A practical approach to patients with anemia and hemolysis
Differential diagnosis algorithm for the evaluation of anemia

1. **ANEMIA**
   - **Assess MCV**
     - **Microcytic MCV**
       - Evaluate potential causes, such as:
         - Chronic disease (lata)
         - Iron deficiency
         - Lead intoxication
         - Sideroblastic anemia
         - Thalassemia
     - **Normocytic MCV**
       - Evaluate potential causes, such as:
         - Acute blood loss
         - Chronic disease
         - Chronic renal insufficiency
         - Hypothyroidism
         - Bone marrow suppression
         - Aplastic anemia
     - **Macrocytic MCV**
       - Evaluate potential causes, such as:
         - Aplastic anemia
         - Drugs (e.g., hydroxyurea, AZT, chemotherapeutic agents)
         - ET 2/4 hefe
         - Folate deficiency
         - Hypothyroidism

2. If above causes are excluded and/or anemia remains persistent and unexplained:
   - **Suspected hemolytic anemia**
     - (e.g., LDH↑ or reticulocyte count of ↑ bilirubin or ↓ hemoglobin)
     - **Positive for hemolysis**
       - Peripheral blood smear** and **Coombs test/DAT
     - Assess findings
     - Schistocytes present
     - Mechanical hemolysis **URGENT HEMATOLOGY CONSULT**
       - Evaluate potential causes, such as:
         - Thrombotic microangiopathy
         - Thrombotic thrombocytopenic purpura (TTP)
         - HUS
         - Abetalipoproteinemic syndrome (ALPS)
         - Abetalipoproteinemia
         - Disseminated intravascular coagulation (DIC)
         - Pregnancy-associated conditions
         - Hypertensioninduced hypertension
         - Cardiac conditions; consult cardiology
         - Acute stress
         - Vascular defect/pathology
     - **Negative for hemolysis**

3. Consider blood loss or impaired RBC production:
   - Evaluate potential causes, such as:
     - Acute blood loss
     - Aplastic anemia
     - Bone marrow suppression
     - Multiple myeloma
     - Chronic disease

4. Immune-mediated hemolytic anemia
   - Consult hematologist and evaluate potential causes, such as:
     - Warm (≥5°C) antibody hemolytic anemia
     - Cold agglutinin disease
     - Autoimmune

5. Hemoglobinopathies
   - Evaluate potential causes, such as:
     - Structural hemoglobin variants
     - Sickle cell anemia

6. Membranopathies
   - Evaluate causes consistent with observed morphology, such as:
     - Congenital spherocytic anemia (CSA)
     - Hereditary spherocytosis
     - Other spherocytosis

7. Enzymopathies
   - Evaluate potential causes, such as:
     - G6PD deficiency
     - Pyruvate kinase (PK) deficiency

8. PNH
   - Order high-sensitivity flow cytometry (HSFC)

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**Abbreviations and Notes:**
- AT = antithrombin.
- BMT = bone marrow transplant.
- CAT = chemotherapeutic agents.
- CDT = carbohydrate-deficient transferrin.
- G6PD = glucose-6-phosphate dehydrogenase.
- HELLP = hemolysis, elevated liver enzymes, low platelet count.
- HUS = hemolytic uremic syndrome.
- LDH = lactate dehydrogenase.
- MCV = mean corpuscular volume.
- MDS = myelodysplastic syndrome.
- NSAIDs = nonsteroidal anti-inflammatory drugs.
- PNH = paroxysmal nocturnal hemoglobinuria.
- PCT = procalcitonin.
- PT = prothrombin time.
- WBC = white blood cell count.

**Additional Notes:**
- Be sure to consider the patient’s age and medical history.
- Hemolytic anemias are often associated with fever, jaundice, and splenomegaly.
- The differential diagnosis for anemia should consider both hematologic and nonhematologic causes.

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**Special Cases:**
- PNH can occur concurrently with bone marrow failure, including aplastic anemia, myelodysplasia, and paroxysmal nocturnal hemoglobinuria.
- SCD may occur with aplastic anemia and leukemia because of the common genetic abnormality in hematopoiesis.
- Aplastic anemia may be more common in patients with chronic infections or autoimmune diseases.

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**References:**
- See Greenberg et al. (2017) for a comprehensive review of anemia evaluation and management.
Markers of hemolysis in different hemolytic diseases

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<tr>
<th>Laboratory parameters</th>
<th>PNH</th>
<th>AIHA</th>
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<tbody>
<tr>
<td>Coombs test (DAT)</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>PNH cells (flow cytometry)</td>
<td>Present</td>
<td>Absent</td>
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<tr>
<td>LDH</td>
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<tr>
<td>Haptoglobin</td>
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<tr>
<td>Indirect bilirubin</td>
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<tr>
<td>Reticulocyte count</td>
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<tr>
<td>RBC morphology</td>
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<tr>
<td>Hemoglobinuria</td>
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<tr>
<th></th>
<th>PNH</th>
<th>AIHA</th>
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<th>TMA</th>
<th>Intravascular devices</th>
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Adapted from Barcelo-Busi 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, —/-/—/— indicates 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.

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:

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CA/SOL-P/0081