HEMOLYTIC ANEMIA
HEMOLYTIC ANEMIA

Definition:
- Those anemias which result from an increase in RBC destruction coupled with increased erythropoiesis (i.e.: ability of Bone Marrow to respond to anemia is unimpaired.)

Classification:
- Congenital / Hereditary
- Acquired
INTRODUCTION

- Genetically Determined hematological disorders.
- Mediated through all the 3 modes of inheritance
  
  E.g. **Autosomal Recessive** - Thalassemia Major, Sickle Cell Anemia

  **Autosomal Dominant** - Hereditary Spherocytosis.

  **X-Link Recessive** - G 6 PD Deficiency.
CLASSIFICATION

Extrinsic Deficit

- Isoimmune
- Rh incompatibility
- Heteroimmune
- ABO incompatibility
- Autoimmune
- Infections & Toxins
Intrinsic Defects

- Membrane Defect
  Hereditary Spherocytosis

- Hb Defects
  Thalassemia
  Sickle cell anemia

- Enzyme Defects
  G 6 PD Deficiency
<table>
<thead>
<tr>
<th>INTRACORPUSCULAR DEFECTS (INTRINSIC)</th>
<th>EXTRACORPUSCULAR FACTORS (EXTRINSIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary</strong></td>
<td><strong>Familial Hemolytic Uremic Syndrome</strong></td>
</tr>
<tr>
<td>• Hemoglobinopathies</td>
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<tr>
<td>• Enzymopathies</td>
<td></td>
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<tr>
<td>• Membrane Cytoskeletal Defects</td>
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<tr>
<td><strong>Acquired</strong></td>
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<tr>
<td>• Paroxysmal Nocturnal Hemoglobinuria</td>
<td>• Mechanical Destruction [Microangiopathic]</td>
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<td></td>
<td>• Toxic Agents</td>
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<td></td>
<td>• Drugs</td>
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<td></td>
<td>• Infectious</td>
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<td>• Autoimmune</td>
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</tbody>
</table>
## Classification

### Intravascular Hemolysis
- PNH
- MAHA
- Transfusion reaction
- AIHA (cold & PCH)
- Enzymopathies with oxidative stress

### Extravascular Hemolysis
- Enzymopathies
- Hemoglobinopathies
- Membranopathies
- AIHA (warm)
GENERAL FEATURES OF HEMOLYTIC DISORDERS

General examination - Jaundice, pallor, bossing of skull
Systemic examination findings - Enlarged spleen
Hemoglobin - From normal to severely reduced
MCV - usually increased
Reticulocytes - increased
Bilirubin - increased [mostly unconjugated]
LDH - increased
LAB FINDINGS (COND..)

• Serum Haptoglobin & Hemopexin – reduced
• Urine urobilinogen - increased
• Blood film-polychromasia & Normoblast
• Bone marrow- Erythroid hyperplasia

In Intravascular hemolysis
• Serum Haemoglobin-increased
• Urine Hemosiderin & Haemoglobin -positive
POLYCHROMATIC CELLS
# Types of Hemoglobins at Various Stages

<table>
<thead>
<tr>
<th>Type</th>
<th>Hemoglobin</th>
<th>α</th>
<th>β</th>
<th>γ</th>
<th>δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic</td>
<td>Gower 1</td>
<td>ζ₂</td>
<td>ε₂</td>
<td></td>
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<tr>
<td></td>
<td>Gower 2</td>
<td>α₂</td>
<td>ε₂</td>
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<tr>
<td></td>
<td>Portland</td>
<td>ζ₂</td>
<td>γ₂</td>
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<tr>
<td>Fetal</td>
<td>Hemoglobin F</td>
<td>α₂</td>
<td>γ₂</td>
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<tr>
<td>Adult</td>
<td>Hemoglobin A</td>
<td>α₂</td>
<td>β₂</td>
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</tr>
<tr>
<td></td>
<td>Hemoglobin A₂</td>
<td>α₂</td>
<td>δ₂</td>
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</tbody>
</table>
CONTD..

