Hemolytic Anemia: Part 1
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Hemolytic Anemia: Part 1*
Kwesi Sackey, MD†

OBJECTIVES
After completing this article, readers should be able to:
1. Explain the role of immune reactions, red blood cell membrane defects, red blood cell enzyme defects, or hemoglobin abnormalities in the development of hemolytic anemia.
2. List the characteristic findings of hemolytic anemia.
3. Describe the significance of a low reticulocyte count in a patient who has chronic hemolysis.
4. Describe the potential complications of red blood cell transfusions.

Introduction
Hemolytic anemia arises from a shortened survival of red blood cells (RBCs) due to an inherent abnormality of the cell, environmental factors, or both. It can be characterized by varying degrees of anemia, jaundice, an enlarged spleen, or combinations of these conditions. If the hemolysis is massive, the urine may become dark due to hemoglobinuria. Findings on examination of the peripheral blood typically include changes in the morphology of the RBCs and an increase in reticulocyte count. A low reticulocyte count usually indicates poor production of RBCs.

The major categories of hemolytic anemia are: 1) immune-mediated (alloimmune or autoimmune), 2) membrane defects (spherocytosis, elliptocytosis), 3) enzyme defects (glucose-6-phosphate dehydrogenase [G6PD] deficiency, pyruvate kinase deficiency), and 4) hemoglobin defects (sickle cell disease, thalassemia).

Alloimmune Hemolytic Anemia

DEFINITION AND EPIDEMIOLOGY
This hemolysis arises from a reaction between an individual’s RBCs and “naturally occurring antibodies” that usually are not present in that individual. The primary alloimmune types are Rh (anti-D) hemolytic disease in the newborn and ABO hemolytic disease. ABO hemolytic disease is several times more common than Rh hemolytic disease.

PATHOGENESIS AND PATHOPHYSIOLOGY
In Rh disease, the mother does not have the Rh antigen on her RBCs (ie, Rh-negative) and, therefore, develops antibodies to the Rh antigen in response to Rh-positive RBCs that leak into her circulatory system during late pregnancy or delivery. The antibodies (immunoglobulin G [IgG]) leak back from the mother into the fetal circulation during subsequent pregnancies, leading to hemolysis only in subsequent Rh-positive fetuses and newborns.

In ABO hemolytic disease, the mother has blood group O, but the fetus has either blood group A or B. During the pregnancy, the mother’s naturally occurring anti-A or anti-B antibodies (IgG), which have developed in response to exposure to commensal bacteria, particularly in the gut, or pollens, may leak across the placenta, causing hemolysis in the fetus or neonate. In ABO incompatible pregnancy, the disease may occur with even the first baby.

CLINICAL FEATURES
Hemolysis and anemia may be so severe in Rh hemolytic disease that it causes intrauterine death (hydrops fetalis) or severe anemia, jaundice, and hepatosplenomegaly soon after birth. The complete blood count (CBC) shows anemia with nucleated RBCs, reticulocytosis, and an absence of spherocytes. Results of the direct antiglobulin test (DAT or Direct Coombs Test) are strongly positive. ABO hemolytic disease is less severe and is characterized by anemia with reticulocytosis, microcytosis, and spherocytosis. Results of the DAT may be weakly positive, but those of the indirect antiglobulin test (IAT or Indirect Coombs Test) are positive.

TREATMENT
The severity of the jaundice determines the need for phototherapy (mild jaundice) or exchange transfusion (severe jaundice). Anemia may persist for up to 8 weeks. Packed RBC transfusion may be needed, depending on the degree of anemia.

Autoimmune Hemolytic Anemia (AIHA)

DEFINITION AND EPIDEMIOLOGY
AIHA is characterized by the production of antibodies against an individual’s own erythrocyte membrane antigens, which leads to hemolysis. The exact incidence is not known, but it is estimated to be less than 0.2 per 100,000 children younger than 20 years of age. The peak incidence occurs in the preschool age group.

PATHOGENESIS AND PATHOPHYSIOLOGY
The hemolysis in AIHA is largely extravascular, usually involves IgG, and occurs primarily in the liver and spleen. The IgG antibody is a warm antibody that is directed, in most cases, against one of the Rh antigens. Classically, the IgG-coated erythrocytes attach to macrophages primarily in the spleen, binding to the macrophage receptors for the Fc fragment (Fc gamma) of IgG. The macrophages then initiate the process of spherening and clearing the IgG-coated RBCs. As the numbers of IgG-RBC complexes grow, the major site of RBC sequestration and...
macrophage binding shifts from the spleen to the liver, due possibly to activation of more complement.

