



hemoc

Diseases Presenting With RBC Breakup

By Allan Platt, PA-C, MMSc

Allan Platt is on the faculty at the Emory University School of Medicine PA program in Atlanta.



Red blood cells (RBCs) normally have a 120-day lifespan; the premature breaking apart of RBCs is called hemolysis. When RBC destruction outpaces bone marrow RBC production, hemolytic anemia occurs. Causes of hemolytic anemia include defects within the RBCs or from elements in the circulation.¹ Many systemic diseases present with hemolysis, such as hereditary red cell disorders, systemic infections, cancer, leukemia, immune disorders, liver disease, enzyme deficiencies and clotting disorders.¹ This article discusses the pathophysiology of hemolysis, the diagnostic workup and the treatment of diseases that cause hemolytic anemia. Clinicians can use clues from the history, physical examination and laboratory blood tests to help diagnose the cause of hemolysis. Patients should be referred to hematologists if the cause is not self-limiting.

Pathophysiology

RBCs are made in the bone marrow from stem cells under the stimulation of the kidney-produced hormone erythropoietin. Materials for RBC production, including iron, B₁₂, folic acid, protein and lipids, are transported from the gut or storage to the bone marrow factory. As the RBC matures, it manufactures hemoglobin and extrudes its nucleus before being released into the blood circulation as a reticulocyte. The reticulocyte count is the best indicator of the response of the bone marrow factory to RBC loss; the count should be elevated in the presence of hemolysis, during which the bone marrow responds by making new red cells.

Anemia is defined as low hemoglobin, low hematocrit or low red cell mass on the complete blood count (CBC). Anemia occurs if bone marrow production cannot keep pace with the hemolytic destruction. RBCs are recycled in the spleen, where hemoglobin is broken down into indirect (uncon-

olysis

jugated) bilirubin, iron and protein. Hemolysis causes an elevated indirect bilirubin, and if the level is greater than 3 mg/dL, jaundice occurs. The enzyme lactate dehydrogenase (LDH) is present in abundance in RBCs. The combination of anemia, high reticulocyte count, high indirect bilirubin and high LDH is the classic biomarker profile of hemolysis.^{1,2}

Hemolysis occurs from within the red cell in the presence of genetic mutations in the hemoglobin structure, red cell membrane problems, enzyme deficiencies or parasite invasion. Mechanical destruction occurs outside the red cell in the circulation from fibrin threads, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS), prosthetic heart valves or immune attack from antigen-antibody reactions. The patient's history, physical examination, laboratory values and certain radiologic findings can help guide the differential diagnosis.¹

Clues From the Medical History

Anemic patients complain of nonspecific symptoms, including increased fatigue, generalized weakness, shortness of breath, non-vertigo dizziness and palpitations. Jaundiced sclera should prompt a hemolysis workup. Fever and recent travel to malaria-, *Bartonella*- or *Babesia*-endemic areas should prompt specific testing. A history of lifelong anemia, early gallstones and a positive family history point to genetic causes such as sickle cell disease, thalassemia, spherocytosis or elliptocytosis. Hemolysis after exposure to a sulfa medication, antimalarials or fava beans suggests glucose-6-phosphate dehydrogenase (G6PD) deficiency.^{1,2}

Exposure to toxigenic *Escherichia coli* from contaminated undercooked meat or water can cause HUS. Pregnancy and hemolysis might indicate preeclampsia and HELLP syndrome (hemolytic anemia, elevated liver enzymes and low platelet count). Mechanical heart valve placement also might be the cause of hemolysis.^{1,2}

Clues From the Physical Examination

Physical examination may reveal jaundiced sclera and pallor in the palpebral conjunctiva, nail beds or palmar creases. The pulse rate may be increased. Fever indicates systemic infection or inflammation. Petechiae or skin bruises indicate low or dysfunctional platelets, DIC, HUS or TTP.^{1,2}

Elevated blood pressure in pregnancy indicates preeclampsia/eclampsia, and very high blood pressure indicates malignant hypertension. An enlarged

liver or spleen may be the source of red cell destruction in lymphoma, metastatic cancer, portal hypertension and mononucleosis.^{1,2}

Clues From Lab Values

The first-pass laboratory workup of hemolysis should include urinalysis, CBC, reticulocyte count, red cell morphology, complete metabolic profile (CMP), direct and indirect Coombs test, hemoglobin electrophoresis, Heinz body stain and osmotic fragility test (OFT). Analyzing these results in combination offer clues to the systemic cause.^{1,2} Free hemoglobin may pass through the glomeruli, causing a red-brown cola-colored urine that tests positive for hemoglobin, but with no RBCs seen.¹

A high reticulocyte count with an elevated LDH level and an elevated indirect bilirubin indicates active hemolysis. An abnormal hemoglobin electrophoresis with decreased hemoglobin A, increased hemoglobin F and hemoglobin A₂ and microcytic anemia with an increased red cell count all indicate beta thalassemia. Target cells also may be seen on the peripheral smear.