• Hb A(α₂β₂) appears at ~1 month of fetal life but does not become the dominant hemoglobin until after birth, when Hb F levels start to decline.
• Hb A₂ (α₂δ₂) is a minor hemoglobin that appears shortly before birth and remains at a low level after birth.
• The final hemoglobin distribution pattern is not achieved until at least 6 month of age and sometimes later.
• The normal hemoglobin pattern is ≥95% Hb A, ≤3.5 Hb A₂, and <2.5% Hb F
THALASSEmia

- Autosomal Recessive Disorder
- Single Gene disorder
- Defect in globin chain synthesis of Hb
- Types
  - α Thalassemia
    - α chain is defective: incompatible with life
  - β Thalassemia
    - β⁺ thalassemia if β chain is absent
    - β⁺ thalassemia is β is partially produced
## Classification

<table>
<thead>
<tr>
<th>α – Thalassemia</th>
<th>β- Thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent carrier</td>
<td>Silent carrier</td>
</tr>
<tr>
<td>α- Thalassemia trait</td>
<td>Thalassemia trait</td>
</tr>
<tr>
<td>Hb H disease</td>
<td>Thalassemia intermedia</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>Thalassemia Major</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY

• Hb. consist of two pairs of amino acid chains α & β.
• Imbalance in the production of these peptide chains of globin leads to abnormal hemoglobinopathies
• Unpaired peptide chains in Hb. is precipitated on RBC membrane
• Premature destruction of RBC in bone-marrow and in peripheral circulation particularly in R-E system of spleen (Ineffective erythropoiesis)
• γ chain synthesis persist after fetal life postnatally also
PATHOPHYSIOLOGY

- Increased fetal HB. With its high affinity for oxygen
- leads to tissue hypoxia
- Stimulate erythropoietin secretion
- Leading to both medullary and extra medullary erythropoiesis
- Resulting in expansion of bone marrow space with characteristic hemolytic facies, pathological fractures of long bones, splenomegaly, and its related complications along with severe degree of Anemia
CLINICAL PROFILE OF THALASSEMIA MAJOR (HOMOZYGOUS)

• Age of onset – From 6 months onwards.

• Thalassemic Facies (Maxillary hypoplasia, flat nasal bridge, frontal bossing)

• Hepatosplenomegaly

• Greenish Brown Complexion (Due to pallor, hemosiderosis & Jaundice)

• Severe degree of persistent and progressive Anemia
CLINICAL FEATURES

• Age of onset – From 6 months onwards.
• Thalassemic Facies (Maxillary hyperplasia, flat nasal bridge, frontal bossing)
• Hepatosplenomegaly
• Greenish Brown Complexion (Due to pallor, hemosiderosis & Jaundice)
• Severe degree of persistent and progressive Anemia needs repeated blood transfusion
• Iron overload - endocrine dysfunction, cardiac & liver dysfunction
• Growth, Development & SMR delayed
PERIPHERAL BLOOD SMEAR OF THALASSEMIA MAJOR
CONT..

• Microcytic hypochromic anemia showing severe degree of anisocytosis and poikilocytosis.
• Target cells, Pencil cells, stomatocytes, helmet cells.
• Immature RBC’s like normoblasts.
• Hb & HCT is extremely low with Reticulocytosis.
• Hb electrophoresis demonstrating Fetal Hb. (α2 Υ2 ) is confirmatory of diagnosis.-  **HbF - 90-96 %, HbA₂ - 3.5% - 5.5% & HbA – 0%**.
• Mutation in beta-globin chain expression.
THALASSAEMIA MAJOR: X – RAY SKULL

Showing Hair on end appearance due to increased diploic space in the skull bones
OTHER TYPES OF THALASSEMIA

Beta thalassemia intermedia (double heterozygous)

- Later age of onset – > 2yrs. Mod degree of Anemia
- Hepatosplenomegaly

Hb electro: -HbF-20-100%, HbA2 -3.5-5.5% & HbA -0-30%
OTHER TYPES OF THALASSEMIA

Beta thalassemia minor
( heterozygous)
• Almost normal
• PS of iron deficiency anemia
Hb electro :HbA2 3.5-7.5%
HbA 80-95%,HbF 1-5%
MANAGEMENT OF THALASSEMIA MAJOR

- Anemia correction - Packed red cell transfusions
- Excess iron removal - chelation therapy
- Management of transfusion transmitted infections
- Management of cardiac and endocrine complications - pituitary, thyroid, parathyroid and gonads
- Treatment of hypersplenism - splenectomy
- Treatment of Osteopenia, leg ulcers & gall stones

Curative treatment – stem cell transplantation
Prevention - Prenatal diagnosis & Genetic counseling
TRANSFUSION REGIMENS IN THALASSEMIA

- PALLIATIVE TRANSFUSION REGIMEN – Increase Hb to 8.5 gm.%
- MODERATE TRANSFUSION – Increase Hb to 9-10.5 gm.%
- HYPERTRANSFUSION REGIMEN - Increase Hb to 10 gm.%
- SUPERTRANSFUSION - Increase Hb to 12gm%
- NEOCYTE TRANSFUSION - To make requirement of transfusion interval longer.
CHELATION THERAPY

Iron overload – Excess GI absorption, Lack of mechanism for excretion of Iron from body & C/C red cell transfusion

Chelation to be started when Sr. Ferritin > 1000 ng/ml or liver iron >2500 micrograms/gm of dry weight.

