

# Hemolytic Anemias: Autoimmune and Beyond

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Presenter's disclosure of conflicts of interest is  
found at the end of this article.

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## Abstract

During JADPRO Live Virtual 2020, Ravi Krishnadasan, MD, FACP, provided an overview of the terminology of hemolysis, laboratory tests used in the diagnosis of hemolytic anemias, and appropriate indications for treatment of the various hemolytic anemias.

**A**lthough hemolytic anemia is most commonly associated with autoimmune causes, not all hemolysis can be diagnosed with a positive direct antiglobulin (Coombs) test.

During JADPRO Live Virtual 2020, Ravi Krishnadasan, MD, FACP, of The University of Arizona Cancer Center, focused on nonimmune hemolytic anemias, outlining the difference between intravascular and extravascular hemolysis, how to interpret relevant diagnostic laboratory tests, and appropriate indications for treatment.

## DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH HEMOLYSIS

As Dr. Krishnadasan explained, hemolysis is derived from the Greek word *aimólysi* meaning “blood breakdown.” In the compensated form of hemolysis, the bone marrow is keeping up with the breakdown of red cells and hemoglobin or hematocrit

remains in the normal range. In the uncompensated form of hemolysis, on the other hand, hemolysis may be occurring faster than the bone marrow is able to keep up. This is called hemolytic anemia.

Dr. Krishnadasan also distinguished between intravascular and extravascular hemolysis. With the former, red cell destruction occurs primarily within blood vessels. With extravascular hemolysis, however, red cell destruction occurs by macrophages in the liver and spleen.

While we make this distinction, said Dr. Krishnadasan, many causes may have elements of both. High lactate dehydrogenase (LDH) with low haptoglobin can be seen in both but may be normal in extravascular hemolysis. Conversely, hemoglobinuria or hemosiderinuria is seen more in intravascular hemolysis.

Intrinsic abnormalities in hemoglobin structure or function, the red blood cell membrane, or the red blood cell metabolism tend to be inherited. Extrinsic causes, which tend

to be acquired, include red blood cell–directed antibodies, disordered vasculature, or the presence of infecting organisms or toxins.

## WORKUP AND LABORATORY TESTING

Dr. Krishnadasan emphasized that in the outpatient vs. inpatient settings, patients tend to have milder anemia, and symptoms typically include fatigue. In addition, providers need to determine whether this an acquired or congenital disorder.

During workup, Dr. Krishnadasan recommended looking at sclera for icterus, listening to the heart for murmurs, which can be heard with mechanical or damaged valves, and examining the abdomen for splenomegaly. Patients with thalassemia may also have frontal bossing and short stature.

Laboratory testing should involve the following: complete blood count (including red cell indices), bilirubin (indirect or unconjugated), LDH, haptoglobin, reticulocyte count, direct antiglobulin (Coombs) test, urine analysis, and peripheral smears. The latter, said Dr. Krishnadasan, may be one of the most important tools in the armamentarium of advanced practitioners.

“Many of you may never have had the opportunity to look at peripheral smears, but the best thing to do is to find someone who can teach you,” he said. “Use the hematopathology report as backup, but do not to rely on hematopathologists. You will sometimes see something that makes you expand your differential.”

Regarding peripheral smears, Dr. Krishnadasan also suggested starting with the cells “you are *least* interested in.”

“Oftentimes, if you focus on the red cells, you will miss clues or hints you may find in the white cells that can help you with your diagnosis,” Dr. Krishnadasan observed.

## OUTPATIENT HEMOLYSIS

### End-Stage Liver Disease

When evaluating a patient with anemia, providers should consider other reasons for hemolysis after ruling out iron deficiency and other causes. One reason may be end-stage liver disease, said Dr. Krishnadasan, who noted that this occurs when increased free cholesterol from abnormal plasma lipoproteins intercalate into outer mem-

branes of red cells causing redundancy and formation of spurs, or acanthocytes. These acanthocytes then travel to splenic macrophages, which remodel the red cell membrane by removing the spurs. This is a typical example of extravascular hemolysis. In severe cases, a liver transplant may be the only solution.

“In most cases of end-stage liver disease, there is not much you can do for patients from a hematologic perspective, but it’s at least something you can recognize,” said Dr. Krishnadasan. “When you are talking to the primary care physician, you can at least give them an explanation as to why this person has an elevated LDH.”

### Red Cell Membrane Abnormalities:

#### Hereditary Spherocytosis and Elliptocytosis

Defects in membrane proteins can yield red cells that have abnormal morphology and less pliability. When traversing splenic venules, they are not as malleable, and they lyse, said Dr. Krishnadasan. These are again cleared by splenic macrophages, and another example of extravascular hemolysis.