In IgM-mediated AIHA, the primary clearance site for antibody-coated RBCs is the liver (80%); the spleen accounts for less than 20% of the clearance. IgM antibodies are generally cold agglutinins and only rarely warm-reacting antibodies. The antibodies typically are directed at the I (eg, in Mycoplasma pneumonia) or the i (eg, in infectious mononucleosis) system of the RBC. IgM-mediated AIHA depends entirely on complement. Steroids affect AIHA by: 1) possibly inhibiting production of antibodies, 2) inhibiting attachment of antibodies and complement to macrophages, or 3) eluting antibodies from RBCs. They are more effective, in decreasing order, in IgG-, IgG+IgC3-, and IgM+IgC3-mediated AIHA. Occasionally, intravascular hemolysis occurs in AIHA; it usually is associated with cold agglutinins.

Splenectomy primarily affects IgG- and IgG+C3-mediated hemolysis, not IgM+C3-mediated hemolysis.

CLINICAL FEATURES

Patients who have AIHA usually present with pallor, jaundice, lethargy, abdominal pain, or low-grade fever. If hemolysis is severe, the urine may be dark. Among the signs are those associated with hyperdynamic circulation, including an enlarged spleen and liver. Laboratory studies reveal normocytic nonmegaloblastic anemia with reticulocytosis or rarely reticulocytopenia. Peripheral smear may show spherocytes, schistocytes, poikilocytes, anisocytes, polychromasia, and nucleated RBCs. Rouleaux formation may be seen on the smear in cold agglutinin disease. Usually the white blood cells (WBCs) and platelets are normal, except in immunopancytopenia (Evans syndrome). Results of the DAT are positive. If the RBC has IgG on its surface, the gamma DAT test result is positive, and if C3 is attached to the RBC, the nongamma DAT test result is positive. In IgM-induced AIHA, only results of the nongamma DAT test are positive. When standard antiglobulin tests for IgG, IgM, and complement are all negative, IgA-induced hemolysis, a rare type of AIHA, should be considered.

PROGNOSIS WITHOUT THERAPY

Anemia of acute onset is more likely to be self-limited and resolve within 6 months; anemia of slow onset is more likely to follow a chronic course. Acute-onset anemia accounts for 70% to 80% of cases. A chronic cause is more likely in the very young (younger than 2 years at onset) and in adolescents (older than 12 years at onset). Occasionally, chronic cases remit spontaneously after several months or years.

THERAPY

Most patients who have AIHA exhibit mild anemia of limited duration and, therefore, do not need therapy. Because most chronic cases are mild, minimal or no intervention is necessary. If treatment is necessary, several modalities are known to be effective.

Most patients who have autoimmune hemolytic anemia exhibit mild anemia of limited duration and, therefore, do not need therapy.

Transfusion

This treatment approach is needed only in life-threatening situations or as a stopgap measure while waiting for other modalities to begin working. The “least incompatible” blood may be the best choice because of cross-matching difficulties. In cold-agglutinin disease, the blood should be infused at body temperature. Exchange transfusion and plasmapheresis are more effective, albeit only temporarily, in cold-agglutinin disease.

Steroids

About 80% of patients who have IgG-induced hemolytic anemia respond to steroids (1 to 2 mg/kg per day). In resistant cases, higher doses of up to 10 mg/kg per day initially may be administered briefly, followed by a rapid decrease to lower maintenance doses (0.5 to 1.0 mg/kg per day or per alternate day). IgM-mediated AIHA usually is unresponsive to steroids.

Intravenous Immune Globulin (IVIG)

IVIG is effective in doses of 1 to 2 g/kg administered over 1 to 2 days. It also may be used in combined cytopenias such as Evans syndrome. The mechanism of action of this therapy is competitive inhibition of uptake of immunoglobulin-coated erythrocytes by Fc receptors and sometimes even by C3b receptors. Impaired attachment of complement to sensitized erythrocytes also has been reported.

Splenectomy

Splenectomy is effective in cases of AIHA in which most of the hemolysis is in the spleen, such as IgG-induced AIHA. It is not as effective in IgM-induced disease because most of the hemolysis in this condition occurs in the liver. The response is excellent in about 60% of cases and improved in about 20%. Improvement is defined as a decrease in the dosage of steroids needed to maintain an acceptable level of hemoglobin (usually >1.55 mmol/L [>10 g/dL]).

Hereditary Spherocytosis (HS)

DEFINITION AND EPIDEMIOLOGY

This hemolytic anemia is caused by a defect in the skeleton of the RBC membrane that generally affects the spectrin component. The characteristic finding is increased numbers of spherocytes in the peripheral blood.

