corticosteroids**

Immunosuppressive therapy, initially with corticosteroids, is usually the first line of treatment for autoimmune disorders of the red cell, particularly in cases of warm autoimmune hemolytic anemia.$^{4,9,39}$ A total daily dose of...
Corticosteroids are the first line of treatment for immune hemolysis.

60 to 100 mg of prednisone produces a clinical response in approximately 80% to 90% of patients with warm autoimmune hemolytic anemia. After 2 or 3 days of therapy, the first indication of a response may be a transient increase in the reticulocyte count, followed by increases in the hemoglobin and hematocrit levels. The DAT (direct Coombs’ test) may continue to be positive despite improvement in other clinical and laboratory measures. Most patients show a response to corticosteroids within 10 to 14 days, but the response may not be maximal until after 3 weeks of therapy.

Patients with life-threatening hemolysis may benefit from larger doses of corticosteroids, such as 100 to 200 mg of methylprednisolone or an equivalent drug, given intravenously in divided doses over 24 hours.

Once the patient has responded to prednisone, the dose can be gradually reduced over the ensuing weeks and months until the lowest possible dose is achieved. Alternate-day prednisone therapy should be started as soon as clinically feasible after the patient is stable. Approximately 20% to 30% of patients achieve a lasting remission with prednisone therapy, 50% continue to require some form of low-dose maintenance prednisone therapy for months, and another 10% to 20% either do not respond to prednisone therapy or require unacceptably high doses.

Corticosteroid therapy has generally not shown clinical efficacy in patients with uncomplicated cold agglutinin autoimmune hemolytic anemia, paroxysmal cold hemoglobinuria, or drug-induced immune hemolysis.

Cytotoxic drugs

If corticosteroid therapy does not produce a remission or if the patient has a relapse, additional immunosuppressive therapy may be needed. Cytotoxic drugs such as azathioprine and cyclophosphamide have been used with some success. In adults, cyclophosphamide 60 mg/m² or azathioprine 80 mg/m² per day can be considered. Some investigators consider cytotoxic drugs to be a third- or fourth-line treatment option.

Splenectomy

In patients with warm autoimmune hemolytic anemia who do not respond to corticosteroid therapy, splenectomy is often the second line of therapy. However, only patients with IgG autoantibody (whose red cells are destroyed primarily in the spleen) would be expected to benefit from splenectomy. Not all patients respond to splenectomy, and those who show an initial response may relapse and require additional immunosuppressive therapy.

The need to give pneumococcal vaccine before the splenectomy, as well as the need for any long-term prophylactic antibiotic therapy, should be assessed in the individual patient.

Intravenous immunoglobulin

A number of studies have examined the efficacy of intravenous immunoglobulin in treating autoimmune hemolytic anemia, primarily of the warm antibody type. However, the success rate has been variable and not as encouraging as in other immune disorders. Flores et al found that 40% of 73 patients with warm autoimmune hemolytic anemia responded to high-dose intravenous immunoglobulin therapy within 10 days, and that hepatomegaly and a low pretreatment hemoglobin level (< 7.0 g/dL) correlated with a positive response. Over half of their patients also received concomitant corticosteroid therapy. These investigators concluded that intravenous immunoglobulin was useful as adjunctive therapy in selected cases of warm autoimmune hemolytic anemia but should not be considered standard therapy.

Laboratory abnormalities in red cell hemolysis

- Hyperbilirubinemia (unconjugated/indirect)
- Decreased serum haptoglobin
- Decreased serum hemopexin
- Increased serum methemalbumin
- Increased serum lactate dehydrogenase
- Increased (mild) serum aspartate aminotransferase
- Increased serum free hemoglobin (hemoglobinemia)
- Increased urine hemoglobin (hemoglobinuria)
Other investigators\textsuperscript{40,46} suggested that intravenous immunoglobulin may have greater efficacy in cases of autoimmune hemolytic anemia secondary to lymphoproliferative disorders, or when used in combination with plasma exchange. Of note: one of the side effects of intravenous immunoglobulin therapy can be hemolysis.\textsuperscript{47-49}

Folic acid
Folic acid (1 mg per day) is usually recommended as long as there is ongoing hemolysis, because this nutrient is necessary for red blood cell maturation.

