# Approaches in Hematology

## Hematology Made Easy

## Approach & ROAD map to hemolytic anemias

*DD of Hemolytic anemia:* Hemolysis could be either:

- Extravascular (RBCs destruction occurs in the spleen, so there is SPLENOMEGALY).

Or

- Intravascular (RBCs destruction occurs in the vessels (circulation), So No Splenomegaly

### Extravascular Hemolysis

- RBCs membrane defect (inherited).
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
  - Hereditary stomatocytosis
  - Hereditary pyropoikilocytosis
  - Hereditary xerocytosis

- Hemoglobinopathies (inherited)
  - Quantitative
    - Beta-thalassemia (major, intermedia and minor)
    - Alpha-thalassemias
  - Qualitative
    - Sickle cell anemia (Hb S)
    - Sickle hemoglobin C disease
    - Sickle beta thalassemia
    - Hemoglobin C disease
    - Hemoglobin D disease
    - Hemoglobin E disease

- autoimmune
  - Warm type AIHA

**Clues for Commonest causes:**

1) Thalassemias (Major & intermedia)
   - Autosomal recessive disease
   - Mongoloid features
   - Prominent maxilla
   - Repeated blood transfusions
   - Signs of iron overload

2) Sickle cell disease
   - Autosomal recessive disease
   - splenomegaly is present only in the early stage of the disease, later on, autosplenectomy occurs.
   - Recurrent Vaso-occlusive crises (abdominal pain, osteomyelitis, aseptic necrosis of the femoral head, stroke, acute chest syndrome)

3) Hereditary Spherocytosis
   - Autosomal dominant disease: strong family history
   - Jaundice related to infection.
   - History of Gall bladder stones

4) Autoimmune Hemolytic anemia (Warm type): Search for underlying disease
   - SLE as in females of Childbearing period (explore features of SLE)
   - Lymphoproliferative disorders
     - CLL inpatients ≥ 50 years (WBC's count must be high with predominant lymphocytes: absolute lymphocytic count ≥ 5000)+ Palpate Lymph nodes.
     - Non-Hodgkin's lymphoma at any age
       - There is no leukocytosis.
       - Palpate lymph nodes
       - ask about B symptoms (night fever, night sweat, weight loss)
     - Drugs: penicillin & cephalosporins

## Intravascular Hemolysis

- Inherited
  - G6PD deficiency anemia
  - Pyruvate kinase deficiency (hereditary non-spherocytic hemolytic anemia) (mixed intravascular & extravascular hemolysis)

- Immune
  - Autoimmune (cold AIHA)
  - Alloimmune (incompatible blood transfusion)
  - Drugs: penicillin, cephalosporins & methyldopa (immune & non-immune)

- Mechanical
  - Microangiopathic hemolytic anemia (MAHA) e g TTP, HUS and DIC, HELLP syndrome, malignant hypertension, scleroderma.
  - Mechanical hemolysis due to prosthetic valve
  - March hemoglobinuria (due to walking)

- Paroxysmal
  - Paroxysmal nocturnal hemoglobinuria
  - Paroxysmal cold hemoglobinuria

- Infections
  - Protozoal: Malaria & babesiosis
  - Viral: COVID-19 (reported), others
  - Bacterial: clostridium infection

- Toxic
  - Snake venom poisoning

- Systemic disease
  - Wilson's disease

**Clues for Commonest causes:**

1) G6PD deficiency
   - XL recessive disease
   - Attacks of hemolysis related to either:
     - Ingestion of fava beans

     Or

     - Drugs (oxidant agents): Sulfa, antimalarials, ciprofloxacin, dapson

     Or

     - Infections

2) Autoimmune hemolytic anemia (cold type) cold agglutinin disease: Search for underlying disease:

- Infections
  - Infectious mononucleosis
    - Sore throat
    - fever
  - Mycoplasma pneumonia
    - atypical pneumonia
    - unnoticed dry cough, fever
    - ± abdominal pain
    - ± diarrhea
    - ± erythema multiform
    - ± pericarditis
  - underlying lymphoproliferative disorders (as warm type of AIHA)

3) Paroxysmal cold hemoglobinuria (attacks of hemolysis occurs with exposure to cold)

4) Incompatible blood transfusions (Allo-immune hemolysis) features of acute hemolytic anemia that occurs either shortly after PRBCs transfusions or few days after transfusions: it could be:

- Immediate (fatal)
  - Severe hemolysis, dyspnea, acute kidney injury, bone pain

Or

- Delayed

5) Paroxysmal Nocturnal hemoglobinuria (PNH)
   - Hemolysis
   - ± thrombophilia
   - ± aplastic anemia
   - BM failure (occurs late)

6) Mechanical hemolysis in patients with prosthetic valves: must exclude other causes.

