Red Blood Cells Disorders

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Objectives

1. Quick revision of the physiology of normal haematopoiesis.
2. Define the term anaemia, its pathophysiology and diagnostic approach.
3. List the common causes and symptoms of iron-deficiency anaemia. State how iron deficiency anaemia may be treated.
4. Define the terms megaloblastic anaemia and anaemia of chronic diseases. In each case discuss their causes, consequences and management.
5. Define the terms aplastic anaemia and myelodysplastic syndrome. In each case an overview of clinical features, diagnosis and treatment is outlined.
6. Define the term haemolytic anaemia including thalassaemia and sickle cell anaemia, and discuss the clinical features, diagnosis and treatment.
Hierarchical model of lymphohematopoiesis. RBC-red blood cell; NK cell-natural killer cell
Erythroid maturation sequence: As proliferation parameters (i.e., rates of DNA and RNA synthesis) and cell size decrease, accumulation of erythroid-specific proteins (i.e., heme and globin) increases, and the cells adapt their characteristic morphology.
Hematopoietic Cytokines

1- Stem cell Factor.

2- IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9.

3- G-CSF.

4- GM-CSF.

5- Erythropoietin.

6- Thrombopoietin.

7- Others

*Glycoproteins that act on cell surface receptors. Initiate complex Second messenger and transcriptional and post-transcriptional regulation.
Anemia

DEFINITION:
Reduction in the number of erythrocytes, or hemoglobin concentration, or packed cell volume (PCV) value below lower normal limit for age and sex.

*Anemia is not a disease, it is rather a manifestation of different diseases.*
# Normal Values for Red Blood Cell Measurements

<table>
<thead>
<tr>
<th>Measure</th>
<th>Units</th>
<th>Normal Range (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>g/dL</td>
<td>Adult Males: 13 – 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult Females: 12 – 16</td>
</tr>
<tr>
<td>Hematocrit (PCV)</td>
<td>%</td>
<td>Adult Males: 40 – 54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult Females: 37 – 47</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>X 10¹²/ L</td>
<td>Males: 4.5 – 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females: 4 – 5.4</td>
</tr>
<tr>
<td>Mean cell volume (MCV)</td>
<td>fL</td>
<td>78 – 98</td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration (MCHC)</td>
<td>g/dL</td>
<td>30 – 34</td>
</tr>
<tr>
<td>Mean cell hemoglobin (MCH)</td>
<td>pg</td>
<td>30 – 36</td>
</tr>
<tr>
<td>Reticulocyte count (absolute number)</td>
<td>/ μL of blood</td>
<td>40,000 - 100,000</td>
</tr>
<tr>
<td>Reticulocyte percentage</td>
<td>% of RBC</td>
<td>0.5 – 1.5</td>
</tr>
</tbody>
</table>
Normal Red Blood Cell

The circulating erythrocyte under normal conditions has an average lifespan of approximately 120 days. It is a non-nucleated, non-dividing cell in which more than 90% of the protein content is the oxygen-carrying molecule, hemoglobin. The erythrocyte's sole responsibility is to deliver oxygen to the tissues of the body. Thus, the primary consequence of anemia is tissue hypoxia. Erythropoiesis is driven by a feedback loop. Oxygen-sensing cells in the area of the juxtaglomerular apparatus of the kidney respond to local tissue hypoxia by increasing production of erythropoietin (EPO), which is the primary regulatory hormone for erythropoiesis.
Etiology Of Anemia

1- Decreased Production of RBC/Hemoglobin (Hypoproliferative Anemia).

2- Increased Destruction of RBC (Hemolysis).

3- Blood Loss.

4- Sequestration.
Effects of Anemia

- **Physiological:**
  - Due to tissue hypoxia.
  - Increased 2,3 DPG in RBC (helps to deliver more oxygen to tissues).
  - Increased Cardiac Output (heart rate and stroke volume).
  - Redistribution of Blood Flow to vital organs.

- **Clinical:**
  - Pallor of the skin and mucous membranes.
  - Easy Fatigability due to muscle hypoxia.
  - Cardiovascular: dizziness, SOB, worsening of IHD and HF.
  - Loss of Concentration due to brain hypoxia.
  - Other effects.
Approach To Anemia

1. **History**

- Bleeding source specially GI and genital.
- Drugs e.g. Aspirin, NSAIDs, sulfa drugs, chloramphenicol etc...
- Family history of anemia, blood transfusion and ethnic background.
- Diet.
- Chronic diarrhoea.
- Recent pregnancy.
- Weight loss and anorexia.

