Autoimmune hemolytic anemia in children and adolescents

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INTRODUCTION — Autoimmune hemolytic anemia (AIHA) refers to a collection of disorders characterized by the presence of autoantibodies that bind to the patient's own erythrocytes, leading to premature red cell destruction. Specific characteristics of the autoantibodies, especially the type of antibody; its optimal binding temperature; and whether complement is fixed influence the clinical picture. In all cases of AIHA, however, the autoantibody leads to a shortened red blood cell survival (ie, hemolysis) and, when the rate of hemolysis exceeds the ability of the bone marrow to replace the destroyed red cells, to anemia and its attendant signs and symptoms.

The pathophysiology, clinical presentation, diagnosis, and treatment of AIHA in children are reviewed here [1]. General approaches to the child with anemia and hemolytic anemia are discussed separately. (See "Approach to the child with anemia" and "Overview of hemolytic anemias in children".)

INCIDENCE — Autoimmune hemolytic anemia (AIHA) in children is relatively rare, with an estimated annual incidence of 1 in 80,000 persons in the general population [2,3], rendering it more common than acquired aplastic anemia but less common than immune thrombocytopenia (ITP). AIHA can affect children of any race or nationality and can present in infancy, especially after an infection, and throughout childhood [4-6]. Teenagers who present with AIHA are more likely to have an underlying systemic illness [7-9].

CLASSIFICATION — A simplistic classification scheme separates autoimmune hemolytic anemia (AIHA) into a primary or a secondary process (table 1). In a series of 265 children with AIHA, 37 percent were primary, 53 percent had an underlying immunological disorder including Evans' syndrome, and 10 percent were post-infectious [10]. At latest follow-up, ranging from 2.4 to 5.6 years among subtypes, 59 to 86 percent of the children were alive and off therapy, but only 33 to 44 percent of the children were in continuous complete remission.

Primary AIHA — In primary AIHA, red blood cell autoantibodies are present and cause hemolytic anemia, but no evidence of an underlying systemic illness exists. Primary AIHA can be subclassified according to the characteristics of the erythrocyte autoantibodies and autoantigens (table 2) [11]:

- **Warm-reactive AIHA** – The most common form of primary AIHA in children involves warm-reactive autoantibodies, usually IgG, that bind preferentially to the red cells at 37ºC, fix complement in some cases, and lead to extravascular hemolysis mainly in the spleen, with resulting splenomegaly, jaundice, and anemia.
- **Paroxysmal cold hemoglobinuria** – A second category of primary AIHA, particularly common in children after a viral-like illness, is paroxysmal cold hemoglobinuria (PCH). PCH is characterized by IgG autoantibodies that bind preferentially at colder temperatures, fix complement efficiently, and cause intravascular hemolysis with hemoglobinemia, hemoglobinuria, and anemia.
- **Cold agglutinin disease** – The third major form of primary AIHA, cold agglutinin disease, is relatively rare in children, but can occur after Mycoplasma infection. In this disorder, IgM autoantibodies bind erythrocyte I/i antigens at colder temperatures and fix complement, which leads to either complement-mediated intravascular hemolysis (like PCH) or immune-mediated extravascular clearance, mainly by hepatic macrophages.

Secondary AIHA — AIHA is considered to be a secondary process when the immune-mediated hemolytic anemia

is only one manifestation of a broader systemic disorder. For example, secondary AIHA can occur in patients with systemic lupus erythematosus or other autoimmune disorders. Secondary AIHA can occur also in association with malignancy, immunodeficiency states, drug exposure, or following certain infections. Sometimes the AIHA is the initial manifestation of the underlying systemic illness, especially for unsuspected immunodeficiency states such as common variable immune deficiency (CVID). (See "Common variable immunodeficiency in children".)

PATHOPHYSIOLOGY OF RED CELL DESTRUCTION — IgG-coated erythrocytes are removed primarily by the spleen, regardless of the presence of complement (figure 1). The amount of surface IgG is correlated with the rate of splenic clearance because Fc receptors on macrophages bind and phagocytose IgG-coated erythrocytes [12,13]. In contrast to IgG-mediated hemolysis, IgM-coated erythrocytes are cleared rapidly within the liver. The amount of complement affects the clearance of IgM-coated cells, with macrophage complement receptors responsible for binding and phagocytosis of erythrocytes [12,14].

Warm-reactive AIHA — In warm-reactive autoimmune hemolytic anemia (AIHA), the IgG autoantibodies coat autologous erythrocytes and may fix complement. These sensitized cells pass through the spleen and other parts of the reticuloendothelial system, where they interact with complement and Fc receptors on the macrophages. Erythrocytes may be fully ingested by macrophages; however, if only a portion of the surface membrane is removed, the erythrocyte reforms into a spherocyte, which is identifiable on the peripheral blood smear (picture 1). For IgG-coated erythrocytes, the majority of immune clearance occurs within the spleen (ie, extravascular hemolysis) (figure 1), which does not lead to hemoglobinemia and/or hemoglobinuria. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs".)

Cold-reactive AIHA — In cold agglutinin disease or paroxysmal cold hemoglobinuria, the autoreactive antibody binds preferentially at 4ºC and fixes complement efficiently. At normal body temperature, virtually no antibody is identifiable on the cell surface, but complement components, particularly C3b, can be identified using the antiglobulin (formerly called Coombs) reagent. If complement is activated to completion on the cell surface, erythrocytes will hemolyze intravascularly, resulting in hemoglobinemia and hemoglobinuria (figure 1). When complement is deposited on the red cell but not fully activated to the point of cell lysis, macrophages within the reticuloendothelial system bind the erythrocytes using complement receptors and engulf them in a manner similar to warm-reactive AIHA [15]. However, complement-coated erythrocytes are cleared by macrophages primarily within the liver rather than the spleen (figure 1). (See "Pathogenesis of autoimmune hemolytic anemia: Cold agglutinin disease".)

CLINICAL PRESENTATION — Most children with autoimmune hemolytic anemia (AIHA) present with signs and symptoms referable to anemia, including weakness, fatigue, shortness of breath, dizziness, pallor, jaundice, and/or dark urine. Less commonly, children with AIHA will present with abdominal pain or fever.

Patient history — The patient with primary AIHA usually has a benign previous medical history and a negative family history. The review of systems should focus on any recent acute infectious illness, signs and symptoms of a potential underlying systemic illness, and concurrent medications.

Physical findings — On physical examination, the child with AIHA often will be pale and jaundiced, especially apparent in the conjunctivae and palms. The presence of skeletal abnormalities suggests the presence of congenital disorders such as Blackfan-Diamond anemia, Fanconi anemia, constitutional aplastic anemia, or beta thalassemia major. Often, tachycardia is present, as is a systolic flow murmur, reflecting a high-output anemic state; however, cardiovascular compromise (eg, congestive failure) is uncommon unless the hemoglobin concentration is <5 g/dL. The liver and spleen may be palpable, but the presence of massive organomegaly or lymph node enlargement should suggest another disorder such as malignancy (eg, leukemia, lymphoma) or infection (eg, HIV, malaria, tuberculosis).

In the classic, uncomplicated case of warm-reactive AIHA, the child will appear jaundiced, but excessive bilirubin will not be present in the urine (ie, hemolytic or "acholuric" jaundice). The passage of dark urine in AIHA, in colors ranging from gold to red to black, usually signifies the presence of hemoglobin (hemoglobinuria), secondary to intravascular hemolysis, and is more suggestive of cold-reactive AIHA.

Laboratory evaluation — A reasonable and appropriate initial laboratory evaluation of the child with AIHA is quite modest. Always, a complete blood count should be ordered, and the hemoglobin concentration may be surprisingly low (<7 g/dL). Red blood cell indices (eg, mean cellular volume [MCV] or red cell distribution width [RDW]) generally are not helpful in establishing the diagnosis. However, abnormalities of the RBC indices occasionally can be seen:

- In the presence of a cold or warm agglutinin, the red cells may pass through the automated counter in small clumps, rather than one at a time, resulting in a spuriously increased mean corpuscular volume (MCV). Due to RBC clumping, the reported MCV will sometimes be at non-physiologic or implausible levels such as 180 to 250 fL. Examination of the peripheral smear can determine whether this phenomenon is present (picture 2). (See "Macrocytosis", section on 'Spurious macrocytosis'.)
- In the presence of large numbers of spherocytes, the mean corpuscular hemoglobin concentration (MCHC) may be elevated, usually to levels >36 g/dL. This finding is not specific to AIHA, however, since it also is present in patients with congenital (hereditary) spherocytosis.

The leukocyte count and platelet count should be normal or elevated; the presence of leukopenia or thrombocytopenia suggests the presence of a bone marrow failure syndrome (eg, aplastic anemia), microangiopathic hemolytic anemia (eg, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura), or bone marrow suppression secondary to an active infection.

In rare instances, autoantibodies against other formed elements in the blood may be present in a patient with AIHA. In such cases, the patient will present with direct antiglobulin test (DAT, formerly called Coombs) positive AIHA, along with thrombocytopenia, and, more rarely, neutropenia (Evans syndrome). (See 'Evans syndrome' below.)

Reticulocyte count — The absolute reticulocyte count usually is elevated from the normal value of 50 to 75 x 10^3/microL and may reach values as high as 600 to 800 x 10^3/microL. A low reticulocyte count occasionally is encountered and may reflect a concomitant accelerated immune-mediated destruction of red blood precursors within the marrow, a temporary suppression of bone marrow activity secondary to infection, and/or a delayed bone marrow response to the hemolytic event [16].

