Chapter 23
Approach to Hemolytic Anemia

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Learning Objectives

1. Develop a systematic approach to evaluating anemia based on the reticulocyte index and basic hemolysis labs.
2. Identify the cause of hemolytic anemia based on a peripheral blood smear and one unique clinical feature.

Clinical Vignette: A 28-year-old woman with *systemic lupus erythematosus* (*SLE*) presents with fatigue and shortness of breath. She denies any signs of bleeding. Medications: Hydroxychloroquine, mycophenolate, dapsone (recently initiated)**.** Labs: Hemoglobin 5 g/dl, Hematocrit 15% (previously 32%), platelets normal, reticulocyte index 4.2%.

A. **What is a reticulocyte index (RI) and why is the RI such an important tool for differentiating the causes of anemia?**

Write the formula for reticulocyte count on the white board.

Teaching points

- When you order a reticulocyte count, you are provided with a total reticulocyte count and percentage.
- However, these values are only useful when the degree of anemia is taken into account.

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- The RI equation determines whether or not the degree of reticulocytosis is appropriate.

B. **The reticulocyte index helps differentiate between underproduction anemia and anemia from destruction or loss of red blood cells. What does an RI less than 2% suggest?**

Add "<2%" and "underproduction" to the white board.

Teaching points

- As a patient becomes increasingly anemic, a normally functioning bone marrow will increase the rate of red blood cell maturation by producing more reticulocytes. Thus, the reticulocyte count and percentage will increase relative to the degree of anemia (RI > 3%) in order to compensate appropriately.
- A dysfunctional bone marrow will not generate an adequate reticulocytsis (RI < 2%) to correct the anemia.
- If a patient is anemic with a low RI, then underproduction is at least contributing to their anemia.
- The differential for underproduction is broad and will not be covered here—major causes include micronutrient deficiency, chornic inflammaiton, malignancy, and bone marrow suppression from a variety of causes.

C. **What would the reticulocyte index be in the setting of acute blood loss or red blood cell destruction?**

Complete the algorithm for ">3%."

Teaching points

- Assuming the bone marrow is functioning appropriately, the RI should be >3% within 24 hours after the development of anemia.
- The history and exam may still help you identify the source of blood loss or further investigation may be warranted if laboratory testing excludes hemolysis as the cause of anemia.
- Note that the RI may be <3% if the blood loss started within less than 24 hours, as there may not have been enough time for the marrow to generate sufficient reticulocytosis. However, an acute blood loss anemia of that extent would typically be clinically apparent without additional laboratory testing.

D. **Our patient has an elevated reticulocyte index but no signs or symptoms of acute blood loss. What additional laboratory tests help confirm that an anemia is due to hemolysis?**

Add labs pointing to hemolytic anemia, as shown in Fig. 23.1.