**Symptoms**

- **General**: fatigue, malaise, weakness.
- **CVS**: palpitations, syncope, dyspnea.
- **Neurological**: headache, vertigo, tinnitus, numbness
Approach To Anemia

2. Physical Examination

- CVS: tachycardia, systolic flow murmur, wide pulse pressure, evidence of CHF.
- Pallor: mucous membranes, conjunctiva (Hb < 9g/dl), skin creases (Hb < 7g/dl).
- Splenomegaly; seen in different hematological and non hematological conditions.
- Lymphadenopathy, bleeding spots.
- Rectal (occult blood).

Others
- Koilonychia (spoon-shaped nails) and Glossitis as in iron deficiency anemia,
- Neurological findings as in pernicious anemia and vitamin B6 deficiency.
- Jaundice as in hemolytic anemia

3. Complete Blood Counts and Blood Film

- Hemoglobin level, WBC count and differential, platelet count, blood film morphology, reticulocyte count and percentage, RBC indices.
Diagnosis of Anemia

ANEMIA

Reticulocyte Count

Not Elevated

MCV

LOW

- Iron deficiency (severe)
- Anemia of chronic disease (some cases)
- Thalassemia trait (retic. count may be elevated)
- Sideroblastic anemias (some cases)
- Lead poisoning (rare in adults)

NORMAL

- Cobalamin (vit.B12) deficiency
- Folate deficiency
- Treatment with drugs that interfere with DNA synthesis and cell division
- Prior cancer chemotherapy
- Myelodysplasia (some cases)
- Hypothyroidism
- Liver disease

HIGH

Elevated

Hemolysis or Blood Loss

No symptoms or signs of blood loss

Hemolysis

Blood Loss

Acquired

- Immune Hemolysis
  - Autoimmune
  - Drug-induced
  - Alloimmune
  - Traumatic (microangiopathic and macroangiopathic) Hemolysis
  - TTP/HUS/HELLP
  - DIC
  - Vasculitis (rare cause)
  - Eclampsia
  - Malignant hypertension
  - Prosthetic heart valves
  - Arterial grafts
  - Hypersplenism
  - Membrane abnormalities
  - Acanthocytes (spur cells)
  - Echinocytes (burr cells)
  - Paroxysmal nocturnal hemoglobinuria
  - Thermal injury (burns)

- Infection
  - Malaria
  - babesiosis
  - Bartonellosis
  - Clostridia toxin
  - Osmotic damage
  - Fresh water drowning

Inherited/Congenital

- RBC Membranopathies
  - Spherocytosis
  - Elliptocytosis
  - Pyropoikilocytosis
  - Stomatocytosis

- RBC Enzymopathies
  - G6PD deficiency
  - Pyruvate kinase deficiency
  - Other rarer deficiencies of enzymes of Embden Meyerhof pathway, Hexose Monophosphate Shunt, or nucleotide metabolism

- Hemoglobinopathies
  - Thalassemias
  - Hemoglobins S, C, D, E
  - Unstable hemoglobins
  - Other rarer hemoglobinopathies
### CLINICAL APPROACH TO ANEMIA (continue)

#### Low or Normal Reticulocytes

<table>
<thead>
<tr>
<th>Hypochromic Microcytic (mean red cell volume MCV &lt; 76)</th>
<th>High Reticulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Iron deficiency</td>
<td>• Treated iron deficiency</td>
</tr>
<tr>
<td>• Thalassemia minor</td>
<td>• Thalassemia major</td>
</tr>
<tr>
<td>• Lead poisoning</td>
<td></td>
</tr>
<tr>
<td>• Sideroblastic anemia</td>
<td></td>
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<tr>
<td>• Chronic disease</td>
<td></td>
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<tr>
<td>• Liver disease</td>
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</table>

<table>
<thead>
<tr>
<th>Normochromic Normocytic (MCV 76 – 96 )</th>
<th></th>
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<tbody>
<tr>
<td>• Chronic disease</td>
<td>• Hemolytic anemia</td>
</tr>
<tr>
<td>• Uremia</td>
<td>• Post hemorrhagic anemia</td>
</tr>
<tr>
<td>• Endocrine disorders (hypo/hyperthyroid, addison’s)</td>
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<tr>
<td>• Connective tissue diseases</td>
<td></td>
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<tr>
<td>• Primary bone marrow abnormalities</td>
<td></td>
</tr>
<tr>
<td>• Myelodysplasia</td>
<td></td>
</tr>
<tr>
<td>• Marrow Infiltration (leukemia, myeloma, infection)</td>
<td></td>
</tr>
<tr>
<td>• Myelofibrosis</td>
<td>• Aplasia</td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td></td>
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<tr>
<td>• Hypoplastic marrow, aplasia</td>
<td></td>
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<tr>
<td>• Liver disease</td>
<td></td>
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<tr>
<td>• Alcohol</td>
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</table>