Peripheral blood smear — Evaluation of the peripheral blood smear is a critical part of the patient workup in AIHA. Numerous small spherocytes usually are present, especially in warm-reactive AIHA (picture 3). A few teardrop shaped red cells or red cell fragments (schistocytes) may be present, but spherocytes should predominate. In the presence of especially severe hemolysis, red blood cell precursors, such as normoblasts, may be present in the circulation (picture 4). The presence of clumped or agglutinated red cells suggests the presence of a cold-reactive AIHA (picture 2). (See "Evaluation of the peripheral blood smear".)

Polychromasia, reflecting an increased number of circulating young red cells (reticulocytes), is commonly observed because reticulocytes are released from the bone marrow to compensate for accelerated erythrocyte destruction (picture 3 and picture 5). Howell-Jolly bodies may be seen on the blood smear, reflecting accelerated erythropoiesis or a prior splenectomy for a hemolytic process (picture 6).

Bone marrow examination — Evaluation of the bone marrow is typically not needed to establish the diagnosis of AIHA, unless there are unusual characteristics to the medical history or physical examination. In some cases, however, bone marrow aspiration may be helpful to exclude a malignant process, myelodysplasia, or one of the bone marrow failure syndromes. In AIHA, the marrow aspirate usually reveals intense erythroid hyperplasia (picture 7 and picture 8), whereas isolated erythroid hypoplasia or aplasia may signify the presence of acquired pure red cell aplasia. (See "Anemia in children due to decreased red blood cell production", section on 'Acquired pure red cell aplasia'.)

Urinalysis — Examination of the urine always should be performed. In children with extravascular hemolysis, the urinalysis may be completely normal. In children with intravascular hemolysis, hemoglobin is released into the plasma, then cleared through the kidneys into the urine. When hemoglobinuria is present, urine dipstick testing will

identify the presence of blood, but microscopic examination will reveal no red blood cells. Chronic hemoglobinuria also will lead to hemosiderin accumulation in uroepithelial cells, which can be detected as a positive iron stain of cells in the urinary sediment.

Direct antiglobulin test — The most important and useful laboratory test to establish the diagnosis of AIHA is the direct antiglobulin test (DAT), formerly known as the Coombs test. The DAT identifies the presence of antibodies and/or complement on the surface of the erythrocyte; results are scored in a semiquantitative manner, based on the amount of red cell agglutination.

Appropriate characterization of the erythrocyte antibodies includes determination of the isotype, the presence of complement, thermal reactivity of the antibody, and the binding specificity to erythrocyte antigens. In less than 5 percent of childhood cases, the DAT is negative despite good clinical evidence for the presence of warm AIHA. In such cases, the amount of IgG on the erythrocyte may be below the threshold for detection by standard Coombs testing. Alternatively, an IgA autoantibody [17] or even a warm-reactive IgM autoantibody may be present [18]. Because IgM and IgA antibodies are not reactive with the standard Coombs reagent, specific research reagents and techniques must be used for their identification.

Other laboratory tests — Selected measurement of serum chemistries should be performed:

- Total bilirubin is elevated in most patients with AIHA because of accelerated erythrocyte destruction; it should primarily be in the unconjugated (ie, indirect) form. Elevated direct (conjugated) bilirubin suggests intrinsic liver disease.
- Elevated serum concentrations of lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are seen in AIHA, reflecting the presence of hemolysis, especially intravascular hemolysis. Alanine amino transferase (ALT) and other hepatic enzymes should not be elevated in AIHA.
- Serum haptoglobin, which binds free plasma hemoglobin, will be low in most cases of AIHA. However, haptoglobin is not synthesized well in young infants; it also is an acute phase reactant, and its concentration may be elevated in the presence of infection or inflammation [19]. For these reasons, quantitation of the haptoglobin level may not be helpful in the evaluation of a young patient with AIHA.

IMMUNOHEMATOLOGIC STUDIES — For patients with laboratory results consistent with hemolysis and a positive DAT (Coombs test), immunohematologic studies are performed to categorize the type of autoimmune hemolytic anemia (AIHA). In many institutions, this testing is performed by the transfusion service, blood bank, or hospital laboratory service. The laboratory should confirm the diagnosis of AIHA with the positive DAT (Coombs test). However, additional factors can affect the location and type of hemolysis in AIHA (table 3). In most pediatric cases of AIHA, the pathogenic antibody is identified as an IgG molecule [6,20,21].

In general, IgG autoantibodies bind to red cell antigens optimally at 37ºC; hence, the descriptive term "warm-reactive" autoantibodies. The presence of IgG on the erythrocyte is sufficient evidence for the presence of an IgG autoantibody; simultaneous detection of complement indicates that the antibody can fix complement as well. The ability of an erythrocyte autoantibody to fix complement plays a critical role in the pathophysiology of immune clearance and the clinical manifestations of hemolysis, as complement augments the destructive effects of the autoantibody.

The presence of complement alone (with no IgG detected) suggests a cold-reactive autoantibody that fixes complement at lower temperatures but binds poorly to erythrocytes at warmer temperatures. When this occurs, the child's serum should be tested for cold-reactive IgG Donath-Landsteiner autoantibodies characteristic of paroxysmal cold hemoglobinuria [22]. These cold-reactive IgG autoantibodies have optimal binding at 4ºC, and often the DAT is negative or demonstrates only the presence of complement. To detect cold-reacting antibodies, special testing must be performed that includes maintaining the temperature of the blood at 37ºC during its collection and transport to the laboratory, before separation of serum for specific testing.

IgM autoantibodies typically have optimal binding to erythrocytes at 0 to 4ºC; hence, these are called cold-reactive

antibodies or cold agglutinins. Cold-reactive IgM autoantibodies in the serum are characteristic of cold agglutinin disease, and they often follow a defined infection with agents such as Mycoplasma pneumoniae [23]. The IgM autoantibody binds optimally in cooler temperatures, but complement activation proceeds optimally at warmer temperatures.

Antigenic reactivity — A "nonspecific" or "panreactive" pattern of reactivity is sometimes reported, which suggests that the autoantibody is binding to a common or universal RBC surface antigen, such as the Rh locus. In such cases, the patient's antibody will react with all red cells with the exception of those from patients with Rh (null). Reactivity against a particular Rh antigen such as c or e is identified [24], but it is not common. Reactivity with the ABO blood group antigens [25] or other major systems such as Lewis or Kell are extremely rare [21,26]. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Characteristics of the antigens'.)

In contrast, IgM autoantibodies frequently have reactivity against polysaccharides on the red cell surface rather than surface proteins. The I/i surface structure is a prototypic polysaccharide autoantigen on the red cell surface and is the target of many IgM antibodies that develop in response to infections [23]. In addition to the important I/i surface antigens, other autoantigens, including the polysaccharide P autoantigen involved in paroxysmal cold hemoglobinuria, also have been reported in IgM-mediated AIHA [24,27,28].

Determination of the antigenic specificity of erythrocyte autoantibodies is important for two reasons. First, an autoantibody with a "panreactive" pattern will bind all cells, which renders finding fully compatible blood for transfusion difficult or impossible. Second, identification of the antigenic specificity also can help predict intravascular lysis caused by complement activation. If the antigen is within the Rh complex, complement-mediated intravascular hemolysis is unlikely. The P antigen system, in contrast, is capable of binding sufficient IgG antibody to allow Donath-Landsteiner antibodies to fix complement completely and allow intravascular lysis [29].

DIFFERENTIAL DIAGNOSIS — The child who presents with autoimmune hemolytic anemia (AIHA) usually has clinical, physical, and laboratory evidence of hemolytic anemia, which involves increased erythrocyte destruction and a compensatory reticulocytosis. The main differential diagnosis includes causes of non-immune hemolytic anemia, such as intrinsic red cell membrane or enzyme defects, as well as extrinsic causes of hemolysis. (See "Overview of hemolytic anemias in children" and "Extrinsic nonautoimmune hemolytic anemia due to drugs and toxins" and "Extrinsic nonimmune hemolytic anemia due to mechanical damage: Fragmentation hemolysis and hypersplenism".) The presence or absence of the findings listed below may be of some help in devising an appropriate differential diagnosis.

Spherocytes and other red cell alterations — Hereditary spherocytosis (HS) can be easily confused with AIHA because of the presence of spherocytes and reticulocytosis in both disorders (picture 1). A positive family history may be obtained in the former and usually is negative in the latter. In addition, the direct antiglobulin test (formerly called the Coombs test) is positive in AIHA and negative in HS.

Patients with microangiopathic hemolytic anemia, such as occurs in hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, may have spherocytes, but more typically they have red cell fragments (schistocytes) in the circulation, along with severe thrombocytopenia, and varying degrees of renal insufficiency and neurologic changes (picture 9). (See "Clinical manifestations and diagnosis of Shiga toxin-producing Escherichia coli (STEC) hemolytic uremic syndrome (HUS) in children" and "Diagnosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults".)

Anemia — Anemia can result from increased erythrocyte destruction (hemolysis), but it can also be the result of decreased erythrocyte production, such as congenital bone marrow failure syndromes, acquired aplastic anemia, or transient red cell aplasia. In contrast to the hemolytic anemias, these disorders typically have a low reticulocyte count. (See "Approach to the child with anemia".) Other important causes of anemia which should be considered in the anemic child include chronic severe iron deficiency, lead poisoning, and alpha or beta-thalassemia trait. (See "Childhood lead poisoning: Clinical manifestations and diagnosis".) Finally, chronic blood loss, usually gastrointestinal, leading to symptomatic anemia is detectable by stool guaiac testing.