Hemoglobin electrophoresis also will identify hereditary hemoglobinopathies such as sickle cell disease. The Heinz body stain will be positive in G6PD deficiency. The direct Coombs test will be positive if there is antibody on the red cells, and the indirect Coombs will be positive if there is antibody in the serum. A thin and thick blood smear should be scanned for red cell morphology and intracellular parasites such as malaria and babesiosis, depending on the travel history. The OFT is helpful to identify red cell membrane problems such as spherocytosis, ovalocytosis and elliptocytosis. Low platelets, elevated prothrombin time (PT) and increased activated partial thromboplastin time (aPTT) may indicate HUS, DIC or TTP. Erythrocyte enzyme assays will help diagnose enzyme deficiencies.^{1,2}

A blood smear read by a trained technologist will give the red cell morphology and can offer significant clues to the cause of hemolysis; thus, it should be among the first tests ordered to narrow the cause.³ This test is not a part of the CBC and must be requested. A suspicion of red cell parasites should be communicated to the hematology laboratory so that thick smears can be performed to scan more red cells. Table 1 lists the different red cell shapes and their significance.

Radiologic findings of bone marrow expansion indicate chronic hemolysis, and one of the hereditary causes should be suspected.

Differential Diagnosis

The differential diagnosis of diseases presenting with hemolysis can be remembered with the mnemonic HEMATOLOGIST.

Hemoglobinopathy. Sickle cell disease is one of the most common hemoglobinopathies. It is a family of hemoglobin phenotypes including types SS, SC, S beta + thalassemia, S beta 0 thalassemia, SD, SE, SS with persistent fetal, SG and SOArab. The definitive test is quantitative hemoglobin electrophoresis. Depending on phenotype, there is a wide spectrum of disease manifestations from mild to very severe. Patients with complications should be →

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Learning Objectives

1. Discuss the pathophysiology of hemolysis.
2. Describe the clues from the medical history that point to hemolysis.

3. Understand the laboratory workup for a patient with hemolysis.
4. Review the differential diagnosis of hemolysis.

Disclosure of Conflict of Interest

Allan Platt indicates no relationships to disclose related to the contents of this article.

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Table 1
RBC Morphology From a Peripheral Smear

| Red Cell Morphology | Significance |
|------------------------------------|--|
| Burr cells | Uremia, liver disease, low potassium, posttransfusion state, stomach cancer, bleeding peptic ulcers |
| Spur cells | Abetalipoproteinemia, postsplenectomy state, alcoholic liver disease, malabsorptive states |
| Stomatocytes | Hereditary, alcoholism, cirrhosis, obstructive liver disease |
| Spherocytes | Hereditary, immune hemolytic anemia, posttransfusion state, hemolytic anemia, water dilution hemolysis, fragmentation hemolysis |
| Schistocytes (helmet cells) | Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, vasculitis, glomerulonephritis, renal graft rejection, carcinomatosis, heart valve hemolysis, burns |
| Elliptocyte | Hereditary, thalassemia, iron deficiency |
| Teardrop cells | Myelophthistic anemias, thalassemia |
| Sickle cells | Sickle cell disease |
| Target cells | Obstructive liver disease, hemoglobinopathies, thalassemias, iron deficiency, postsplenectomy state |
| Parasites | Malaria, babesiosis, bartonella |
| Bite cells | G6PD deficiency |

Adapted in part from: Bull BS. Morphology of the erythron. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, eds. *Williams Hematology*. 7th ed. New York, NY: McGraw-Hill; 2005:369-385.

managed by comprehensive sickle cell centers if available. All children should be on prophylactic daily penicillin and screened for stroke risk using transcranial Doppler ultrasound (TCD). Bone marrow transplant has been curative but carries 10% mortality, and there are few patients with sibling matches. Hydroxyurea is an effective preventive medication that decreases pain crisis, blood transfusions and hospital admissions. It has been shown to prolong life and is effective in children in preventing complications.⁴

Hemoglobinuria. Paroxysmal nocturnal hemoglobinuria manifestations include episodic intravascular hemolysis, hemoglobinuria, abdominal pain, thrombotic episodes and increased infections. Red cells are more susceptible to complement-mediated injury, causing hemolysis and burgundy-colored urine. Hemolysis can occur at any time of day, but urine findings are most noticeable in the morning, when the urine is concentrated. Diagnosis is based on the presence of positive sucrose and acid hemolysis tests. Treatment is reserved for those with severe symptoms and includes folate for red cell production

and eculizumab, an FDA-approved humanized monoclonal antibody against complement protein C5 that inhibits terminal complement activation.⁵