Alternate therapy for refractory cases
Cyclosporine shows promise in autoimmune hemolytic anemia refractory to conventional therapy, or when an alternative to splenectomy is being considered, according to several papers, mostly case reports.\textsuperscript{50-52} The dosage was usually 4 to 6 mg/kg/day by mouth, and side effects were minimal.

Plasma exchange has been used in a few cases, often as an adjunct to other therapies in refractory cases.\textsuperscript{53-55}

Vincristine, danazol, and other therapies have been used in small numbers of refractory cases.\textsuperscript{9,46,56,57}

Treating specific hemolytic diseases
Underlying diseases and infections associated with autoimmune hemolytic anemia or paroxysmal cold hemoglobinuria should be treated, and any drugs implicated or proven as a cause for the patient’s immune hemolysis should be stopped.\textsuperscript{46}

In cold agglutinin disease, avoiding cold ambient temperatures is often all that is necessary to provide symptomatic relief.\textsuperscript{9,21,46} In addition, in hospitalized patients, intravenous solutions may need to be warmed before infusion. Corticosteroids and splenectomy have not generally been shown to be effective in patients with cold antibody autoimmune hemolytic anemia.

Transfusion reactions. When treating proven or suspected alloimmune hemolysis secondary to transfusion it is critical to discontinue the transfusion, as there is a direct relationship between morbidity and mortality and alloimmune hemolysis. The primary complications with transfusion-associated alloimmune hemolysis are acute renal failure and disseminated intravascular coagulation. Treatment is primarily supportive. The efficacy of corticosteroids or intravenous immunoglobulin in such cases has not been validated and cannot be recommended as standard therapy. Additional reviews on the treatment of hemolytic transfusion reactions should also be consulted.\textsuperscript{27-29}

Prevention and treatment of hemolytic disease of the newborn are beyond the scope of this review, and the interested reader is referred to excellent reviews elsewhere.\textsuperscript{7,9,30,31}

Transfusion Consultation with a transfusion medicine specialist is extremely important in hemolysis. Finding compatible blood for patients with autoimmune hemolytic anemia can often be difficult and challenging.\textsuperscript{58-60} The antibody in patients with warm autoimmune hemolytic anemia typically demonstrates activity against all red cells (except Rh-null red cells); therefore, all crossmatches will be “incompatible.” Transfused red cells will also become coated with antibody and undergo immune hemolysis at the same rate as the patient’s own red cells.\textsuperscript{60} Thus, the beneficial effect of transfusion in immune hemolysis will be temporary.

There is always a risk of an acute or delayed hemolytic transfusion reaction after any transfusion, and an immune hemolytic process may make such reactions more difficult to detect and prevent. However, in patients clearly in need of transfusion because of cardiovascular, central nervous system, or pulmonary decompensation, red cells should not be withheld, even if crossmatch compatibility cannot be confirmed or guaranteed.\textsuperscript{55,56} Other important supportive measures in such patients include maintenance of blood volume with intravenous fluids and volume expanders, oxygen therapy, and maintenance of renal function.

Although transfusion can precipitate warm-antibody autoimmune hemolytic anemia in otherwise-normal patients, it is less clear whether transfusion alone increases the severity of autoimmune hemolytic anemia in patients who already have ongoing immune hemolysis.\textsuperscript{59,61}
FOLLOW-UP AFTER REMISSION

Close clinical observation is necessary for months and years after remission, as unpredictable relapses may occur in those who have warm or cold autoimmune hemolytic anemia. Patients should be educated and counseled to seek medical attention at the first sign of a possible relapse. Likewise, continued observation is important in the event a lymphoproliferative or autoimmune disorder manifests itself over time in patients with idiopathic autoimmune hemolytic anemia.

REFERENCES