7) Micro-angiopathic hemolytic anemia (MAHA) that occurs in thrombotic microangiopathy (TMA) either
   - TTP (Thrombotic thrombocytopenic purpura): DX with ≥ 3 out of 5 criteria
     - MAHA
     - Thrombocytopenia
     - Renal impairment
     - Fever
     - confusion or stroke-like features
     - + fragmented RBCs (Schistocytes) in blood film (neurosigns + fever → point to TTP)
   - HUS (Hemolytic uremic syndrome)
     - MAHA

- Thrombocytopenia
- Renal insufficiency
- + fragmented RBCs (Schistocytes) in blood film.

❖ DIC

- Bad general condition (sepsis, shock, etc.)
- Cancer
- Advanced liver disease
- Bleeding from any site
- Multi-organ failure
- ↑ PT, ↑ PTT, ↑ INR, low pletelets, low Hb

8) Drugs (immune or non-immune mediated)
   - Penicillin
   - Cephalosporins
   - Alpha methyl dopa
   - Antibiotics
   - NSAIDs

9) Wilson's disease
   - Autosomal recessive disease
   - Acute liver failure or chronic liver cirrhosis
   - ± Neurological features (tremors, chorea, or ataxia ± dementia)
   - ± Hemolysis (intravascular hemolysis)
   - Sometimes complicated é AKI ± Kayser Fleischer rings (slit lamp exam)

## Focused History:

### Present history:

- If presenting symptom is jaundice or fatigue/dizziness/dyspnea
  Onset, course, duration, first attack or not, associations (color of urine, left flank pain), what increase, what decrease?!
- If attacks (think about Sickle cell anemia, G6PD, PNH, Paroxysmal cold hemoglobinuria)
  Precipitation of attacks:
  - drugs & fava beans → G6PD def
  - Infection → G6PD def, Sickle cell anemia, cold AIHA
    - All are precipitated by infections (e.g. Mycoplasma pnemoniae in cold AIHA, IMN and viral infections in other types)
  - Dark urine + hemolysis at night or early morning → PNH
  - Hemolysis preceded by blood transfusion (ABO incompatibility).

- Association
  - Recurrent severe abdominal pain, bone pain, osteomyelitis, inability to walk (aseptic necrosis of femoral head) → suspect Sickle cell anemia.

- Stroke, leg ulcers, acute pulmonary symptoms → suspect Sickle cell anemia.

- General symptoms:
  - Bleeding tendency, purpura, confusion, lateralizing signs, fever → suspect TTP.
  - Bleeding tendency, purpura, oliguria ± volume overload signs ± preceding history of diarrhea → suspect HUS
  - Weight loss + lumps → suspect lymphoma as an underlying cause of warm AIHA, in old age suspect CLL also.
  - Joint pain, photosensitivity, butterfly rash, discoid rash, oral ulcers, skin lesions, chest pain, frothy urine or oliguria/hematuria, confusions, fits → suspect SLE as an underlying cause of warm AIHA.
  - Skin changes (dark skin) + change in facial appearance (prominent maxilla), joint pain, dyspnea, hypogonadism features (impotence in males & amenorrhea in females in a patient with long-standing history of Jaundice + blood transfusion → suspect Thalassemia.
  - Associated tremors & abnormal movements → suspect Wilson.

## Past history

- Recurrent admission due to hemolytic anemia + abdominal pain ± bone problem ± stroke in young → suspect Sickle cell anemia.
- History of DVT/Pulmonary embolism, Budd Chiari syndrome, Portal vein thrombosis, cerebral venous thrombosis
  - In males: PNH, then Anti-phospholipid syndrome (APS) secondary to SLE → warm AIHA
  - In females: APS / SLE, then PNH
- History of recurrent frequent blood transfusion since childhood →
  - Thalassemia major → frequent
  - Thalassemia intermedia → less frequent
  - Sickle cell anemia → less frequent
  - G6PD def is less frequent.
  - Hereditary Spherocytosis → less frequent
- Operations: History of cholecystectomy due to gall stones → Hereditary spherocytosis, Sickle cell anemia.
- Orthopedic operations: Sickle cell anemia
- Drug history
  - Sulfa, antimalarial → G6PD deficiency
  - Antibiotics/NSAIDs → Drug induced hemolytic anemia.
  - Drugs → warm AIHA

## Family history

- Thalassemia & Sickle cell → could be present.
- Hereditary Spherocytosis → usually present
- G6PD def: family history in mother's family

## Gynecological history (females)

- Amenorrhea in chronic hemolytic anemia in pt with Mongoloid → pituitary insufficiency due to iron overload.
- History of Abortions: APS / SLE

