A practical approach to patients with anemia and hemolysis

Markers of hemolysis in different hemolytic diseases[3,4]

Laboratory parameters	PNH	AIHA
Coombs test (DAT)	**Negative**	**Positive**
PNH cells (flow cytometry)	**Present**	**Absent**
LDH	↑	
Haptoglobin	↓	
Indirect bilirubin	↑	
Reticulocyte count	↑*	
RBC morphology	No specific abnormalities	
Hemoglobinuria	Sometimes	

	PNH	AIHA	Membrane/ enzyme defects	CDA	TMA	Intravascular devices
Hemoglobin (Hb)	−−/−−−	− to −−−	−/−−	−−/−−−	−−/−−−	−
Reticulocytes	− to ++	− to +++	+ to +++	−/=	+	+
Schistocytes	=	=	=	=	++	+
LDH	+++	+/++	+	+	++	++
Haptoglobin	−−−	−−−	−−−	−−	−	−−
Bilirubin	+	+	++	+	+	+
Ferritin	− to +	=/+	++	+++	=/+	=/+
Platelets	=/−	=/−−	=/−	=	−−	=/−
WBC	=/−	=	=	=	=	=/−
Hemosiderinuria	+ to +++	=/+	=	=	=/+	=/+

Adapted from Barcellini W et al., 2015. Values are expressed in a semi-quantitative style to indicate the different intensity of alteration in the various hemolytic syndromes, as follows: +/++/+++ indicate an increase from mild to severe, −/− −/− − − indicate a reduction, and **=** indicates values within the normal range.

* In PNH, reticulocyte counts may be normal or decreased in patients with concurrent bone marrow failure.[7]
AIHA, autoimmune hemolytic anemia; BM, bone marrow; CDA: congenital dyserythropoietic anemia; DAT, direct antigen test; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; TMA, thrombotic microangiopathies; WBC, white blood cells.

References:
1. Janz TG, Johnson RL, Rubenstein SD. *Emerg Med Pract.* 2013;15(11):1-15; quiz 15-16. **2.** Kim Y, Park J, Kim M. *Blood Research.* 2017;52(2):84-94. **3.** Barcellini W, Fattizzo B. *Dis Markers.* 2015;2015:635670. **4.** Tefferi A. *Mayo Clin Proc.* 2003;78(10):1274-1280. **5.** Tsuji A, Tanabe M, Onishi K, et al. *Intern Med.* 2004;43(10):935-938. **6.** Kujovich JL. *Obstet Gynecol Clin North Am.* 2016;43(2):247-264. **7.** Parker CJ, Russell EW. In: Greer JP, ed. *Wintrobe's Clinical Hematology.* 13th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014. **8.** Borowitz MJ, Craig FE, Digiuseppe JA, et al. *Cytometry B Clin Cytom.* 2010;78(4):211-230.

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Differential diagnosis algorithm for the evaluation of anemia[1–7]

Anemia
(Hb <120 g/L)

Microcytic MCV
(<81 fL)

Evaluate potential causes, such as:[1]
- Chronic disease (late)
- Iron deficiency
- Lead intoxication
- Sideroblastic anemia
- Thalassemia

Normocytic MCV
(81–100 fL)

Macrocytic MCV
(>100 fL)

Evaluate potential causes, such as:[1]
- Aplastic anemia
- Drugs (e.g., hydroxyurea, AZT, chemotherapeutic agents)
- ETOH abuse
- Folate deficiency
- Hypothyroidism
- Liver disease
- MDS
- Reticulocytosis
- Vitamin B_{12} deficiency

Hemolysis
(i.e., ↑ LDH or ↑ reticulocyte count or ↑ bilirubin or ↓ haptoglobin)
NOTE: Reticulocyte count: ↓ (impaired BM/underproduction) vs. ↑ (blood loss)

NO

Consider blood loss or impaired RBC production*

Evaluate potential causes, such as:[1]
- Acute blood loss
- Aplastic anemia
- BM suppression
- Chronic disease
- Chronic renal insufficiency
- Hypothyroidism
- Multiple myeloma

YES

Coombs test (DAT) (−) (+)

Hematologist consult

Peripheral blood smear:
For example: schistocytes

YES → **RBC morphology**

NO

High-Sensitivity Flow Cytometry (HSFC): PNH cells?

YES → **PNH**‡

NO

Evaluate other causes

Evaluate potential causes, such as:[3]
- Blood loss or impaired RBC production*
- Congenital hemolytic syndromes
- Infective/toxic/metabolic causes
- Oxidative changes

Immune-mediated hemolytic anemia

Evaluate potential causes, such as:[3]
- Alloimmunization
- Cold agglutinin disease
- Warm (>37°C) antibody hemolytic anemia

Schistocytes

Evaluate potential causes of mechanical hemolysis, such as:[3–5]
- Acute fatty liver disease (AFLD)
- Aortic stenosis
- Disseminated intravascular coagulation (DIC)
- HELLP syndrome
- Pregnancy-induced hypertension
- Thrombotic microangiopathy (TTP/HUS/aHUS; consider ADAMTS13 testing)
- Valvular defect/prosthesis

Hemoglobinopathies†

Evaluate potential causes, such as:[2]
- Structural hemoglobin variants
- Thalassemia
- Sickle cell anemia

Membranopathies
(e.g., spherocytes, elliptocytes)

Evaluate causes consistent with observed morphology, such as:[2]
- Congenital dyserythropoietic anemia (CDA)
- Hereditary elliptocytosis
- Hereditary spherocytosis

Enzymopathies

Evaluate potential causes, such as:[2]
- G6PD deficiency
- Pyruvate kinase (PK) deficiency

* PNH can occur concurrently with bone marrow failure, including aplastic anemia, hypocellular MDS, and unexplained cytopenias.[8]
† RBCs may appear hypochromic and microcytic because of iron deficiency resulting from hemoglobinuria.[7]
‡ In PNH, reticulocyte counts may be normal or decreased in patients with concurrent bone marrow failure.[7]
AZT, azidothymidine; BM, bone marrow; DAT, direct antiglobulin test; ETOH, ethanol; HELLP, Hemolysis + Elevated Liver enzymes + Low Platelet count; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.