HS is the most common cause of hemolytic anemia in people of Northern European heritage, with a prevalence of 1 in 5,000, although it possibly is four or even five times more prevalent. It can be found in other population groups as well. It is inherited in autosomal dominant fashion in 75% of cases. Inheritance in the remaining cases is either autosomal recessive, new mutations, or
autosomal dominant with reduced penetrance.

PATHOLOGY,
PATHOPHYSIOLOGY, AND
PATHOGENESIS

The defect in the RBC membrane is not uniform and may affect one or more chemical membrane components. In the classic autosomal dominant form, the defect may be in either beta spectrin, ankyrin, or protein 3. In the recessive form, the defect is in either the alpha spectrin or protein 4.2.

Because several different membrane components have been identified in HS, it is difficult to define the exact mechanism involved in the development of the spherocyte shape. A unified concept is that any form of imbalance among membrane components results in budding of the membrane. The “bud” or fragment is removed rapidly in the reticuloendothelial system, leading to loss of surface area. The RBC membrane is flexible, but it can stretch or expand its surface area by only about 3% before rupturing. The spherocyte may not have an easy transit through the splenic cords to the venous sinuses because of its shape. It has been suggested that the combination of limited glucose availability because of competition with phagocytes plus impaired glucose metabolism from a low pH of 6.3 to 7.0 during the delayed transit impair formation of adenosine triphosphate. Oxidants released by activated phagocytes may damage the RBCs further in transit. This combination of oxidative and biochemical changes damages cell membranes, and when repeated, causes irreversible membrane damage. Exposure of phosphotidylserine (normally located in the inner bilayer) to the outer membrane surface causes macrophage binding and consequent destruction.

CLINICAL ASPECTS

Patients may be diagnosed as early as in the neonatal period or in adulthood with or without symptoms. The cardinal features are anemia, jaundice, and splenomegaly. Some patients may have all three, but others are asymptomatic and are detected only on family screening. Anemia is the most common presentation (50% of cases); each of the other clinical features may be present at diagnosis in 10% to 15% of cases. During the course of the illness, about 50% of patients develop jaundice, and 50% develop a palpable spleen in the first year of life. By adulthood, up to 95% of patients would have developed a palpable spleen.

LABORATORY DIAGNOSIS

Anemia is much more likely to be severe in early childhood (<1.55 mmol/L [<10 g/dL]) than later in life. The reticulocyte count almost invariably is elevated, but hyperbilirubinemia occurs in only about 50% of cases. The mean corpuscular hemoglobin concentration is increased (>36) in 50% of patients who have HS, but the mean corpuscular hemoglobin and mean corpuscular volume usually are normal. Peripheral smear may show the classical spherocytes in up to 80% of cases and occasionally nucleated RBCs. The definitive diagnostic test is the incubated osmotic fragility test, which shows a pattern of increased fragility in HS.

DIAGNOSTIC DIFFICULTIES

Neonatal HS

Most patients are symptomatic in the neonatal period, usually with jaundice appearing in the first 48 hours. Occasionally, the jaundice appears later. Anemia generally is not severe unless it is compounded by physiologic anemia, and splenomegaly is uncommon. Because the bone marrow response to anemia in the neonatal period is not brisk, particularly during the period of physiologic anemia, reticulocytosis is not a dependable sign. Serum haptoglobin as an indicator of hemolysis is not reliable in the neonatal period. Fetal RBCs generally are more resistant to osmotic hemolysis; therefore, the unincubated osmotic fragility test is not recommended, although the incubated test is reliable. ABO incompatibility (which is 40 to 50 times more common than HS) may be associated with enough microspherocytes as to produce a positive result on the osmotic fragility test; results of the indirect antiglobulin test, however, are positive. Bacterial sepsis may simulate a picture similar to neonatal HS. Family studies and follow-up with repeat testing for osmotic fragility eventually yield a diagnosis.

Mild HS

About 20% to 30% of patients who have HS have such mild disease that they remain asymptomatic or only very mildly or occasionally symptomatic until adulthood, when they present with complications such as gallstones. History may reveal transient episodes of jaundice with or without right upper quadrant pain. Results of clinical examination may include mild splenomegaly, and hematologic studies may reveal compensated hemolysis with minimal reticulocytosis and few spherocytes. The incubated osmotic fragility test usually provides the diagnosis. Hemolysis may be aggravated by pregnancy or exercise, and it may be familial or appear sporadically in families that include severely affected members.