## Focused exam:

### General examination

- Pallor & jaundice → all types.
- Prominent maxilla, depressed nasal bridge, frontal bossing → Thalassemia major, intermedia (less)
- Dark skin → iron overload
- Leg ulcers → sickle cell anemia
- LL edema in Thalassemia → suspect right-sided failure.
- Hemiplegia with Past history of stroke in young → Sickle cell anemia, PNH, APS
- DVT → PNH, AP
- Lymphadenopathy → Lymphoma & CLL with warm AIHA
- Butterfly rash, discoid rash → SLE + warm AIHA

### Local exam:

- If Splenomegaly → all Extravascular hemolysis
- If No Splenomegaly → confirm by U/ S first → if normal spleen → intravascular hemolysis causes + sickle cell anemia
- Hepatomegaly → Thalassemia

## Diagnostic workup for hemolytic anemias:

### A. Basic investigations

- CBC: look for low HgB, and normal MCV to prove anemia. Sometimes MCV is high due to reticulocytosis.

  - If low + hemolysis → Thalassemia
  - If associated neutrophilic leukocytosis with established hemolysis → reaction of BM to hemolysis.
  - If associated Lymphocytic leukocytosis in old age patients → suspect associated CLL or viral infection.
  - Platelets could be high as a reaction to hemolysis.

  - If bicytopenia (hemolytic anemia + thrombocytopenia)
    DD:
    - TTP/HUS/ DIC
    - Evans Syndrome (autoimmune hemolytic anemia + thrombocytopenia)

- SLE
- PNH

- Blood film: look for certain pictures of Hemolysis: polychromasia.
  - Fragmented RBC's (Schistocytes) → in TTP, HUS, DIC
  - Spherocytes → present in Hereditary Spherocytosis & AIHA (warm type Autoimmune hemolytic anemia)
  - Sickle-shaped cells → in Sickle cell anemia
  - Heinz bodies → in hemolytic attack of G6PD deficiency
  - LFTs → in all hemolytic anemias (High indirect bilirubin)
  - RFTs → creatinine could be high in certain hemolytic anemias.
    - Intravascular hemolysis particularly ABO incompatibility & Wilson disease → Acute kidney injury.
    - TTP/HUS
    - SLE with AIHA
    - DIC

- urine analysis should be done in all hemolytic anemias:
  - If hemoglobin ± hemosiderin → all cases of intravascular hemolysis.
  - If just urobilinogen → Extravascular hemolysis

- ESR: high if underlying SLE, lymphoma, CLL.

B. Specific investigations

- Retics: must be high ≥ 2.5 % to prove hemolysis.
- LDH: high in all types.
- Haptoglobin: significantly low in intravascular hemolysis

Extravascular causes:

- If SPLENOMEGALY ➞ Extravascular hemolysis (must confirm by US scan).
- If Mongoloid or prominent maxilla → HB electrophoresis
  - Major: high HgB A2
  - Intermedia: high HgB F
- If suspicious Hereditary Spherocytosis
  - Do Osmotic fragility test.
  - Most specific test: flow cytometry for the eosin-5′-maleimide (EMA) binding test
- If suspicious Sickle cell anemia
  - Sickling test or HB electrophoresis which is more accurate (HgB S)
- If suspicious Warm AIHA
  - Do Coomb's test.

- If suspicious underlying SLE
  - Do ANA, anti-ds DNA, C3 & C4
- If suspicious underlying CLL
  - Do blood film: smudge cell.
  - Flowcytometry: CD 5, 19, 23
- If suspicious underlying lymphoma
  - Do Excisional LN biopsy + staging by imaging + immunophenotyping.
- If the cause of unclear: do all such labs.
  - Coomb's test + HgB electrophoresis + osmotic fragility test for EMA binding test.

Intravascular causes:

- If suspected Cold AIHA
  - Coomb's test
- If suspected G6PD
  - During attack: blood film searching for Heinz bodies.
  - In between: G6PD enzyme assay
- If Suspected PNH
  - Do CD 55 & 59
- If suspected MAHA
  - blood film for Schistocytes
- If suspected DIC
  - Do PT, PTT, INR, CBC (low platelets), serum fibrinogen (low), FDPs (high)
- If suspected Wilson
  - Do serum ceruloplasmin.
  - Copper in 24 hours urine collection
  - Liver biopsy
- If suspected mechanical valve hemolysis.
  - do ECHO
- If cause is unclear
  - Do blood film, Coomb’s test.
  - CD55 & CD 59, G6PD assay
  - Exclude drug related hemolysis.
  - Exclude rare inherited hemolysis.
  - Exclude DIC
  - Wilson screen if compatible