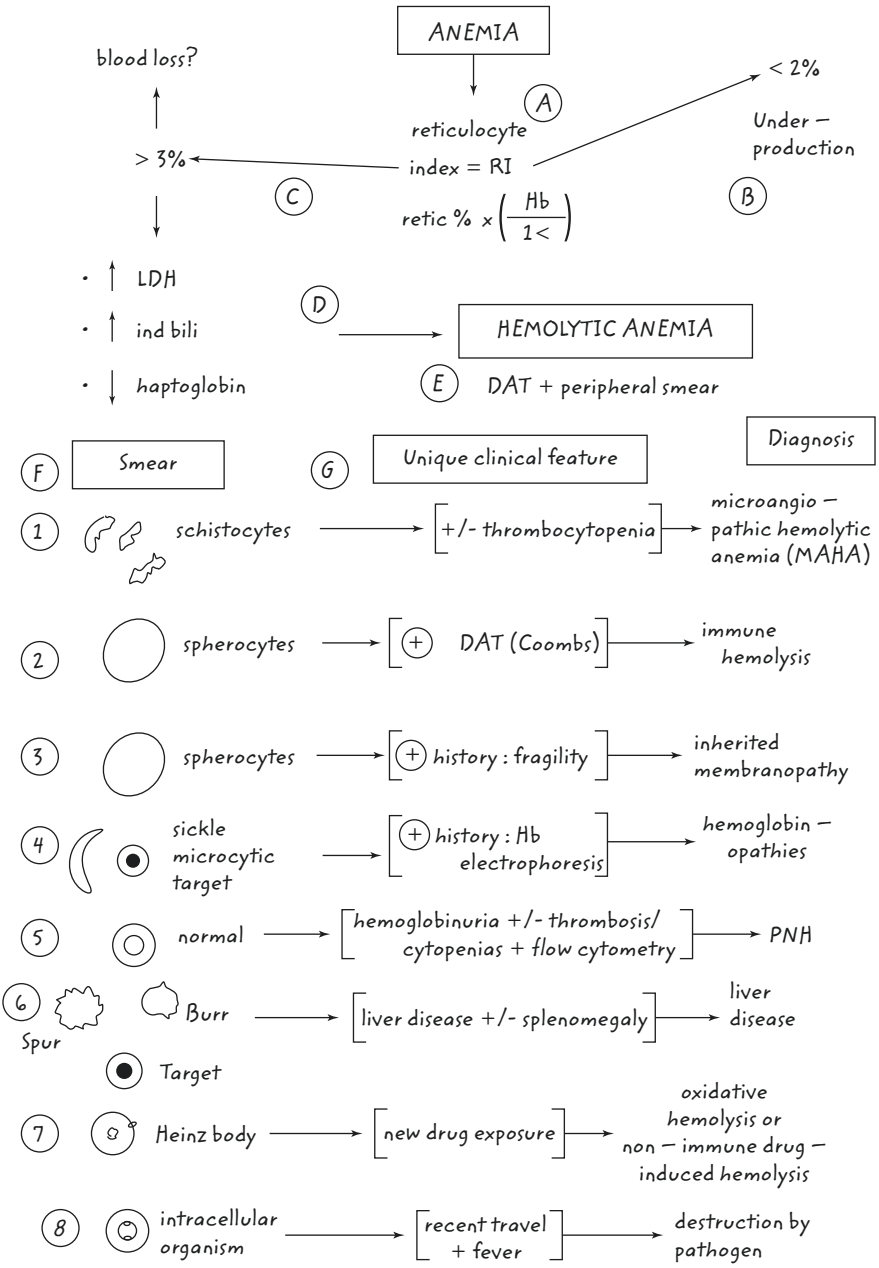

Fig. 23.1 Approach to Hemolytic Anemia, A–G

Teaching points

- Elevated lactate dehydrogenase (LDH): Released from the hemolyzed RBC. Elevation is not specific to hemolytic anemia as LDH is found in many types of cells in the body (e.g., WBC, myocytes).
- Elevated indirect bilirubin: Hemoglobin released from hemolyzed RBCs is broken down into bilirubin but, again, elevated bilirubin is not specific for hemolysis.
- Low haptoglobin: Haptoglobin is an acute phase reactant generated in the liver. Levels could either be inappropriately normal due to inflammation despite ongoing hemolysis, or low in the setting of liver dysfunction in the abscence of hemolysis.

E. **Our patient is found to have elevated LDH and indirect bilirubin, and a low haptoglobin level. We continue to suspect hemolytic anemia. What additional tests should we order?**

Write down "DAT" and "peripheral smear," as shown in Fig. 23.1.

- Direct Antiglobulin Test (DAT), also known as a Coombs test, is typically positive in patients with an autoimmune process leading to their anemia.
- A peripheral blood smear is critical in assessing the characteristic changes in RBC morphology that help make the appropriate diagnosis.

F. **The peripheral smear is extremely useful in figuring out the cause of hemolytic anemia. What are some RBC abnormalities you can see in patients with hemolytic anemia?**

Draw the common abnormalities as listed by learners (1–8 in the figure). Group spur cells (acanthocytes), burr cells (echinocytes), and target cells together. Also draw two spherocytes (for immune hemolysis and inherited membranopathy), as shown in Fig. 23.1. *Consider drawing these before starting your talk.*

G. **It is useful to think of the common causes of hemolytic anemia in terms of their characteristic peripheral smear findings and at least one "unique clinical feature." What is the most likely diagnosis in each case with the associated clinical feature?**

Write down the key clinical features next to each peripheral smear. Ask learners to provide the most likely diagnosis in each case. The table below provides helpful notes. Focus primarily on microangiopathic hemolytic anemia (MAHA) and immune mediated. These are the two most common, acute, and urgent groups of diseases. If time is limited, it is reasonable to address these two entities exclusively while mentioning that the complete differential is quite broad including many rarer, less acute, and less severe diseases. See Teaching Points below for further details, although this table does not need to be written on the white board.