Drugs used -

• Desferrioxamine – (parenteral) remove extracellular iron
• Deferiprone – (oral) both intra and extra cellular iron
• Deferasirox – (oral) both intra and extra cellular iron
SICKLE CELL DISEASE

Mutation of beta globin-6 Glutamate → Val.
Deoxy HbS (polymerised)

→ Ca^{2+} influx, K^{+} leakage

→ Stiff, viscous sickle cell

→ venocclusion

→ microinfarctions, ischemic pains

→ autoinfarction of spleen

→ decreased RBC survival

→ anemia, jaundice, gallstones, leg ulcers
CONT..

- The disease can manifest only if Homozygous.
- Heterozygous individuals - Trait or Carrier state.
- Generally Asymptomatic. Only under stress situation manifest clinically in the form of crises. E.g. Hypoxia/Sepsis

• Hemoglobin electrophoresis
  - HbS >80%, HbF -1-20%, HbA2 -2- 4.5%
• Sickling test - Positive
CRISIS

• Aplastic crisis - Severe Anemia of BM suppression due to Parvo virus B19
• Hyperhemolytic crisis - Severe hemolysis in peripheral circulation and R-E system
• Vaso-occlusive crisis - Hand-Foot disease, avascular necrosis of bones, acute chest syndrome, stroke, priapism, painful abdominal crisis
• Sequestration crisis - Shock because of the pooling of the blood in R-E system: Spleen and Liver
HEREDITARY SPHEROCYTOSIS PATHOPHYSIOLOGY

• Sodium pump failure because of the membrane defect due to spectrin & ankyrin deficiency resulting in

  Influx of sodium and water

  Loss of biconcave shape

  Spherical shape (Microspherocytosis)
• Clinical Triad - Anaemia, Jaundice, Splenomegaly
• Complications - Hemolytic & aplastic crisis, gall stones
• PS - Spherocytosis
• Osmotic fragility increased
• Treatment - Splenectomy
• Screen family members
G-6 P D DEFICIENCY

Generally asymptomatic
Manifests only when exposed to Oxidant Drugs
Intra-vascular Hemolysis
• Hemoglobinuria
• Heinz Bodies & blister cells in Peripheral smear
• G6PD estimation diagnostic
**KNOWN OXIDANT INSULTS**

<table>
<thead>
<tr>
<th>Antibacterials</th>
<th>Others</th>
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</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Phenacetin</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Vitamin K analogs</td>
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<tr>
<td>Nalidixic acid</td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Probenecid</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Phenazopyridine</td>
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<tr>
<td><strong>Antimalarials</strong></td>
<td><strong>CHEMICALS</strong></td>
</tr>
<tr>
<td>Primaquine</td>
<td>Phenyldiazepine</td>
</tr>
<tr>
<td>Pamaquine</td>
<td>Benzene</td>
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<tr>
<td>Chloroquine</td>
<td>Naphthalene</td>
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<tr>
<td>Quinacrine</td>
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**ILLNESS**

- Diabetic acidosis
- Hepatitis
- Sepsis
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

- Acquired chronic H.A
- Persistent intra vascular hemolysis
- Pancytopenia
- Lab: Hemoglobinuria, hemosiderinuria, increased LDH, bilirubin
- Risk of venous thrombosis
- C/F – Hemoglobinuria during night
- P.S – Polychromatophilia, normoblasts
- B.M – Normoblastic hyperplasia
- Differential diagnosis- flow cytometry CD59-, CD55-RBC, WBC
  - Hams’ acidified serum test
• Result from RBC destruction due to RBC autoantibodies
AUTOIMMUNE HEMOLYTIC ANEMIA- TYPES

Primary AIHA
• Warm AI hemolysis: Antibody binds at 37degree C(IgG)
• Cold AI Hemolysis: Antibody binds at 4 degree C(IgM & complement)
• Paroxysmal cold Hemoglobinuria (IgG & compliment)

Secondary AIHA
• Drugs, infections, primary immunodeficiency, malignancy, autoimmune disorders
TO CONCLUDE

Hemolytic anemia recognised by clinical picture - history & physical exam, lab test to confirm hemolysis and peripheral smear to guide further tests.

**Spherocytes** - AIHA, hereditary spherocytosis

**Schistocytes** - HUS, TTP or DIC & heart valve hemolysis

• **Blister Cells** - oxidative damage - G6PD

• **Sickle cells** - sickle cell anemia

• **Heinz bodies** - G6PD deficiency
THANK YOU