Severe HS

Fewer than 5% of patients have severe disease that probably results from the recessive form of the disease. They usually present with severe anemia in infancy and may become dependent on transfusions. Splenectomy leads to resolution of anemia and appearance of spherocytes in the peripheral blood.

COMPLICATIONS

Even though chronic hemolytic anemia is the norm in HS, other forms of anemia can complicate the picture. Viral-induced bone marrow aplasia follows infection with parvovirus B19 in any patient who has a hematologic disease that is charac-
Hemolytic Anemia

HEMATOLOGY

A number of viral illnesses that are accompanied by reactive reticuloendothelial system hyperactivity may be associated with a hyperhemolysis that is characterized by increasing anemia, reticulocytosis, and jaundice. These episodes usually are not severe, and they resolve spontaneously.

Pigment gallstones may occur as early as 3 years of age, although the peak incidence is in adolescence and adulthood. The reported incidence is 5% among those younger than 10 years of age, 40% to 50% in the 10- to 40-year age group, and 55% to 75% among those older than 40 years. Approximately 50% of the stones produce no symptoms and are detected best by ultrasonography. Other reported complications result from chronic anemia and persistent bone marrow hyperplasia. These include delayed growth and sexual development, frontal bossing, and other craniofacial features seen in hemolytic diseases such as sickle cell disease and thalassemia.

MANAGEMENT

During the first 6 years of life, if the patient has compensated anemia, is growing well, and can keep up with his or her peers in most activities, it is prudent to limit intervention to 1 mg/d of folic acid supplement. Subsequently, depending on the severity of the disease, splenectomy is indicated because the response rate is 100%. The primary benefit of splenectomy is that it enables the RBC to have a near-normal life span, which can eliminate complications such as gallbladder disease.

The risk of postsplenectomy sepsis (PSS) is decreased after 5 years of age and can be reduced further by administering pneumococcal, H influenzae, and meningococcal vaccines, ideally at least 2 weeks before surgery. S pneumoniae accounts for 50% to 70% of cases of PSS, and 80% of the strains are present in the currently available polyvalent vaccines. If affected patients are immunized before 2 years of age, immunization should be repeated after 2 years of age. Other organisms responsible for PSS include Escherichia coli and staphylococci.

The prevalence of G6PD deficiency varies among populations and appears related to the prevalence of malaria in certain geographic areas.

The development of gallstones may be an indication for splenectomy, but both cholecystectomy and splenectomy may not be indicated or necessarily performed simultaneously. The management of symptomatic gallstones is elective cholecystectomy, but asymptomatic cholelithiasis may be managed by observation alone or elective cholecystectomy. Because the incidence of an accessory spleen is 20% to 30%, liver-spleen scans are recommended prior to splenectomy and in cases of failure of response or recurrence of hemolysis. Following splenectomy, most physicians advocate the use of prophylactic oral penicillin administered BID until at least 18 years of age. Alternatives include erythromycin or amoxicillin.

PROGNOSIS

The response to splenectomy in uncomplicated HS is 100% except in the presence of accessory spleens. Even though spherocytes persist in circulation, they have a near-normal life span in the absence of the spleen. Postsplenectomy blood changes include increased hemoglobin, decreased reticulocyte count, and the appearance of Howell-Jolly inclusion bodies and target cells.

G6PD Deficiency

DEFINITION AND EPIDEMIOLOGY

This hemolytic anemia results from oxidative damage to RBCs as a consequence of the loss of the protective effect of the enzyme G6PD. The prevalence of G6PD deficiency varies among populations and appears related to the prevalence of malaria in certain geographic areas. For example, the rate is higher in regions of Africa in which malaria is endemic. The disease also occurs at a higher frequency in Mediterranean regions.

Different variants characteristically are found in different regions. G6PD Mediterranean is found pre-
been observed in vivo that the incidence of *P. falciparum* parasitemia is lower in G6PD-deficient heterozygous females (Gd+/Gd-) than in people who are not deficient and in G6PD-deficient hemizygous males (Gd). Affected females, therefore, are relatively protected from the effect of malaria and live to pass on the x-linked deficient gene. It is not clear how this protection is effected, although it is known that the malaria parasite can synthesize its own G6PD enzyme, which is different from the human enzyme.