Dark urine — Dark urine caused by the presence of hemoglobin in the urine (hemoglobinuria) can be confused with concentrated urine or the presence of bilirubin or porphyrin precursors in the urine. Urinalysis can distinguish these conditions from true hemoglobinuria, which causes a positive dipstick test for blood and protein without the presence of red blood cells on microscopic analysis. Hemoglobinuria is uncommon and indicates intravascular hemolysis from pathological states including AIHA, glucose 6-phosphate dehydrogenase (G6PD) deficiency, or rarely paroxysmal nocturnal hemoglobinuria (PNH). Myoglobinuria from rapid and extensive muscle breakdown can mimic hemoglobinuria on urinalysis, but the two pigments can be distinguished chemically. (See "Urinalysis in the diagnosis of kidney disease", section on 'Red to brown urine'.) Hemolytic anemia can occur in several of the porphyrias; specialized testing is required in order to make this diagnosis. (See "Porphyrias: An overview".)

Jaundice — The child who presents with jaundice must be evaluated for the presence of underlying liver disease. Measurement of transaminases and coagulation factors can be useful in assessing hepatic function. Serologic testing for hepatitis viruses, cytomegalovirus, and Epstein-Barr virus may be prudent if liver disease is suspected. In hemolytic anemia, the indirect (unconjugated) bilirubin fraction is typically elevated. In contrast, an elevated direct (conjugated) bilirubin level suggests intrinsic liver disease. (See "Classification and causes of jaundice or asymptomatic hyperbilirubinemia" and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia".)

SECONDARY AUTOIMMUNE HEMOLYTIC ANEMIA — Autoimmune hemolytic anemia (AIHA) occurring in association with another systemic illness is referred to as secondary AIHA (table 1). Children with secondary AIHA often have a broad dysregulation of their immune system. Particularly in older children, a substantial number of cases of warm-reactive AIHA actually are secondary AIHA [21]. This observation demonstrates the need to consider the possibility of an underlying systemic illness in all children with AIHA.

Autoimmune disease — Perhaps the most common form of secondary AIHA in older children occurs in association with a broad autoimmune disease such as systemic lupus erythematosus [30]. Other systemic autoimmune or inflammatory disorders (eg, Sjögren syndrome, scleroderma, rheumatoid arthritis, dermatomyositis, ulcerative colitis, autoimmune thyroiditis) also have been associated with AIHA [21,31]. Children with these disorders probably have a genetic susceptibility with immune dysregulation, which leads to the expansion and proliferation of autoreactive B lymphocytes. Often there is a family history of autoimmune disorders (not necessarily immune-mediated hematologic conditions) such as lupus, thyroid disease, or rheumatoid arthritis. (See "Systemic lupus erythematosus (SLE) in children: Treatment, complications, and prognosis", section on 'Hematologic abnormalities' and "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis", section on 'Autoimmunity'.)

Children with congenital immunodeficiency also can develop secondary AIHA, almost certainly caused by altered immune regulation [32]. AIHA can present in children as the initial manifestation of an unsuspected congenital immunodeficiency disorder, particularly common variable immune deficiency (CVID). Children with acquired immunodeficiency, including those infected with the human immunodeficiency virus, can develop erythrocyte autoantibodies and secondary AIHA caused by polyclonal B lymphocyte activation and poor immune regulation by T lymphocytes.

Evans syndrome — A special association exists between AIHA and other autoimmune cytopenias, especially thrombocytopenia. When a child has concurrent AIHA and thrombocytopenia (ITP), the disorder usually is referred to as Evans syndrome. Some children with Evans syndrome also have autoimmune neutropenia. In two large reviews, the clinical course of Evans syndrome was found to be chronic and relapsing; treatment (eg, steroids, intravenous immunoglobulin, cyclosporine, chemotherapy) has been similar to, although less satisfactory than, the treatment of patients with isolated AIHA or ITP [33,34]. (See 'Treatment' below and "Immune thrombocytopenia (ITP) in adults: Initial treatment and prognosis" and "Treatment of autoimmune hemolytic anemia: Warm agglutinins", section on 'Summary and recommendations'.)

Because many patients with Evans Syndrome have underlying immune dysregulation, it is appropriate to consider Evans syndrome in young patients with AIHA. A variety of immunoregulatory abnormalities in Evans syndrome have

been proposed [35], but no specific underlying immune defect has been identified. Autoantibodies apparently are directed against specific antigens on each of the various blood cell types, without cross-reactivity [36]. If Evans syndrome is suspected, it is important to rule out the presence of autoimmune lymphoproliferative syndrome (ALPS). In one study, as an example, 7 of 12 children with Evans syndrome had abnormal tests of T cell function suggestive of ALPS [37]. Evans syndrome is also associated with common variable immunodeficiency. (See "Autoimmune lymphoproliferative syndrome (ALPS): Clinical features and diagnosis" and "Common variable immunodeficiency in children", section on 'Autoimmune disease'.)

Malignancy — Secondary AIHA can occur in the setting of malignancy, occasionally presenting before the underlying diagnosis has been made. Adults with chronic lymphocytic leukemia, lymphoma, or multiple myeloma may have erythrocyte autoantibodies in association with their abnormal B lymphocyte clone [38,39]. AIHA also can occur in children with Hodgkin lymphoma, acute leukemia, myelodysplasia, or following allogeneic hematopoietic cell transplantation [40-42]. The pathogenesis of the erythrocyte autoantibodies in association with cancer is unknown, but an underlying immune deficiency may lead to both autoimmune phenomena and malignancy. Particularly for children with AIHA secondary to an underlying immune deficiency such as CVID or ALPS, malignancy can present during or even after the hemolytic anemia. (See "Hematologic consequences of malignancy: Anemia and bleeding".)

Infection — Infection is another important cause of AIHA. Most children who present with PCH have had a recent viral-like illness [5,43], but the specific pathogen usually is not identified. In the past, PCH most commonly developed in patients with syphilis; this cause is rarely observed today. Occasionally a specific infectious agent, including Mycoplasma pneumoniae [44], Epstein-Barr virus [45,46], measles, varicella, mumps, and rubella, triggers AIHA. Most of these infections are associated with IgM autoantibodies with a specificity for the I/i polysaccharide antigen system on red cells [23], although reactivity with the P polysaccharide antigen has been reported [47,48]. Reactivity of anti-I red cell antibodies with mycoplasma antigens suggests that the erythrocyte autoantibodies may result from immunologic cross-reactivity. Most cold agglutinins associated with varicella infection have anti-Pr activity [49].

Acute bacterial infections also can cause hemolytic anemia, but from a different mechanism. The T antigen on the erythrocyte surface is considered a "cryptic" antigen and normally is not available for binding. Infection with bacteria harboring neuraminidase (sialidase) activity, such as Clostridial or Pneumococcal species, leads to sialic acid removal and subsequent exposure of the T antigen. Many persons have naturally occurring cold-reactive IgM antibodies with anti-T specificity, allowing hemolysis to result in this setting [50]. Concomitant G6PD-deficiency can exacerbate hemolytic anemia during infections.

Transplantation — AIHA can develop in the setting of allogeneic hematopoietic cell transplantation, typically in the first two to six months post-engraftment. Most of these cases respond to treatment, but some can become resistant to treatment and end fatally [51,52]. Similarly, the dramatic expansion of pediatric solid organ transplantation has led to an increased number of AIHA cases, sometimes in conjunction with immune thrombocytopenia. In this setting, it remains unclear whether the etiology reflects the activity of donor lymphocytes (eg, from transplants involving liver or small bowel with spleen) or the strong immunosuppression used to prevent organ rejection [53,54].

Drugs — Although not common in children, erythrocyte autoantibodies and hemolysis in association with drug exposure may cause secondary AIHA. This process was described classically after therapy with methyldopa, but red cell autoantibodies have been reported in association with many different pharmaceutical agents [55]. Medications that are particularly important in causing AIHA in children include penicillins, cephalosporins, tetracycline, erythromycin, probenecid, acetaminophen, and ibuprofen. In a 2014 review of this subject, piperacillin was identified as the most frequent etiologic agent [56].

The mechanism of drug-induced hemolytic anemia typically results from generation of autoantibodies, although the drug may be required to form a hapten or even a ternary complex with the erythrocyte [57]. (See "Pathogenesis of autoimmune hemolytic anemia: Warm agglutinins and drugs", section on 'Drug-related immune hemolysis'.)

TREATMENT — Optimal treatment of a child with autoimmune hemolytic anemia (AIHA) depends initially upon the severity of the anemia, the signs and symptoms, and the characteristics of the autoantibodies. In the setting of severe intravascular hemolysis, for example, maintaining a good renal blood flow and urine output is imperative. The characteristics of the antibodies are paramount; for example, children with cold-reactive autoantibodies should avoid cold stimuli to prevent autoantibody binding, whereas those with warm-reactive autoantibodies usually respond best to glucocorticoids. The following table includes treatment modalities that are useful in children with primary AIHA, emphasizing the differences among the three major clinical conditions: warm-reactive AIHA, paroxysmal cold hemoglobinuria, and cold agglutinin disease (table 2).

Transfusion — In most cases of AIHA, transfusions can be avoided and specific therapy can be instituted, depending upon the particular type.