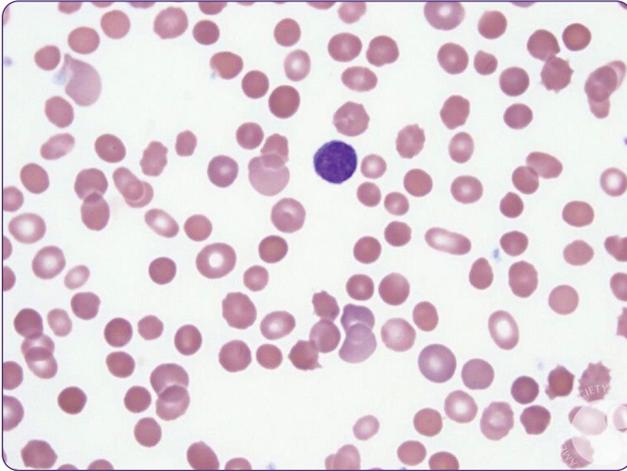
According to Dr. Krishnadasan, hereditary spherocytosis is common in northern Europeans, and approximately 75% of cases are autosomal dominant (Figure 1). Treatment for many cases consists of only observation. For more significant anemia, Dr. Krishnadasan recommended folic acid supplementation. With more symptomatic severe hemolysis, providers should also consider splenectomy, which requires lifelong splenic vaccinations.

### Valve Hemolysis

Although valve hemolysis occurs relatively frequently, it is underdiagnosed, said Dr. Krishnadasan. Hemolysis occurs as red cells traverse valves causing mechanical damage, or as it flows across a stenosed native valve flow rates increase, causing shearing.

Mechanical valves may have a smaller-than-normal diameter, said Dr. Krishnadasan, who underscored the importance of a cardiovascular exam in the workup of anemia.

“You should listen for murmurs, but aortic stenosis is what I primarily listen for,” he said. “Regurgitation murmurs may also cause some amount of hemolysis.”



**Figure 1.** Hereditary spherocytosis. This image was originally published in ASH Image Bank. Teresa Scordino. ASH Image Bank 2021; Image 00060308. Copyright © 2021 American Society of Hematology.

Patient with valve hemolysis are Coombs negative, but laboratory testing can show increased bilirubin, LDH, and reticulocyte count, as well as low haptoglobin. This can be compensated in some patients, but in severe cases, the valve should be replaced.

“If you get hemoglobin above 10, you can slow the flow rates across the valve and see less shearing,” said Dr. Krishnadasan (Figure 2).

### G6PD Deficiency

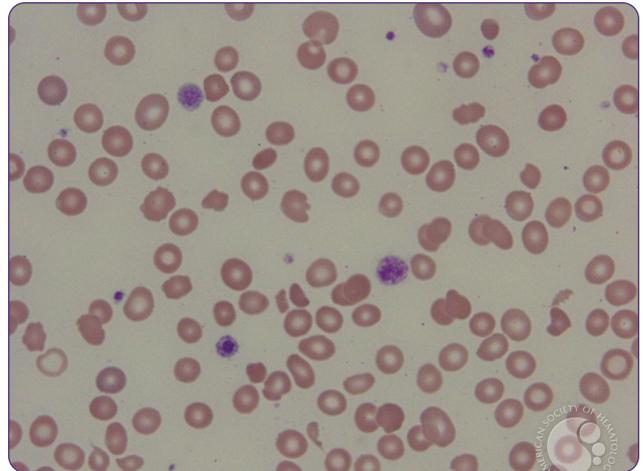
Deficiency of G6PD, an enzyme involved in red blood cell metabolism, affects more than 400 million people worldwide (most commonly males in the malaria belt: Africa, Mediterranean countries, and Asia because it is X-linked). Because of enzyme deficiency, cells become more susceptible to oxidant damage, which denatures hemoglobin and forms Heinz bodies.

“Anyone with G6PD deficiency has to avoid a number of drugs that can induce oxidant stress and lead to hemolysis,” said Dr. Krishnadasan, who noted that the leukemia drug rasburicase can cause anemia in this population.

Treatment recommendations for G6PD deficiency include avoiding oxidant drugs and fava beans.