**PATHOLOGY, PATHOPHYSIOLOGY, AND PATHOGENESIS**

The enzyme G6PD participates in the first step of a series of enzymatic reactions that result in the production of the reduced form of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH). NADPH, in turn, keeps glutathione in the reduced form (GSH). Glutathione is important for preserving sulfhydryl groups in cellular proteins, thereby protecting the cells from oxidative damage. Because the primary role of the RBC is to carry oxygen, an adequate quantity and quality of G6PD is essential for survival, particularly in the phase of first step of a series of enzymatic reactions. The enzyme G6PD participates in the first step of a series of enzymatic reactions that result in the production of the reduced form of the enzyme nicotinamide adenine dinucleotide phosphate (NADPH). NADPH, in turn, keeps glutathione in the reduced form (GSH). Glutathione is important for preserving sulfhydryl groups in cellular proteins, thereby protecting the cells from oxidative damage. Because the primary role of the RBC is to carry oxygen, an adequate quantity and quality of G6PD is essential for survival, particularly in the phase of fetal development.

Favism is a classic cause of acute hemolysis in G6PD deficiency.

exposure to oxygen radicals.

The G6PD protein in the RBC is the same as that found in other somatic cells. Thus, severe deficiency of the enzyme affects all cells of the body to variable degrees. However, the effect of G6PD deficiency is potentially more deleterious to the RBC than to somatic cells because the mature RBC is incapable of synthesizing any more proteins, including G6PD and other enzymes. The half-life of the enzyme in normal RBCs is 60 days; reticulocytes may have up to five times the activity of older mature red cells. Steady-state RBC survival studies in those who have G6PD deficiency have shown life spans of 90 to 100 days.

The G6PD gene is a single one located on the X chromosome, making deficient males hemizygodes and deficient females homozygotes. Female heterozygotes may have normal or low levels of G6PD, depending on the extent of lyonization of the X chromosome. Deficiency of G6PD probably is not just quantitative, but rather equally qualitative. In some cases, evidence suggests that the deficiency is related to a short half-life of the enzyme. Even though the RBCs in the deficient individual have a reduced level of enzyme or dysfunctional enzyme, the cells hemolyse only when injured by an exogenous factor. Upon initial exposure to an oxidative agent, GSH is converted to glutathione disulfide. Because failure to regenerate NADPH and, hence, GSH, the stores of the latter quickly become depleted. Further exposure leads to oxidation of sulfhydryl groups of hemoglobin and possibly other proteins to sulfoxides or sulfides. The particles of denatured hemoglobin, Heinz bodies, attach to the cell membrane, causing irreversible damage and lysis. Although most of the lysis occurs intravascularly, resulting in hemoglobinemia and hemoglobinuria, there may be an extravascular component, which can explain the presence of splenomegaly in some cases. The younger RBCs that have a relatively higher enzyme content are relatively more resistant to hemolysis.

Favism is a classic cause of acute hemolysis in G6PD deficiency. Fava beans contain the beta glycosides vicine and convicine. These substances may undergo auto-oxidation as part of their natural metabolism, producing free oxygen radicals that then oxidize GSH and lead to a cascade of events. Acute hemolysis that occurs upon exposure to fava bean is characterized by: 1) unpredictability (only 25% of adults at risk develop hemolysis, and the risk may vary in the same individual from one exposure to another), 2) influence of dose and body weight, 3) quality of beans (raw beans are more likely to cause the reaction than cooked, frozen, or canned beans), 4) maturity of the beans (young beans that have a much higher content of beta glycosides are more likely to induce hemolysis), and 5) the activity of beta glycosidases in the beans as well as in intestinal mucosa, which influences the rate and amount of active aglycones released.

Drug-induced Hemolysis

A plethora of drugs and chemicals have been associated with either hemolysis in vitro or subclinical and clinical hemolysis in the presence of G6PD deficiency (Table). These substances all have the ability to stimulate the pentose phosphate pathway in RBCs, which can lead to oxidation of NADPH either directly or indirectly. Because some drugs consistently cause hemolysis (eg, primaquine) and others rarely do (eg, aspirin), other inherent (genetic) or acquired factors are believed to play a part in the pathogenesis.

Infection-induced Hemolysis

During the process of phagocytosis of bacteria, a major metabolic event is the generation and release of peroxides by the phagocytosing granulocytes. These peroxides subsequently lead to release of oxygen radicals, which stimulate the cascade that leads to hemolysis. The mechanism by which viral infections such as viral hepatitis induce hemolysis has not yet been elucidated.

**CLINICAL ASPECTS**

There are three primary clinical presentations of G6PD deficiency: neonatal jaundice, acute hemolysis beyond the neonatal period, and chronic hemolysis (congenital non-spherocytic hemolytic anemia).

