ARUP Consult

# Hemolytic Anemias Testing

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**Abbreviations**

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|---|---|
| aHUS | Atypical hemolytic uremic syndrome |
| DIC | Disseminated intravascular coagulation |
| LDH | Lactate dehydrogenase |
| HHA | Hereditary hemolytic anemia |
| HELLP | Hemolysis, elevated liver enzymes, low platelet count |
| HPLC | High-performance liquid chromatography |
| HUS | Hemolytic uremic syndrome |
| PCH | Paroxysmal cold hemoglobinuria |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| RBC | Red blood cell |
| TMA | Thrombotic microangiopathy |
| TTP | Thrombotic thrombocytopenic purpura |
| WBC | White blood cell |

INDICATIONS FOR TESTING
Anemia and evidence of hemolysis

**ORDER**
- CBC with Platelet Count and Automated Differential
- Reticulocytes, Percent and Number
- Lactate Dehydrogenase, Serum or Plasma
- Haptoglobin
- Bilirubin, Total, Serum or Plasma

Presence of the following may provide clues to the etiology of the anemia:
- Increased reticulocyte count, LDH, bilirubin
- Decreased haptoglobin
- Abnormal peripheral smear (eg, polychromasia, spherocytes, schistocytes, sickle cells, stomatocytes, Heinz bodies, basophilic stippling, unusual RBC inclusions, and agglutination)

Note: Lack of any of the above does not rule out hemolytic anemia

Consider Hereditary Hemolytic Anemia Cascade if HHA is suscpected (eg, thalassemias, hereditary spherocytosis, G6PD deficiency)

**CONSIDER**
DIC, TTP, HELLP, HUS, aHUS, mechanical cardiac valve, vasculitis, malignant hypertension

Normal AND Clinical presentation consistent with TMA

**ORDER**
D-Dimer

Increased → DIC

Pregnant → Consider HELLP

**ORDER**
ADAMTS13 Reflex Panel or ADAMTS13 Activity
**OR**
*E. coli* Shiga-like Toxin by EIA
(depending on presentation)

- ADAMTS13 activity <10% → TTP
- Normal → aHUS
- Positive Shiga toxin and history of diarrheal illness → Classical HUS

Microangiopathic RBC destruction

Schistocytes, thrombocytopenia

Unusual RBC inclusions → If infection suspected, consider malaria, bartonella (oroya fever), babesia

Spherocytes, pyropoikilocytes, elliptocytes or acanthocytes → Consider RBC membrane disorder (hereditary spherocytosis, hereditary elliptocytosis, autoimmune hemolysis)

Consider RBC Band 3 Protein Reduction
- Positive → Consider molecular testing
- Negative → Direct Coombs (Anti-Human Globulin)
  - IgG+
    - No → Recluse spider venom, clostridium sepsis
    - Yes → Autoimmune hemolytic anemia (consider drug induced, hemolytic disease of the newborn, autoimmune disease)
  - +C3 → Cold agglutinins disease, PCH → Confirm PCH with Donath Landsteiner testing

- Sickle cells → Consider sickle cell disease (diverse genotypes): SS, SC, SE, Sβ thalassemia, S Lepore → HPLC
- Basophilic stippling → Acquired
  - No → Congenital 5' nucleotidase deficiency → Consider 5' Nucleotidase testing
  - Yes → Consider lead poisoning → Consider Lead, Blood (Venous)
- Polychromasia only with or without platelet decrease → Consider PNH → **ORDER** PNH, High Sensitivity, RBC and WBC
- Polychromasia without other reproducible morphologic abnormality → Consider
  - Pyruvate kinase deficiency
  - Hexokinase deficiency
  - Other enzyme defects

  → Consider one or more of the following tests
  - Pyruvate kinase
  - Hexokinase
  - Glucose phosphate isomerase
- Agglutination → Consider cold agglutinins disease → **ORDER** Direct Coombs (Anti-Human Globulin) → Positive for complement
  - No → Warm autoimmune hemolytic anemia
  - Yes → Cold agglutinins testing → Cold agglutinins disease
- Heinz bodies → Consider
  - Glucose-6-phosphate dehydrogenase deficiency
  - Unstable hemoglobin defects
  - Glutathione metabolism defects
  - Hemoglobin H disease

  → Consider one or more of the following tests
  - Isopropanol heat stability testing
  - Glucose-6-Phosphate Dehydrogenase (*G6PD*) 2 Mutations
  - Enzymes of glutathione cycle

  → For hemoglobin disorders, consider Hemoglobin Evaluation Reflexive Cascade



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