However, if the anemia is causing cardiovascular compromise (usually when the hemoglobin concentration is below 5 g/dL), strong consideration must be given to transfusing the patient with erythrocytes to provide the needed oxygen-carrying capacity. Administering a transfusion to a child with erythrocyte autoantibodies may seem complicated and intimidating, but it also may be life-saving. Although transfusions can lead to additional hemolysis, it must be emphasized that, despite the risks, transfusion therapy should not be withheld from a patient with AIHA and life-threatening anemia.

Identification of compatible erythrocytes to transfuse into a child with AIHA can be problematic. The Transfusion Service or Blood Bank may need extra serum and cells for testing, well in advance of the possible erythrocyte transfusion. If the autoantibody is reactive with all donor units (ie, the antibody is "pan-reactive"), no units of blood will be deemed "fully compatible" based on the crossmatch, although certain units may be designated "least incompatible" with the patient's serum. Available adsorption techniques to remove autoantibodies may allow the identification of clinically important alloantibodies that also may be present [58]. (See "The incompatible crossmatch", section on 'AIHA and concurrent alloantibodies'.)

When the actual erythrocyte transfusion is given, acute symptomatic transfusion reactions are not common, even when transfusing "least incompatible" units of blood [59]. Because transfused donor cells generally survive in patients with AIHA similar to the patient's own erythrocytes, transfusion should be helpful, even if the transfused erythrocytes last in the circulation for only a short period of time. On the rare occasion when a transfusion results in more severe hemolysis, with substantial hemoglobinemia and hemoglobinuria, vigorous hydration will help prevent renal dysfunction. (See "Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure)".)

If the autoantibodies fix complement and cause intravascular hemolysis, a prudent procedure is to begin the transfusion at a slow rate, checking both plasma and urine samples periodically for the presence of free hemoglobin. Warming the blood during infusion is useful for patients with cold-reactive autoantibodies. (See "The incompatible crossmatch", section on 'Immediate management'.)

Glucocorticoids — Glucocorticoids remain the best primary therapy for warm-reactive AIHA, particularly for children with IgG antibodies, as they interfere with the basic pathophysiology and immune destruction of erythrocytes. Glucocorticoids inhibit the Fc receptor-mediated clearance of sensitized erythrocytes [60], which likely accounts for their rapid effect within 24 to 48 hours. They may also diminish the production of autoantibodies, but this effect may require several weeks.

For the very anemic child with warm-reactive AIHA, intravenous methylprednisolone should be administered every six hours at a dose of 1 to 2 mg/kg for the first 24 to 72 hours. Oral prednisone at a total dose of 1 to 2 mg/kg per day is then used after the child is more clinically stable. Typically, high doses are used for two to four weeks, followed by a slow taper over two to six months, based upon the hemoglobin concentration, reticulocyte count, and direct antiglobulin test results. Using this approach has resulted in an overall response rate of approximately 80 percent [61].

In contrast, children with PCH usually have a self-limited hemolytic process, but may need a short course of

glucocorticoids to reduce hemolysis and improve anemia. Less commonly, glucocorticoids may be beneficial in cold-agglutinin disease [62].

Warming — For patients with cold-reactive antibodies, keeping the patient warm at all times is important and includes:

- Avoiding exposure to cold environments (eg, radiology suite)
- Warming the patient's room with additional space heaters, if needed
- Use of socks and warm clothing
- Using a blood warming apparatus during any intravenous infusions and especially during any transfusion of fluids which have been refrigerated, such as erythrocytes.

Intravenous immunoglobulin — Intravenous immunoglobulin (IVIG) induces a potent blockade of the reticuloendothelial system [63] and offers an attractive therapeutic option for adults with AIHA. Unfortunately, most children with AIHA do not respond to IVIG therapy, even at the very high doses (1 g/kg per day for five days) advocated in this setting [64]. At this time, IVIG should **not** be considered standard therapy for children with AIHA.

Exchange transfusion — Exchange transfusion is another attractive therapeutic option for AIHA because the autoantibodies, complement components, and coated erythrocytes all can be removed from the patient simultaneously. More commonly, however, plasmapheresis or plasma exchange is used [65], even in very small infants [66]. (See "Therapeutic apheresis (plasma exchange or cytapheresis): Indications and technology".) Patients with IgM autoantibodies respond better to plasmapheresis than do those with IgG autoantibodies because the larger IgM molecules are found mostly within the intravascular space [67,68]. In addition, at warm temperatures IgM autoantibodies are bound less tightly to red cells than are IgG autoantibodies, allowing them to be removed more easily by plasmapheresis. In contrast, IgG autoantibodies diffuse into the extravascular space, so that plasmapheresis removes only a portion of the total IgG autoantibodies.

Rituximab — The anti-CD20 monoclonal antibody rituximab (Rituxan) has been successfully used to treat some children with either primary or secondary AIHA that are refractory to or dependent on glucocorticoids [1,69-72]. This is an off-label use of rituximab, based on single-arm, non-randomized trials, but the results to date are quite encouraging. Even in children with increased risk of infection (eg, infants or patients with immunodeficiency [73]), rituximab seemed to be well-tolerated and lead to remission in 50 to 60 percent of patients. Four weekly intravenous infusions (375 mg/m^2/dose) lead to good therapeutic responses. Although hematological responses are encouraging, profound hypogammaglobulinemia and prolonged absence of circulating B cells will occur after rituximab therapy [69]. Therefore intravenous immunoglobulin (IVIG) may be useful as replacement therapy **after** rituximab use [74].

As a result of the above observations, rituximab has now become the preferred treatment of choice for children who do not respond to treatment with glucocorticoids, and is generally suggested before resorting to splenectomy. (See "Treatment of autoimmune hemolytic anemia: Warm agglutinins", section on 'Rituximab'.)

Splenectomy — Splenectomy is the time-honored therapy for the child with chronic or recalcitrant AIHA [61,75] and works by removing the main site of erythrocyte destruction (figure 1). Splenectomy also may benefit the patient with AIHA by removing a major site of autoantibody production, similar to its effects in immune thrombocytopenia (ITP).

Children with IgG autoantibodies respond better to splenectomy than do those with IgM autoantibodies, but the success of splenectomy cannot be predicted before surgery. Specifically, radiolabeled red cell survival studies are not reliable indicators of the clinical response to splenectomy [76]. (See "Red blood cell survival: Normal values and measurement", section on 'Sites of RBC destruction'.)

In a study of 52 patients with AIHA who underwent splenectomy, with absent surgical mortality and low morbidity, an excellent response was reported in 64 percent, and an improved status in another 21 percent [77]. However, splenectomy is to be avoided in young children whenever possible because of the possibility of post-splenectomy

sepsis caused by encapsulated bacterial organisms. (See "Prevention of sepsis in the asplenic patient".)

Before splenectomy is performed (whenever possible), or shortly thereafter, children should receive immunization with both the polysaccharide vaccine (Pneumovax) and a protein-conjugated polyvalent vaccine (Prevnar) to enhance their humoral immune response against Streptococcus pneumoniae. They also should receive anti-Haemophilus and meningococcal vaccines at this time. (See "Prevention of sepsis in the asplenic patient", section on 'Immunizations'.)

Post-splenectomy care — Children who undergo splenectomy should receive penicillin twice a day for at least two years after surgery; many clinicians prefer life-long post-splenectomy penicillin prophylaxis. Erythromycin can be used if the patient is allergic to penicillin. After splenectomy, children with fever higher than 38.5ºC (101.5ºF) should seek **immediate** medical attention for the possibility of bacterial sepsis. (See "Prevention of sepsis in the asplenic patient", section on 'Antibiotic prophylaxis'.)

Refractory disease — For the child with refractory AIHA, more aggressive therapy may be required to alleviate the symptoms of anemia and to help the child achieve a more normal lifestyle. The long-term use of glucocorticoids or immunoglobulin generally is unacceptable because of side effects, costs, and inconvenience. No simple algorithm can be proposed that is correct for all patients; instead, the clinician should individualize therapy for each patient, depending upon the hematologic response and side-effects. Several treatment options are available for such children, although each is less effective than either glucocorticoids or splenectomy.

Danazol — An effective immunomodulatory agent is danazol, a semisynthetic androgen that can reduce cell-bound IgG and complement [78] and decrease IgG production [79]. The primary adverse side effects of danazol are elevations in the hepatic transaminases and mild masculinizing effects; as a result, females typically do not tolerate use of this agent.

Azathioprine — Azathioprine is another immunosuppressive agent that primarily affects T lymphocyte helper function and thereby diminishes autoantibody synthesis. Clinical responses to azathioprine may require more than two to three months of therapy, with dose escalation to 150 to 200 mg/day [61].

Cyclosporine — Cyclosporin A is another immunosuppressive agent that also primarily affects T lymphocytes. Long-term use of cyclosporin has been associated with nephrotoxicity, hypertension, and a risk of second malignancy, and it should be reserved for children with refractory AIHA.

Mycophenolate mofetil, tacrolimus, and sirolimus — These immunosuppressive agents have been employed in patients with relapsed, resistant AIHA, including those following solid organ transplantation, or complicated by Evans syndrome, acquired pure red cell aplasia, and/or autoimmune lymphoproliferative syndrome (ALPS) [80-83]. As with danazol, their use may allow "steroid sparing," resulting in reduced doses of glucocorticoids required to maintain remission.