Enzyme deficiency. Inherited pyruvate kinase (PK) deficiency is the most common cause of hereditary nonspherocytic hemolytic anemia. There is a history of lifelong anemia and complications similar to those of hereditary hemolytic anemia. There is no specific treatment, only supportive care including transfusion for symptomatic anemia. Other rare red cell enzyme deficiencies include pyrimidine-5'-nucleotidase deficiency, phosphofructokinase deficiency, phosphoglycerate kinase deficiency, aldolase deficiency and triosephosphate isomerase deficiency. These are diagnosed by performing erythrocyte enzyme assays. These patients should be referred to a hematologist for lifelong management.⁶

Membrane problems. Hereditary spherocytosis (HS) is caused by the inheritance of red cell membrane protein abnormalities that result in sphere formation, membrane budding and increased permeability to sodium. The red cells appear as round red balls instead of the normal biconcave

disk shape with an area of central pallor.⁷

Hereditary elliptocytosis is caused by an abnormal structural protein, which causes a defective red cell membrane. Elliptocytes resemble Good & Plenty candy pieces on a peripheral smear.

The shape of ovalocytes is somewhere between the elongated elliptocytes and the beach ball appearance of spherocytes. Mutations in a number of distinct genes account for hereditary spherocytosis and elliptocytosis, while a single genetic defect accounts for all cases of hereditary ovalocytosis.⁸

Antibodies. In immune acquired hemolytic anemia, hemolysis is caused by antibodies or complement proteins attached to the red cell membrane. The direct Coombs test is positive in the presence of antibody on the red cell membrane, and the indirect Coombs test is positive in the presence of antibody in the patient's serum. Causes include alloimmune, autoimmune and drug-induced hemolytic anemia.^{9,10}

Warm-reacting IgG antibodies occur secondary to lymphoproliferative syndrome (30%), collagen vascular diseases (20%), other tumors (20%) or as idiopathic disease (20%). Laboratory findings are anemia with an increased reticulocyte count, and blood smear shows microspherocytes. Direct Coombs test is positive for IgG or IgG and C'. This is responsive to steroids and/or splenectomy.^{9,10}

Cold-reacting IgM antibodies occur secondary to viral and mycoplasma infections, with lymphoproliferative disease and as idiopathic disorders in the elderly. Patients are usually unresponsive to treatment with steroids or splenectomy.^{9,10}

Trauma to the red cells. Artificial heart valves can cause mechanical destruction of RBCs as they pass through the valve. Hemolysis usually is mild and subclinical but is severe in up to 15% of patients with certain prostheses, such as ball-cage and bileaflet valves. It is uncommon with tissue valves, although hemolytic anemia may be the initial presentation of porcine valve failure.¹¹ The peripheral smear shows variable numbers of schistocytes and smaller red cell fragments. Hemolysis also can occur during vigorous sports activities or running on hard surfaces. This usually is self-limited and does not require treatment.¹²

Overactive clotting system. When clotting occurs in multiple sites in the vascular system, the fibrin threads act like razor wire to slice red cells as they speed through. This causes a hemolytic picture, and schistocyte or helmet cells are seen in the peripheral blood smear. Lab results may show

elevated PT and aPTT. Among the conditions that can cause this are TTP, HUS, DIC, preeclampsia, HELLP syndrome and malignant hypertension. A hematology consultation is recommended.^{13,14}

Liver disease. Severe liver disease from any cause may be associated with abnormal lipid loading in red cell membranes, causing spur cell formation and a shortened red cell survival. Zieve syndrome is associated with alcoholic fatty liver and cirrhosis, severe upper abdominal and right upper quadrant pain, jaundice, hyperlipidemia and hemolytic anemia. The condition improves when alcohol consumption is stopped.¹⁵

Oral ingestions and other agents. Lead poisoning can cause central nervous system symptoms, hepatitis, renal insufficiency, hypertension, abdominal pain and hemolytic anemia. Acute and occasionally severe hemolytic anemia is a rare complication of therapy with interferon alfa. Amyl nitrite and butyl nitrite, primarily via inhalation, can cause hemolysis. Topical anesthesia with benzocaine or lidocaine, either as a spray or cream, can cause severe methemoglobinemia with cyanosis and dyspnea. Dapsone, used in the treatment of leprosy, can cause hemolysis and methemoglobinemia. Ribavirin used to treat hepatitis C infection has been reported to cause hemolytic anemia.¹⁶

G6PD. The inheritance of G6PD deficiency is X-linked. Males who inherit the deficient gene are fully affected. Homozygous females also are fully affected. Drugs or other oxidants may cause increased oxidant stress within the red cell, causing precipitation of hemoglobin into Heinz bodies and thereby causing hemolysis. Demonstration of Heinz bodies with methyl violet stain is the most useful test during acute hemolysis. G6PD deficiency can be confirmed by enzyme assay in two to three months when the erythrocytes have a more normal age distribution. With the Mediterranean variant, activity usually is low during the acute hemolytic episode. The patient should be educated to avoid medications listed in Table 2.^{17,18}