**Neonatal Jaundice**

Acute hemolysis in the neonatal period is characterized by the onset of jaundice on the second or third day of life that is out of proportion to the degree of anemia. Because the degree of jaundice may vary from mild to severe, its management can range from simple observation to exchange transfusion. Not all infants who have G6PD deficiency develop neonatal jaundice, and in those who have...
do, the inciting agent or contributing factors cannot always be identified clearly. Neonatal jaundice has been described in variants of the enzyme in different parts of the world, such as Nigeria, Singapore, or Sardinia. No correlation between the degree of deficiency and the incidence of neonatal jaundice has been documented. The dissociation between the severity of anemia and the degree of jaundice has prompted the hypothesis that neonatal jaundice in a G6PD-deficient neonate may be an exaggerated physiologic jaundice (due to enzyme deficiency in the neonatal liver) or may be due to acute hemolysis caused by an inciting agent such as an infection, drugs, or chemicals such as naphtha-

TABLE. Drugs To Be Avoided in G6PD Deficiency

<table>
<thead>
<tr>
<th>Antimalarials</th>
<th>Analgesics</th>
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</thead>
<tbody>
<tr>
<td>• Primaquine*</td>
<td>• Aspirin|</td>
</tr>
<tr>
<td>• Pamaquine</td>
<td>• Acetaminophen|</td>
</tr>
<tr>
<td>• Chloroquine++</td>
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</tbody>
</table>

**Sulfonamides and Sulfones**

• Sulfanilamide
• Sulfaipyridine
• Sulfaquinoxaline
• Sulftalidine
• Sulfecectamide
• Sulfixazoxide (Gantrisin)
• Sulfasalazine
• Diphenylsulfone**
• Sulfoxone**
• Glucosulfone sodium
• (Sulfamethoxazol)
• Sulfonyleurea

**Other Antibacterial Compounds**

• Nitrofurans
  — Nitrofurantoin
  — Furazolidone
• Nitrofurazone
• (Nalidixic acid)
• Chloramphenicol
• p-Aminosalicylic acid
• (Ciprofloxacin)

**Antimalarials**

• Primaquine*  
• Pamaquine  
• Chloroquine++

**Sulfonamides and Sulfones**

• Sulfanilamide  
• Sulfaipyridine  
• Sulfaquinoxaline  
• Sulftalidine  
• Sulfecectamide  
• Sulfixazoxide (Gantrisin)  
• Sulfasalazine  
• Diphenylsulfone**  
• Sulfoxone**  
• Glucosulfone sodium  
• (Sulfamethoxazol)  
• Sulfonyleurea

**Other Antibacterial Compounds**

• Nitrofurans
  — Nitrofurantoin
  — Furazolidone
• Nitrofurazone
• (Nalidixic acid)
• Chloramphenicol
• p-Aminosalicylic acid
• (Ciprofloxacin)

*Reduced dose can be given under surveillance if necessary.
+Can be given under surveillance if necessary.
++May cause hemolysis in healthy individuals if given in large doses. Many other drugs may produce hemolysis in particular individuals.
"Paracetamol acetaminophen is a safe alternative.
"Moderate doses probably are safe in most cases.
"Menadione 1 mg parenterally is safe for the prophylaxis of hemorrhagic disease of the newborn.

Drugs in bold should be avoided by people who have any form of G6PD deficiency. Drugs not in bold also should be avoided by G6PD-deficient persons of Mediterranean, Middle Eastern, or Asian origin.

Drugs in parentheses reflect single case reports or unpublished information.


anemia, jaundice, splenomegaly, and hepatomegaly. In severe cases, cardiovascular decompensation may occur.

Laboratory findings in acute hemolysis include normochromic normocytic anemia of varying degrees with reticulocytosis. Variations in size (anisocytosis) lead to an increase in red cell distribution width. The peripheral smear may show small cells (poikilocytes), some of which are spherocytic or fragmented. Somewhat characteristic findings include “bite” cells, which are RBCs with areas that are bitten off (presumably by macrophages), and “hemighosts”, which are RBCs that contain an uneven distribution of hemoglobin. Using special stains (supravital stains) such as methyl violet, inclusion bodies called Heinz bodies (denatured hemoglobin) may be found attached to the cell membrane from the interior of the cell. The WBC count usually is elevated as a result of hyperactivity of the marrow, but the platelet count may be normal, elevated, or reduced.

Serum haptoglobin is reduced, and there is usually increased unconjugated hyperbilirubinemia and, in severe cases, hemoglobinemia. Hemoglobinuria is a common finding.

Management of a severe acute hemolytic episode includes removal of the inciting agent, brisk hydration to ensure adequate urine output that will prevent clogging of renal tubules, and transfusion if clinically indicated. However, most acute hemolytic episodes are mild and self-limiting, even in the face of continuing exposure, because there is an increased level of enzymes in the remaining younger population of cells. Anemia usually resolves in 3 to 6 weeks. Folic acid 1 mg/d may need to be administered during this period of increased bone marrow erythroid activity. The differential diagnosis includes autoimmune hemolytic anemia, hemolytic-uremic syndrome, and malaria-induced hemolysis.