Teaching Points

Smear + Clinical Feature → likely diagnosis	Further differential/notes
Schistocytes +/− thrombocytopenia → Microangiopathic Hemolytic Anemia (MAHA)	• Thrombotic thrombocytopenic purpura (TTP) most commonly due to an inherited deficiency of ADAMTS13 (enzyme responsible for cleaving vWF). The classic pentad of MAHA, thrombocytopenia, altered mental status fever, and acute kidney injury (AKI) is not necessary for the diagnosis, only MAHA and a confirmed ADAMTS13 activity level <10%. • Hemolytic Uremic Syndrome—most commonly presenting in children due to Shiga toxin producing E. coli (STEC) infections. More rarely due to complement dysregulation related to other infection or medications. Diagnosed by the classic triad of MAHA, thrombocytopenia, AKI with either evidence of STEC infection or compliment dysregulation • Disseminated intravascular coagulation (DIC)—coagulopathy, thrombocytopenia, and low fibrinogen • Malignant hypertension • Prosthetic valve • Pre-eclampsia
Spherocytes + positive Direct Antiglobulin Test (DAT) → Immune-mediated Hemolysis	• Most commonly idiopathic, but consider the following potential underlying causes: • Medications—antibiotics, NSAIDs, chemotherapy and quinine • Infectious—e.g., HIV, EBV • Autoimmune disease—e.g., lupus, rheumatoid arthritis, scleroderma, dermatomyositis • Lymphoprolipherative disease • Immunodeficiency—e.g., combined variable immune deficiency • Transfusions/transplant
Spherocytes, negative DAT and personal or family history of anemia → Inherited membranopathy	• Hereditary spherocytosis(elevated mean corpuscular hemoglobin concentration + positive fragility test)
Sickle cells or microcytosis and target cells + personal or family history of anemia → Hemoglobinopathy	• Sickle Cell • Thalassemia: Alpha thalassemia more common in people of Southeast Asian descent, and • Beta thalassemia in people of African and Mediterranean descent.
Normal smear + hemaglobinuria +/− unexplained thrombosis or cytopenias → Paroxysmal Nocturnal Hemoglobinuria (PNH)	• PNH is a rare clonal disorder that presents with hemolysis, thrombosis, and bone marrow failure. Confirmed with flow cytometry.

Smear + Clinical Feature → likely diagnosis	Further differential/notes
Spur, burr or target cells + liver disease +/− splenomegaly → Hemolysis of liver disease	• This is a commonly misdiagnosed as DIC (for example, low fibrinogen, low platelets, and elevated INR). However, these abnormalities are due to liver synthetic dysfunction rather than consumption. • Alterations in the cholesterol to lipid content of the RBC membrane make the RBCs less deformable and more fragile. • Hypersplenism leads to increased RBC sequestration and can also result in increased RBC clearance within the enlarged spleen.
+/− Heinz bodies + new drug exposure → Non-immune drug induced hemolysis	• Oxidative hemolysis, more common in the setting of G6PD deficiency—e.g., • Dapsone, nitrofurantoin, and primaquine • Other mechanisms—e.g., heavy metals, interferon, and insect or snake bites
+/− Intracellular organism + recent travel and fever → Destruction by pathogen	• Malaria • Babesiosis • Clostridial sepsis

Returning to Our Case

Based on concerns for active hemolysis, a peripheral blood smear was performed, revealing numerous spherocytes and her DAT returned positive the next day. She was diagnosed with acute immune-mediated hemolytic anemia related to her SLE.

Return to Objectives and Emphasize Key Points

1. Develop a systematic approach to evaluating anemia based on the reticulocyte index and basic hemolysis labs.

    - When the cause for anemia is not clear, use the RI as the initial step in evaluating the etiology—The Reticulocyte Index (RI) determines if the reticulocytosis is appropriate for the degree of anemia, thus differentiating underproduction anemia from blood loss or hemolytic anemia.
    - Hemolysis labs—RI of >3%, an elevated LDH and indirect bilirubin, and a low haptoglobin will establish hemolysis as the cause of anemia.
    - Smear and DAT—Always obtain a peripheral blood smear and DAT to help identify the etiology of hemolysis.

2. Identify the cause of hemolytic anemia based on a peripheral blood smear and one unique clinical feature.

    - The most common causes for clinically significant acute hemolytic anemia are MAHA and immune-mediated hemolysis.
    - MAHA is diagnosed by schistocytes on the peripheral smear and is often associated with thrombocytopenia.
    - Immune hemolysis will often have spherocytes on peripheral smear and is confirmed with a positive DAT.

Resources

1. Hutchinson RE, Davey FR. Hematopoiesis. In: Henry JB, editor. Clinical diagnosis and management by laboratory methods. 19th ed. Philadelphia: WB Saunders; 1996.
2. Dhaliwal G, Cornett P, Tierney L Jr. Hemolytic anemia. Am Fam Physician. 2004;69(11):2599–607.
3. Sabatine MS. "Anemia" 5.1. In: Pocket medicine: the Massachusetts General Hospital handbook of internal medicine. Philadelphia: Wolters Kluwer; 2017.
4. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654–66.
5. Owen JS, et al. Erythrocyte echinocytosis in liver disease. Role of abnormal plasma high density lipoproteins. J Clin Invest. 1985;76(6):2275–85.
6. Cooper RA, et al. Role of the spleen in membrane conditioning and hemolysis of spur cells in liver disease. N Engl J Med. 1974;290(23):1279–84.