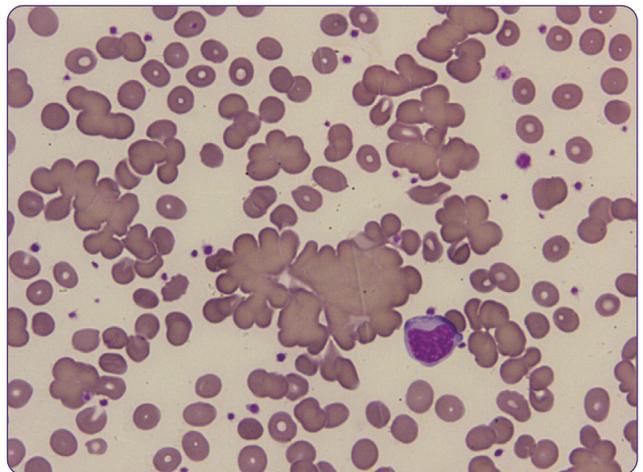
### Cold Agglutinin Hemolytic Anemia

According to Dr. Krishnadasan, cold agglutinin hemolytic anemia is often found incidentally



**Figure 2.** Microangiopathic hemolytic anemia secondary to artificial aortic valve malfunction. This image was originally published in ASH Image Bank. John Lazarchick. ASH Image Bank 2021; Image 1068. Copyright © 2021 American Society of Hematology.

and noted by the hematology technician. Signs of cold agglutinin include agglutination at temperature below 37°C and markedly elevated mean corpuscular volume. In some cases, cold agglutinin can be associated with IgM kappa monoclonal gammopathy of undetermined significance, lymphoproliferative diseases, or autoimmune disease. It may also be associated with mycoplasma or cytomegalovirus. The Coombs test is usually positive for complement C3, and IgG negative (Figure 3).



**Figure 3.** Cold agglutinin disease. This image was originally published in ASH Image Bank. John Lazarchick. ASH Image Bank 2021; Image 1053. Copyright © 2021 American Society of Hematology.

For mild cases, treatment involves staying in a warm environment and avoiding cold exposures, even breathing cold air. In severe cases, the standard of care is rituximab (Rituxan), which works extremely well, said Dr. Krishnadasan.

### **Paroxysmal Nocturnal Hemoglobinuria**

Paroxysmal nocturnal hemoglobin often presents with thrombosis, anemia, or pancytopenia and can present in both inpatient and outpatient settings. Patients may also describe darker urine in the morning.

This disorder is caused by a mutation in the *PIGA* gene, which codes for a transmembrane protein that anchors a number of surface proteins, including CD55 and CD59, which are important in the regulation of complement.

Treatment is either eculizumab (Soliris), which is administered every 2 weeks, or ravulizumab (Ultomiris), which was approved more recently and is administered every 2 months. Hematopoietic stem cell transplant is also an option. For patients with pancytopenia, said Dr. Krishnadasan, antithymocyte globulin plus cyclosporine is another option.

## **INPATIENT HEMOLYSIS**

### **Microangiopathic Hemolytic Anemia (MAHA)**

Microangiopathic hemolytic anemia can be seen in a number of acute situations such as disseminated intravascular coagulation (DIC), thrombocytopenic purpura (TTP), and HELLP syndrome. It is caused by activation of platelets and coagulation cascade, which leads to fibrin strands slicing red cells as they travel through the vasculature. This leads to intravascular hemolysis and very high levels of LDH.

“Treatment varies based on the clinical scenario,” said Dr. Krishnadasan. “With DIC, we often observe and treat based on whether there is

bleeding vs. clotting, and with TTP we are moving towards plasmapheresis or plasma exchange.”

### **Infection**

According to Dr. Krishnadasan, there are a number of infections that can lead to hemolysis. With many bacterial causes, such as *Clostridium sepsis*, *Streptococcus*, *Staphylococcus*, and *Enterococcus*, this can be a direct toxic effect. In the northeast and in California, parasitic causes (e.g., ticks) can be seen and diagnosed with peripheral smear.

### **Drug-Induced Hemolysis**

As Dr. Krishnadasan explained, there are three mechanisms of drug-induced hemolysis: hapten-mediated, ternary, and autoantibody. Treatment primarily consists of discontinuing the drug, which should lead to improvements in the hemoglobin within approximately 2 weeks.

### **Warm Autoimmune Hemolytic Anemia**

Warm autoimmune hemolytic anemia occurs when IgG (rarely IgA) binds antigens on red cells at 37°C. The antibody and part of the red cell membrane is phagocytosed in the reticuloendothelial system, primarily the spleen. Part of the membrane attached to the antibody is removed, which leaves microspherocytes that circulate but ultimately may become trapped in the spleen.

Warm autoimmune hemolytic anemias have components of both intravascular and extravascular hemopoiesis. Standard-of-care is glucocorticoids up front, and second-line treatment includes rituximab, splenectomy, cyclophosphamide, and other immunosuppressives. ●

### **Disclosure**

Dr. Krishnadasan had no conflicts of interest to disclose.