**Acute Hemolysis**

Most patients who have G6PD deficiency are asymptomatic until exposed to an inciting agent, at which time they may develop acute hemolysis. The onset of hemolysis usually is within 24 to 48 hours of exposure. Initial manifestations may include acute abdominal pain, vomiting or diarrhea, low-grade fever, and hemoglobinuria (cola-colored urine), followed by the appearance of jaundice and symptoms of anemia such as lethargy and irritability. Physical examination usually reveals lene balls (camphor balls), which are used extensively in stored cloth diapers in developing countries.

**Chronic Hemolysis**

A small minority of patients who have G6PD deficiency develop chronic hemolysis. The amount or
quality of G6PD leads to continuous oxidation of sulfhydryl groups. Almost all of the cases described have represented different mutations. Clinically, these patients (almost without exception males) present with jaundice that sometimes occurs in the neonatal period and anemia. Jaundice, anemia, splenomegaly, and development of gallstones become chronic problems. The CBC shows anemia with reticulocytosis that may exceed 20%. RBC morphology is unremarkable except for polychromasia. Other features include low haptoglobin and hyperbilirubinemia. These patients also are at risk for acute episodic hemolysis following exposure to oxidative agents. Management is the same as for other patients who have chronic hemolysis and includes administration of folate, observation, and transfusion if clinically indicated. In some patients, the severity of hemolysis decreases after puberty. Splenectomy may be indicated for patients who have severe splenomegaly with or without increased splenic function, and such surgery may lead to a decrease in transfusion requirements.

**DIAGNOSIS**

When G6PD deficiency is suspected, a “screening test” usually is ordered. This semiquantitative test is designed not to miss any patient who potentially has the disease, making it possible that individuals who do not have G6PD may be included. Further, the total enzyme concentration may be elevated during acute hemolysis, particularly in the presence of a high reticulocyte count, leading to normal or near-normal values. The screening test also may miss heterozygotes. All of these conditions can lead to false-positive or false-negative results. The usual cutoff indicating “deficiency” is less than 30% of normal activity because levels above this point are not likely to be associated with clinically significant hemolysis. Ideally, all patients in whom a screening test suggests G6PD deficiency should have the results confirmed with quantitative assays. Quantitative assays may be affected by two conditions. The younger RBC population that is present during or soon after acute hemolysis contains higher enzyme levels, which may lead to higher quantitative values. Therefore, the best time to perform this test is several weeks following hemolysis, specifically when the reticulocyte count has normalized. Findings in heterozygote females may reveal normal or severe deficiency levels, depending on the percentage of ionized deficient RBCs. Test results of mothers of heterozygotes for chronic nonspherocytic hemolytic anemia usually are normal either because the patient is a new mutation or because the mother is a heterozygote who is phenotypically normal.

Because different populations have different types of G6PD and new mutations are appearing frequently, G6PD electrophoresis should be performed to determine the disease variant. Making this determination also is helpful in management decisions because variants have differing clinical responses to similar drugs or chemicals (Table). Prenatal diagnosis, if requested by parents of affected children, can be made by performing G6PD assay on amniotic fluid cells, but a preferred, more accurate diagnostic procedure is to be performed on chorionic villi biopsy and DNA analysis.

**MANAGEMENT**

Because the enormity of G6PD deficiency as a health problem varies geographically, neonatal screening should be recommended and instituted only in areas in which there is a high prevalence. Cord blood screening currently is performed in Thailand, Malaysia, and Sardinia and is recommended in several countries in Western Africa, southern Africa, and the Middle East. Information gained can be used in management in the immediate neonatal period, such as avoiding known offending drugs and observing for neonatal jaundice for up to 4 days. Deficient individuals should have a medical bracelet (where available) for identification of the disorder and always should carry a plasticized card listing drugs and chemicals that could induce hemolysis.

Favism has been associated unequivocally with the African type of deficiency, but not so consistently with other deficiencies. This author feels that in areas of the world where beans are a dietary staple, most notably in the Middle East, qualitative assays (electrophoresis) should be performed before giving advice on ingestion of beans, based on the type of deficiency. If the type of deficiency prevailing in a specific region is not associated commonly with favism and electrophoresis cannot be performed, an alternative is to educate the patient, parents, teachers, and the population at large about the clinical features of favism. Once a deficient individual develops favism, bean ingestion or exposure should be limited. This approach may be considered risky and controversial, but malnutrition from such a dietary restriction may be a greater health issue than one or two episodes of favism. For affected patients who have the relatively difficult-to-treat *P vivax* or *P malaria* malaria and for whom primaquine is the drug of choice, this drug should be administered at a lower dose for a longer period to attempt to limit the degree and duration of hemolysis (Table).