Cytotoxic agents — Cytotoxic agents that can reduce autoantibody formation include vincristine, vinblastine, and cyclophosphamide. Although few data exist on their efficacy in children with AIHA, these agents should be considered for the refractory patient [84,85]. These agents generally are myelosuppressive and potentially mutagenic, and they should be used with caution in children.

SUMMARY AND RECOMMENDATIONS

- Autoimmune hemolytic anemia (AIHA) is caused by anti-erythrocyte autoantibodies that lead to premature red cell destruction. If the rate of hemolysis exceeds the ability of the bone marrow to replace the destroyed red cells, this leads to anemia. (See 'Introduction' above.)
- In primary AIHA, there is no evidence of an underlying systemic illness. Primary AIHA can be subclassified according to the characteristics of the erythrocyte autoantibodies, particularly the temperature at which they bind to red cells (warm-reactive versus cold-reactive AIHA). There are three major categories of primary AIHA (table 2) (see 'Primary AIHA' above):

- Warm-reactive AIHA – The most common form in children involves warm-reactive autoantibodies, which lead to extravascular hemolysis mainly in the spleen, with resulting splenomegaly, jaundice, and anemia. (See 'Warm-reactive AIHA' above.)
- Paroxysmal cold hemoglobinuria (PCH) – This form of primary AIHA is characterized by cold-reactive autoantibodies that cause intravascular hemolysis with hemoglobinemia, hemoglobinuria, and anemia. It is particularly common in children after a viral-like illness.
- Cold agglutinin disease – This form is relatively rare in children, but can occur after Mycoplasma infection. It is mediated by cold-reactive IgM autoantibodies causing intravascular hemolysis or immune-mediated extravascular clearance in the liver.

- Secondary AIHA can occur in patients with systemic lupus erythematosus or other autoimmune disorders, immunodeficiency states, drug exposure, malignancy, or following certain infections (table 1). Particularly in older children, a substantial number of cases of warm-reactive AIHA actually are secondary AIHA. (See 'Classification' above.)
- Most children with AIHA present with signs and symptoms referable to anemia, including weakness, shortness of breath, dizziness, pallor, jaundice, and/or dark urine. The presence of dark urine in AIHA suggests intravascular hemolysis, and is more suggestive of cold-reactive AIHA. (See 'Clinical presentation' above.)
- The initial laboratory evaluation of a child with suspected AIHA should consist of a complete blood count, reticulocyte count, direct antiglobulin test (DAT, formerly known as the Coombs test), urinalysis for hemoglobinuria, and microscopic examination of the blood smear. In cases of AIHA, the DAT should be positive, indicating the presence of IgG autoantibodies. Elevations of unconjugated bilirubin, lactate dehydrogenase (LDH), and aspartate aminotransferase (AST) are common but not diagnostic; elevations of alanine aminotransferase (ALT) are not. (See 'Laboratory evaluation' above.)
- For patients with laboratory results consistent with hemolysis and a positive DAT (Coombs test), immunohematologic studies should be performed to categorize the type of AIHA, and include antibody isotype (IgG, IgM, or IgA), titer, and thermal reactivity (table 3). (See 'Immunohematologic studies' above.)
- The possibility of secondary AIHA should be considered particularly in patients with thrombocytopenia (Evans syndrome), marked hepatosplenomegaly, a history of recent viral infection, or use of certain drugs (eg, one of several antibiotics, or probenecid). (See 'Secondary autoimmune hemolytic anemia' above.)
- Different treatments are indicated for each of the three major types of primary AIHA (warm-reactive, paroxysmal cold hemoglobinuria, and cold agglutinin disease) (table 2). Children with cold-reactive autoantibodies should avoid cold stimuli to prevent autoantibody binding, whereas those with warm-reactive autoantibodies usually respond best to glucocorticoids. (See 'Treatment' above.)

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Topic 5934 Version 20.0

GRAPHICS

Classification of autoimmune hemolytic anemia

Primary*
Warm-reactive
Paroxysmal cold hemoglobinuria
Cold agglutinin disease
Secondary¶
Generalized autoimmune disease (eg, systemic lupus erythematosus)
Immune deficiency
Malignancy
Medication exposure
Infections

* Primary autoimmune hemolytic anemia (AIHA) refers to disorders with only immune-mediated hemolytic anemia and no evidence of an underlying systemic disorder.
¶ Secondary AIHA refers to disorders with immune-mediated hemolytic anemia in the presence of another condition.

Courtesy of Russell E Ware, MD, PhD.

Graphic 57399 Version 5.0

Laboratory characteristics, pathophysiology, and therapy for primary autoimmune hemolytic anemia observed in children

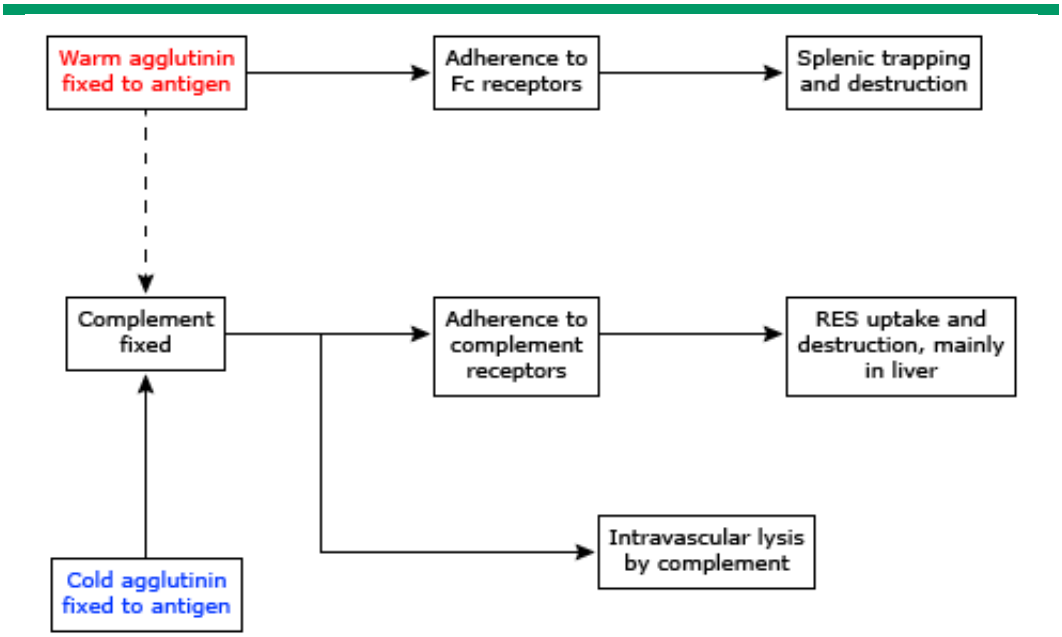
Parameter	Warm-reactive AIHA	Paroxysmal cold hemoglobinuria	Cold agglutinin disease
Autoantibody isotype	IgG	IgG	IgM
Optimal thermal reactivity	Warm	Cold	Cold
Ability to fix complement	Variable	Yes	Yes
Positive DAT (Coombs test)	IgG, ± C3	C3, ± IgG	C3
Erythrocyte autoantigen	Rh, others	P	I or i
Type of hemolysis*	Extravascular	Intravascular	Both
First-line therapy	Glucocorticoids	Avoidance of cold	Avoidance of cold
Secondary therapy	Splenectomy, Rituximab•	Glucocorticoids	Rituximab•

AIHA: autoimmune hemolytic anemia; IgG: immunoglobulin G; IgM: immunoglobulin M; DAT: direct antiglobulin test (Coombs test); C3: complement.
* Extravascular or intravascular hemolysis.
• This is an off-label use of rituximab.

Courtesy of Russell E Ware, MD, PhD.

Graphic 55710 Version 5.0

Immune-mediated clearance of erythrocytes in autoimmune hemolytic anemia (AIHA)



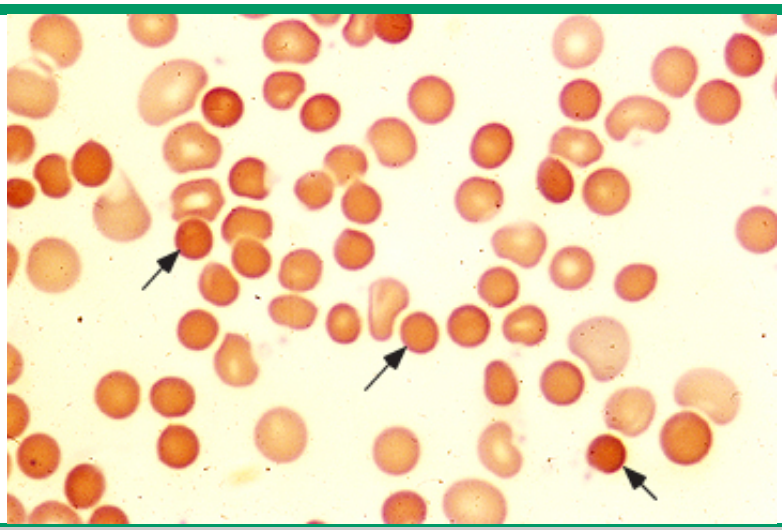
In warm-reactive AIHA, immunoglobulin G (IgG) autoantibodies are bound to erythrocytes, but typically do not fix complement efficiently. IgG-coated cells enter the spleen and other parts of the reticuloendothelial system (RES), where they interact with Fc receptors on macrophages. Erythrocytes may be completely engulfed and destroyed by this interaction or may have only a portion of their membrane removed. In the latter case, the red cells will reshape into spherocytes, which are then destroyed on their next pasage through the spleen. In cold-reactive disease, complement is typically fixed very efficiently and intravascular lysis by the complement cascade can occur. Alternatively, the presence of surface-bound complement (C3) can lead to extravascular red cell destruction by the spleen and other portions of the RES, such as the liver.