Infection. Intra-erythrocytic parasites (malaria and babesiosis) lyse red cells as they emerge. These parasites can be identified on examination of a thick smear slide. *Clostridium perfringens* septicemia may cause massive hemolysis.¹⁹ Bartonella, or Oroya fever, is caused by *Bartonella bacilliformis* and transmitted by sand flies of the genus *Phlebotomus* upon travel to the Peruvian Andes.²⁰ Another tropical parasite that causes hemolysis is

Table 2

Causes of Hemolysis in G6PD Deficiency

| | | |
|-------------------------------|-----------------|----------------------|
| Aspirin (high dose, >3 g/day) | Nitrofurantoin | Sulfapyridine |
| Dapsone/chlorproguanil | Niridazole | Thiazole sulfone |
| TMP-SMX | Phenazopyridine | Toluidine blue |
| Furazolidone | Phenylhydrazine | Trinitrotoluene |
| Isobutyl nitrite | Pamaquine | Fava beans |
| Methylene blue | Primaquine | Ascorbic acid (>1 g) |
| Nalidixic acid | Sulfacetamide | Vitamin K analogs |

Adapted from: Dhaliwal G, Cornett PA, Tierney LM Jr. Hemolytic anemia. *Am Fam Physician*. 2004;69(11):2599-2606; Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet*. 2008;371(9606):64-74; and Frank JE. Diagnosis and management of G6PD deficiency. *Am Fam Physician*. 2005;72(7):1277-1282.

Leishmania donovani. Fever, hemolysis and travel to an endemic area should prompt testing.

Splenic destruction. Splenomegaly and hypersplenism can occur secondary to infections, portal hypertension, infiltration with leukemia or lymphoma and collagen vascular diseases. The spleen is the primary site of red cell recycling. When the spleen is congested, red cell destruction can be accelerated, causing hemolytic anemia. The underlying cause should be treated, or the spleen can be removed surgically.²¹

Thalassemias. Thalassemias must be considered in a hemolytic anemia with a low mean corpuscular volume. Thalassemia, the most common inherited cause of anemia worldwide, is caused by the inheritance of genetic abnormalities that decrease synthesis of alpha or beta chains, leading to decreased production of hemoglobin A. This causes a lifelong microcytic anemia with hemolysis. Clues from the CBC include low hemoglobin and an increased red cell count; the mean corpuscular hemoglobin concentration is low, and the red blood cell distribution width is normal. The peripheral smear may show target cells.²² □

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Self-Assessment Questions: Hemolysis

1. Which one of the following is the normal lifespan of a red blood cell?

- a. 35 days
- b. 75 days
- c. 120 days
- d. 170 days

2. Red blood cells are produced made in the bone marrow from which one of the following cells?

- a. Mast cells
- b. Parietal cells
- c. Stem cells
- d. Glial cells

3. Which one of the following structures recycles red blood cells and is where hemoglobin is broken down into indirect bilirubin, iron, and protein?

- a. The liver
- b. The spleen
- c. The ileum
- d. The duodenum

4. Hemolysis causes an elevated indirect bilirubin, and if the level is greater than 3 mg/dL, jaundice occurs.

- a. True
- b. False

5. Hemolysis after exposure to all of the following substances except which one suggests glucose-6-phosphate dehydrogenase (G6PD) deficiency?

- a. A sulfa medication
- b. Erythromycin
- c. Antimalarials
- d. Fava beans

6. First-pass laboratory workup of hemolysis should include all of the following except

which one?

- a. Urinalysis
- b. Direct and indirect Coombs test
- c. Reticulocyte count
- d. Liver function tests

7. Which one of the following indicates G6PD deficiency?

- a. Elevated reticulocyte count
- b. Positive Heinz body stain
- c. Presence of IgM antibodies
- d. Red-brown cola-colored urine

8. Which one of the following is the most common cause of hereditary nonspherocytic hemolytic anemia?

- a. Pyruvate kinase deficiency
- b. Bartonella
- c. Zieve syndrome
- d. Malaria

9. Which one of the following hemolysis causes is transmitted by sand flies in the Peruvian Andes?

- a. Pyruvate kinase deficiency
- b. Bartonella
- c. Zieve syndrome
- d. Malaria

10. Which one of the following is associated with alcoholic fatty liver and cirrhosis, severe

upper abdominal and right upper quadrant pain, jaundice, hyperlipidemia and hemolytic anemia?

- a. Pyruvate kinase deficiency
- b. Bartonella
- c. Zieve syndrome
- d. Malaria

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