**SUGGESTED READING**


PIR QUIZ

Quiz also available online at www.pedsinreview.org.

6. Rh and ABO alloimmune hemolytic anemia share which one of the following characteristics?
   A. Availability of effective postnatal treatment.
   B. Intensity of positive result on direct antiglobulin test.
   C. Likelihood of manifestation in the first child in a family.
   D. Occurrence of spherocytes.
   E. Severity of intrauterine impact.

7. Among the following clinical findings, which is most likely to be similar in patients who have either immunoglobulin G (IgG) or IgM autoimmune hemolytic anemia?
   A. Association with Mycoplasma infection.
   B. Peripheral smear findings.
   C. Primary site of red blood cell sequestration.
   D. Response to corticosteroids.
   E. Response to splenectomy.

8. A 5-year-old boy has hereditary spherocytosis. Splenectomy will increase his risk for:
   A. Bacterial sepsis.
   B. Gallstones.
   C. Hyperuricemia.
   D. Megaloblastic anemia.
   E. Viral-induced bone marrow aplasia.

Earning CME Credit–Completing the PIR Quiz

The American Academy of Pediatrics (AAP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. Pediatrics in Review (PIR) was planned and produced in accordance with the ACCME Essentials.

The AAP designates this activity for up to 38 hours in Category 1 of the Physician’s Recognition Award of the American Medical Association (3 hours per completed print issue of PIR and 2 hours per completed compact disc issue of PIR). Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

PIR Quiz: A short quiz can be found at the end of each article in PIR. You may complete the quiz by recording your answers on the PIR Quiz Card (bound into the January issue) or by going online at www.pedsinreview.org. Each question has a single best answer. The answers to the questions appear on the inside front cover of each print issue and under the options in the online version.

1999 Credit Deadline: February 28, 2000. If you want to receive CME credit in 1999, a completed PIR Quiz Card must be received in the PREP Office by February 28, 2000. Credit reply material received after February 28, 2000, will be applied to the following year. Your CME certificate will be mailed within 1 month after your credit reply material is received. If you test online, all quizzes must be completed by February 28, 2000.

Expiration of Credit: December 31, 2001. Credit for completing the 1999 PIR will be awarded for up to 2 years. Credits will be posted to the year in which they are submitted.

Verification of Credit will be mailed by: April 30, 2000. You will receive a complimentary transcript by April 30, 2000, containing a summary of CME credits earned in 1998 through AAP programs. If you require a transcript at any other time of the year, there will be a $25 processing fee.

Mail form to: American Academy of Pediatrics - PREP Office, 141 Northwest Point Boulevard, PO Box 927, Elk Grove Village, IL 60009-0927

PREP Education Award: The AAP PREP Education Award recognizes Academy Fellows who earn a minimum of 150 AAP-approved CME credits over 3 consecutive years. The Award will automatically be mailed in the summer of 2000 to all individuals who qualify. To qualify for the PREP Education Award, an Academy Fellow must:
   - Earn a minimum of 75 credit hours through participation in PREP or PREP The Course, and
   - Earn the remaining credit hours (75 hours) through other Academy-sponsored or -approved CME activities, including AAP Spring Session or Annual Meeting; AAP CME courses; ACQIP; AAP-PT; Pediatric UPDATE Audiocassette Program; or other AAP-approved courses.

Other Organizations Granting Credit: PIR has been approved for credit as follows:
   - American Academy of Pediatrics (AAP); up to 38 hours of credit toward the AAP PREP Education Award
   - American Osteopathic Association (AOA); up to 12 hours, Category 2-B
   - National Association of Pediatric Nurse Associates and Practitioners (NAPNAP); up to 38 contact hours
   - Canadian Paediatric Society has approved PREP as one method for pediatricians to demonstrate maintenance of competence (MOCOMP)
   - American Academy of Physician Assistants accepts AMA Category 1 credit for the PRA from organizations accredited by the ACCME.
   - PREP has been reviewed and accepted by the American Academy of Family Physicians (AAFP) for up to 38 prescribed Hours. Term of approval begins January 1999. Enduring materials are approved for 1 year with the option to request renewal.
Hemolytic Anemia: Part 1
Kwesi Sackey
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