RES: reticuloendothelial system.

Adapted from: Ware RE. Autoimmune Hemolytic Anemia. In: Nathan and Oski's Hematology of Infancy and Childhood, 5th Ed, Nathan DG, Orkin SH (Eds), WB Saunders Company, Philadelphia 1998.

Graphic 64888 Version 4.0

Spherocytes

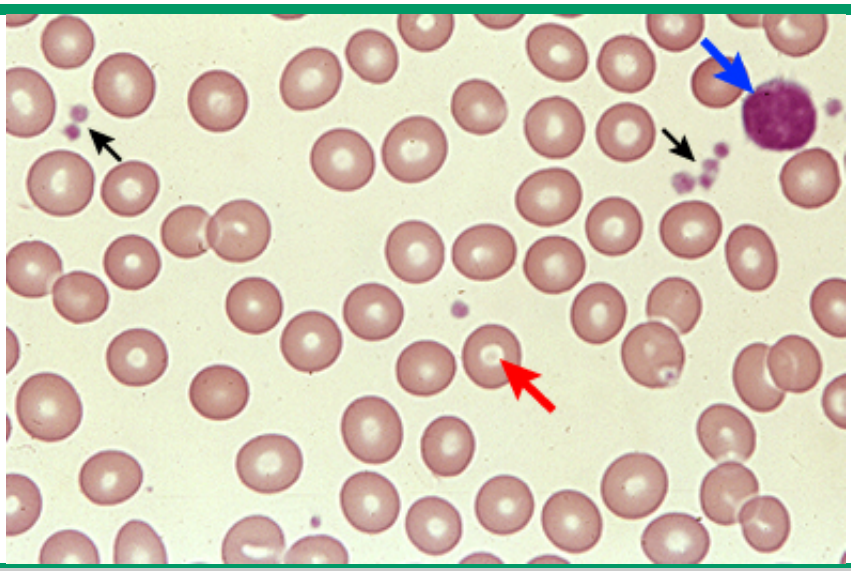


Peripheral blood smear shows multiple spherocytes which are small, dark, dense hyperchromic red cells without central pallor (arrows). These findings are compatible with hereditary spherocytosis or autoimmune hemolytic anemia.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70611 Version 1.0

Normal peripheral blood smear

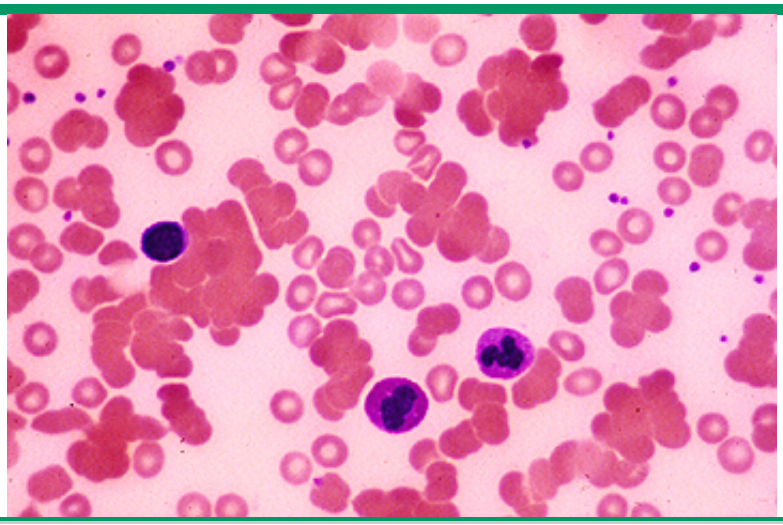


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Red blood cell agglutination due to a cold agglutinin

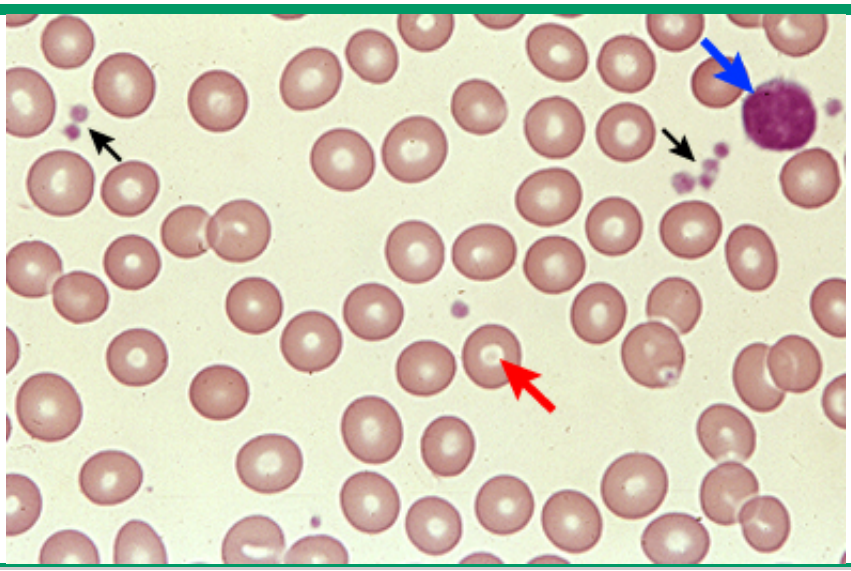


Peripheral blood smear from a patient with cold agglutinin hemolytic anemia shows marked red blood cell agglutination into irregular clumps.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50522 Version 3.0

Normal peripheral blood smear

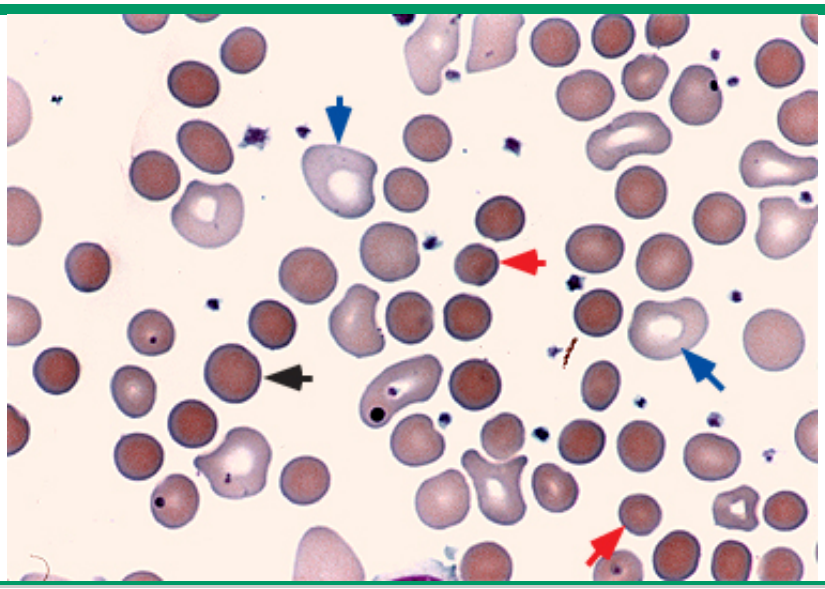


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Peripheral blood smear in autoimmune hemolytic anemia (AIHA)

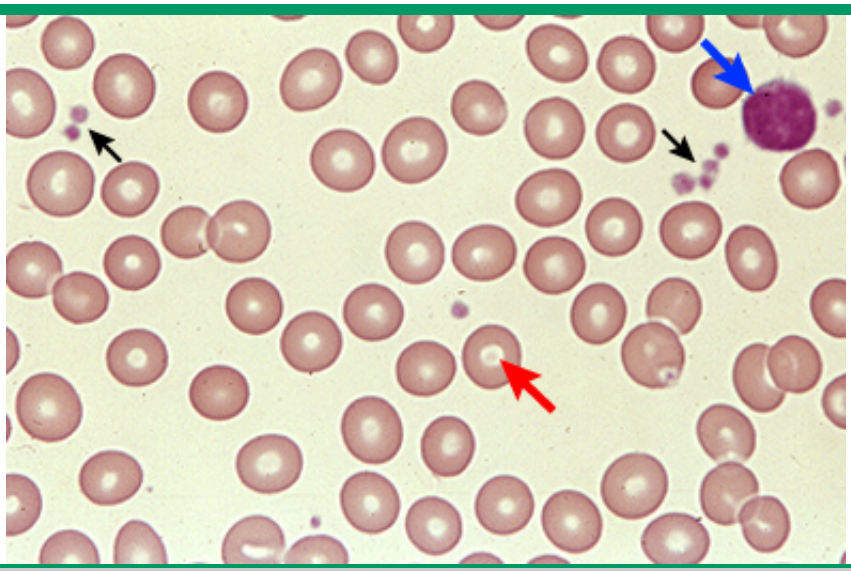


This peripheral blood smear from a patient with autoimmune hemolytic anemia (AIHA) due to a warm-reactive IgG antibody demonstrates the presence of many dark red small microspherocytes (red arrows) and larger spherocytes (black arrow) (x1000). Many large irregular blue-tinted red cells are also present,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

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

Graphic 53523 Version 3.0

Normal peripheral blood smear



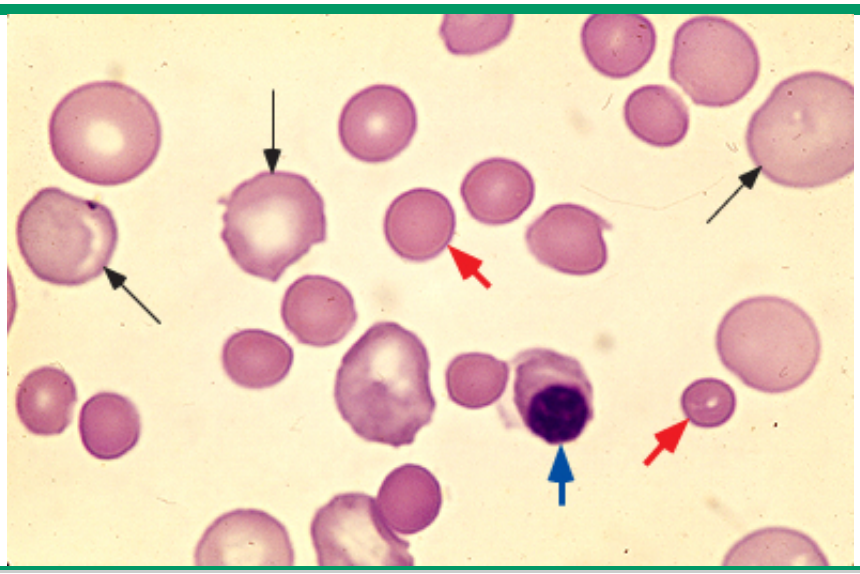
High power view of a normal peripheral blood smear. Several

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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Peripheral smear in severe autoimmune hemolytic anemia

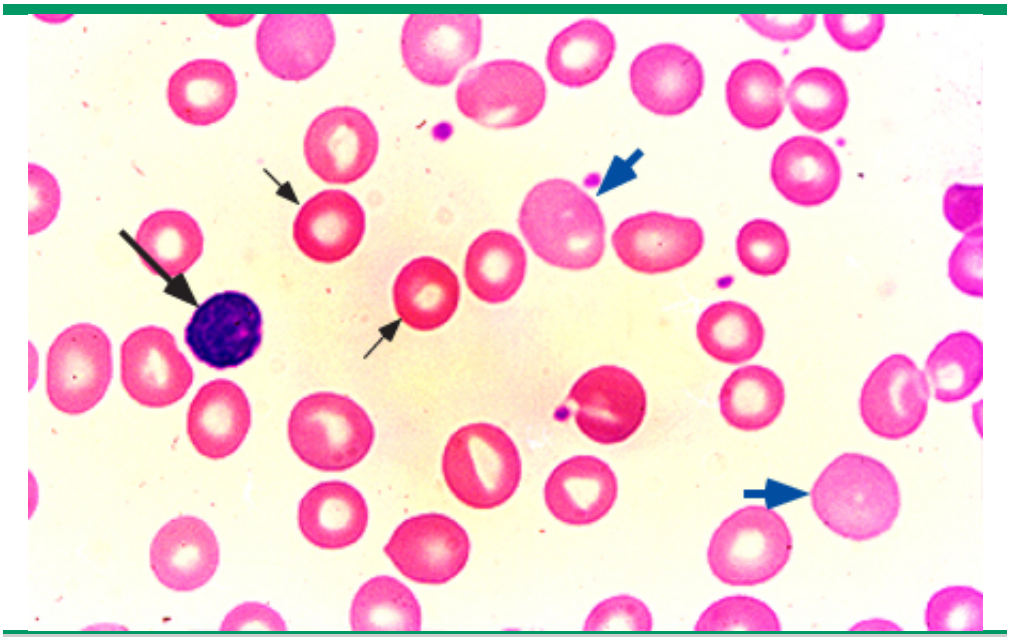


Peripheral blood smear from a patient with Coombs positive autoimmune hemolytic anemia. The smear shows the presence of many spherocytes (red arrows), one nucleated red blood cell (blue arrow), and a number of larger polychromatophilic red cells (black arrows), representing a reticulocytosis in response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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50601 Version 2.0

Polychromatophilia due to increased reticulocytes

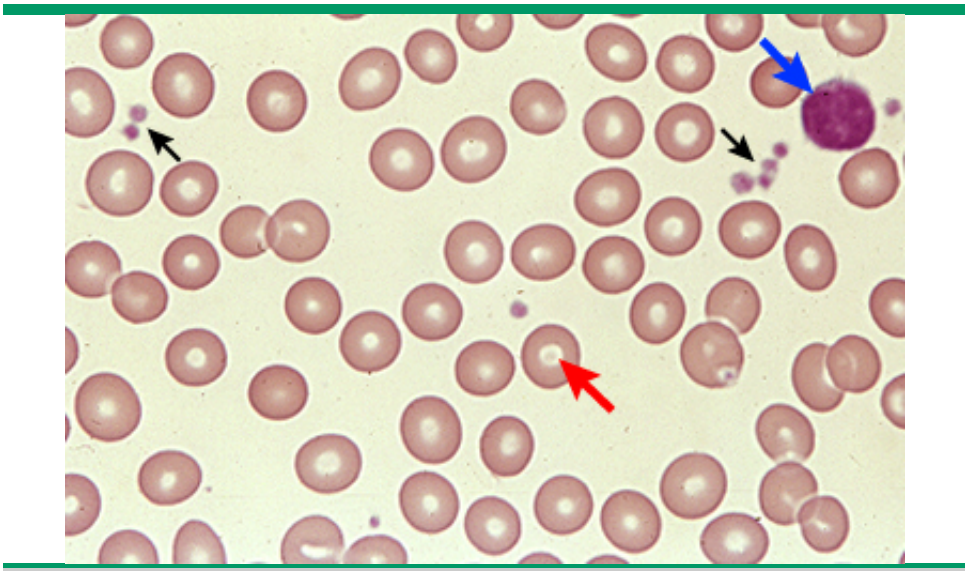


Peripheral blood smear taken from a patient with increased reticulocytes. Unlike mature red cells (thin black arrows), which have central pallor and are the same size as the nucleus of a small lymphocyte (thick arrow), reticulocytes (blue arrows) are larger, have a blue tint, and lack central pallor because they are not biconcave discs. (Wright-Giemsa stain).

Courtesy of Stanley Schrier, MD.

Graphic 67042 Version 2.0

Normal peripheral blood smear



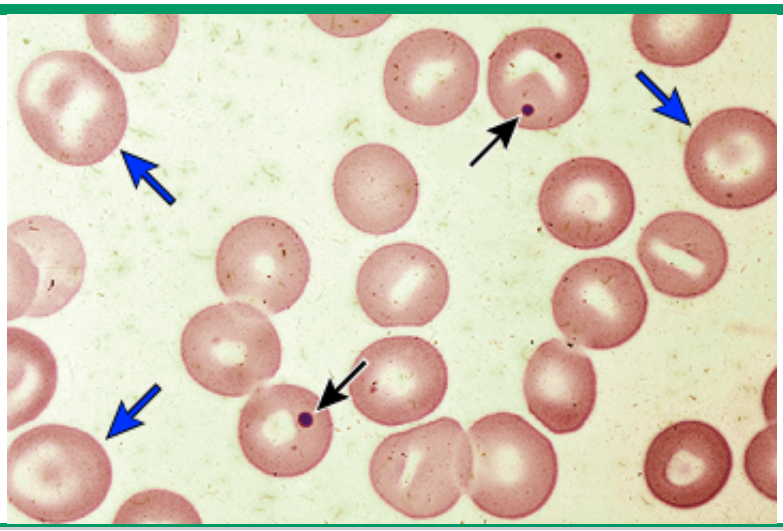
High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the

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

Howell-Jolly bodies following splenectomy

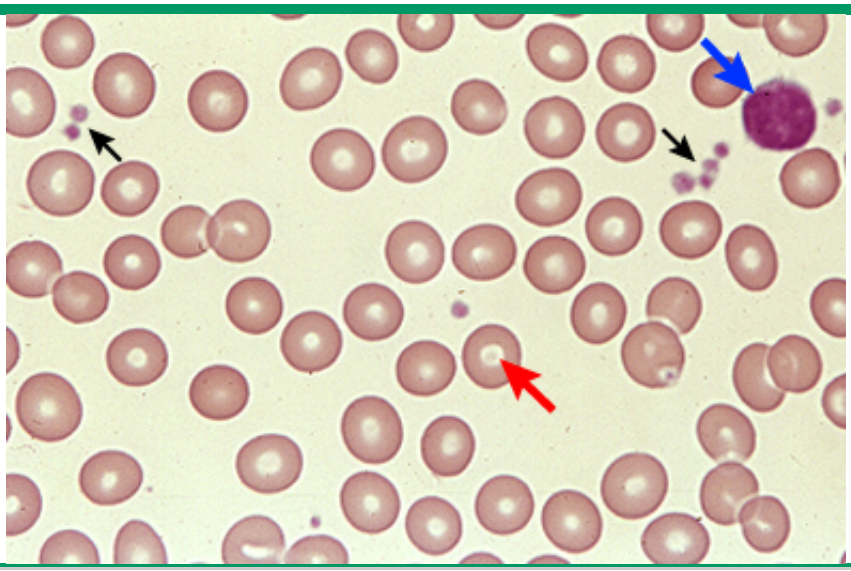


This peripheral blood smear shows two red blood cells (RBC) that contain Howell-Jolly bodies (black arrows). Howell-Jolly bodies are remnants of RBC nuclei that are normally removed by the spleen. Thus, they are seen in patients who have undergone splenectomy (as in this case) or who have functional asplenia (eg, from sickle cell disease). Target cells (blue arrows) are another consequence of splenectomy.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 60588 Version 5.0

Normal peripheral blood smear

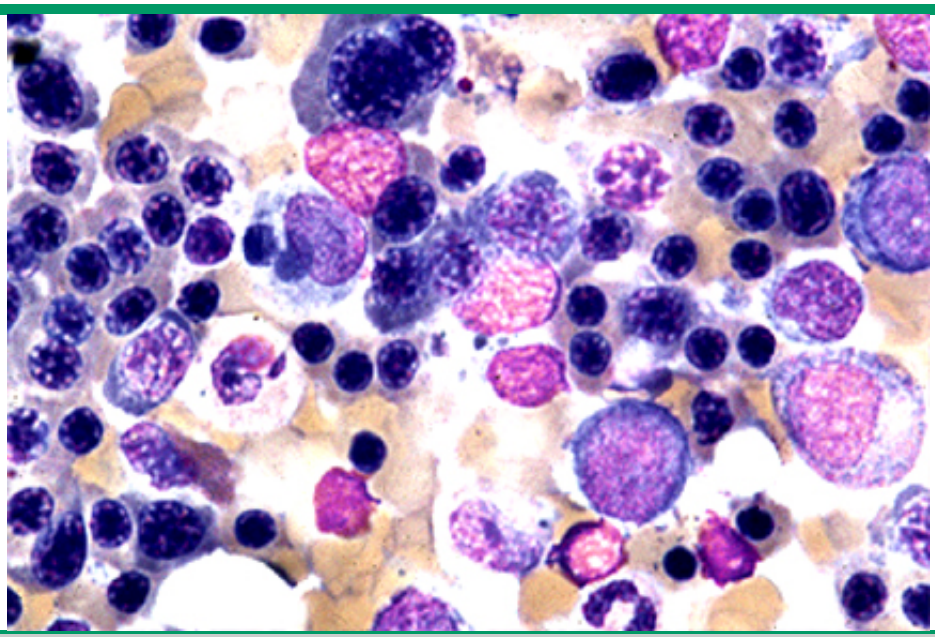


High power view of a normal peripheral blood smear. Several platelets (black arrows) and a normal lymphocyte (blue arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central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

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 2.0

Erythroid hyperplasia

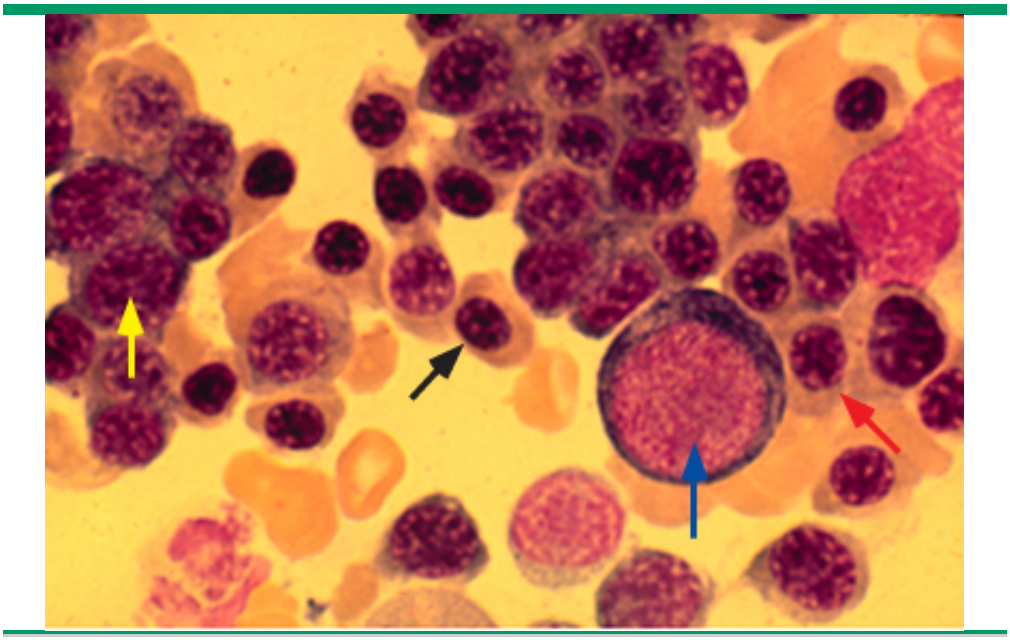


Bone marrow aspirate from a patient with chronic hemolytic anemia showing markedly increased numbers of red cell precursors (erythroid hyperplasia). The majority of the cells in this field are basophilic or polychromatophilic normoblasts, with varying degrees of darkly staining nuclear chromatin. (Wright-Giemsa stain).

Courtesy of David S Rosenthal, MD.

Graphic 75057 Version 1.0

Erythroid precursors in the bone marrow



Normal bone marrow shows an erythropoietic island with a large proerythroblast (blue arrow) surrounded by basophilic (yellow arrow), polychromatophilic (red arrow), and orthochromic (black arrow) normoblasts.

Courtesy of Stanley L Schrier, MD.

Graphic 68933 Version 2.0

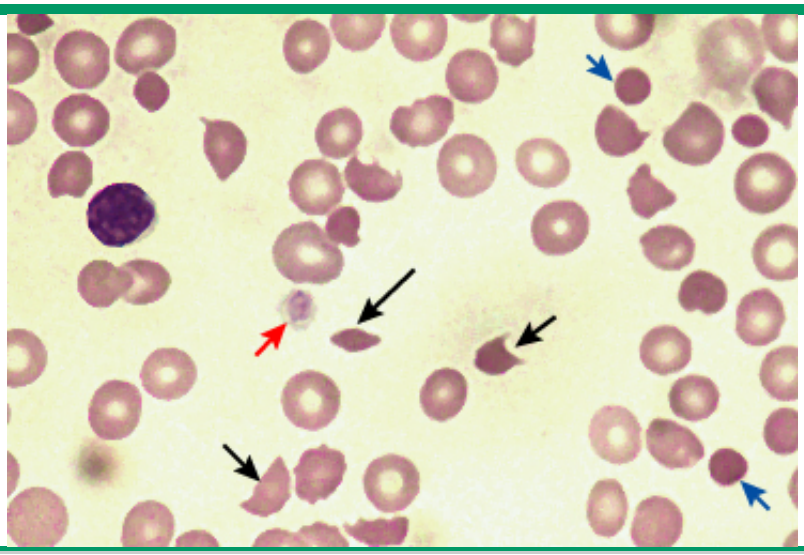
Factors affecting the rate and location of erythrocyte destruction in childhood autoimmune hemolytic anemia

Characteristics of the autoantibody
Antibody isotype (eg, IgG, IgM, IgA)
Antibody titer (high vs. low)
Thermal reactivity (optimal binding temperature)
Ability to fix complement
Characteristics of the erythrocyte antigen
Specificity of the antigen
Surface density of the antigen
Characteristics of the reticuloendothelial (RE) clearance
Avidity of the Fc and complement receptors
Preferential location of clearance (hepatic vs. splenic)

Courtesy of Russell E Ware, MD, PhD.

Graphic 63603 Version 1.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

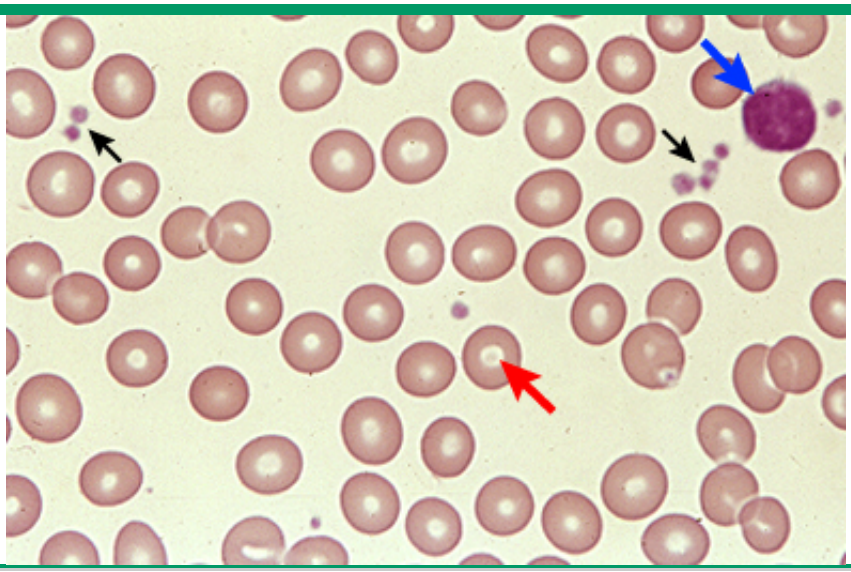


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (small black arrows), other fragmented red cells (large black arrow); microspherocytes are also seen (blue arrows). The platelet number is reduced; the large platelet in the center (red arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 5.0

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

Disclosures

Disclosures: **Russell E Ware, MD, PhD** Nothing to disclose. **Donald H Mahoney, Jr, MD** Nothing to disclose. **Stephen A Landaw, MD, PhD** Employment (Spouse): Mass Medical Society (New England Journal of Medicine).

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