<table>
<thead>
<tr>
<th>Macrocytic/Megaloblastic (MCV &gt; 96 )</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Megaloblastic • low vit B12</td>
<td>• Treated vit B12 or folate deficiency</td>
</tr>
<tr>
<td>• Drugs (MTX, cyclophosphamide, arsenic)</td>
<td></td>
</tr>
<tr>
<td>Macrocytic</td>
<td></td>
</tr>
<tr>
<td>• Hypothyroidism</td>
<td></td>
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</table>
# Red Blood Cell Morphology as a Clue to the Diagnosis of Anemias

## RBC Morphology

<table>
<thead>
<tr>
<th><strong>RBC Morphology</strong></th>
<th><strong>Representative Causes of Anemia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcytosis</td>
<td>Iron deficiency, anemia of chronic disease, thalassemia, and (rarely) lead poisoning, vitamin B6 deficiency, or hereditary sideroblastic anemias</td>
</tr>
<tr>
<td>Macrocytosis</td>
<td>Polychromatophilia (reticulocytosis), vitamin B12 (cobalamin) or folate deficiency, myelodysplasia, use of drugs that inhibit DNA synthesis</td>
</tr>
<tr>
<td>Target cells</td>
<td>Thalassemia, hemoglobins C, D, E, and S, liver disease, abetalipoproteinemia</td>
</tr>
<tr>
<td>Microspherocytes</td>
<td>Autoimmune hemolytic anemia, alloimmune hemolysis, hereditary spherocytosis, some cases of Heinz body hemolytic anemias</td>
</tr>
<tr>
<td>Schistocytes and fragmented RBCs</td>
<td>Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, vasculitis, malignant hypertension, eclampsia, traumatic hemolysis due to prosthetic heart valve or damaged vascular graft, thermal injury (burns), post-splenectomy</td>
</tr>
<tr>
<td>Teardrop cells</td>
<td>Myelofibrosis, myelophthisis (bone marrow infiltration by neoplastic cells)</td>
</tr>
<tr>
<td>Sickle cells</td>
<td>Sickle cells Hemoglobin SS, SC.</td>
</tr>
<tr>
<td>Basophilic stippling</td>
<td>Hemolysis, lead poisoning, thalassemia</td>
</tr>
<tr>
<td>Bite&quot; cells or &quot;blister&quot;cells</td>
<td>Glucose-6-phosphate dehydrogenase deficiency, other oxidant-induced &quot;hemolysis, unstable hemoglobins</td>
</tr>
</tbody>
</table>
Approach To Anemia (continue)

Other Investigations are guided by the clinical impression after the initial evaluation.

1-Iron Studies.
2-Measurement of vitamin B12 and Folate serum levels.
3-Bone Marrow Aspirate and Biopsy.
4-Coomb's Test.
5-Osmotic Fragility test.
6-Hemoglobin Electrophoresis.
7-RBC enzyme studies.
8-Chromosomal studies, Molecular studies.
9-Other studies.
Normal Blood Film
Reticulocytes
Tear Drop Cells
Basophilic Stippling
Macrocytes and Hypersegmented Neutrophil
Hypochromia and Microcytosis
Fragmented RBC
Bone marrow iron stores

- Normal
- Moderately increased
- Severely increased
Aplastic Bone Marrow Biopsy
Megaloblastic Bone Marrow
Iron Deficiency Anemia

**Iron Metabolism:**

**IRON INTAKE (Dietary)**
- “average” adult diet = 10-20 mg Fe/day
- absorption = 5-10% (0.5-2 mg/day)
- Fe absorption increases with
  - increased erythropoiesis e.g. pregnancy
  - anemia
  - Fe depletion
- males have a positive Fe balance
- menstruating females have a negative Fe balance

**PHYSIOLOGIC CAUSES OF INCREASED IRON REQUIREMENTS**
- infancy-growth spurt 2x basal need
- puberty-growth spurt, menarche 3x basal need
- pregnancy 4x basal need
- blood donation 4x basal need
  - 500 mL blood = 250 mg Fe

**IRON ABSORPTION**
- occurs in duodenum mainly.
**IRON TRANSPORT**

- Majority of non-heme Fe in plasma is bound to a beta-globulin called transferrin
- Transferrin
  - carries Fe from mucosal cell to RBC precursors in marrow.
  - carries Fe from storage pool in hepatocytes and macrophages to RBC precursors in marrow.

**IRON STORAGE**

- Fe is stored in two forms: ferritin and hemosiderin.
- Ferritin
  - ferric Fe complexed to a protein called apoferritin.
  - hepatocytes are the main site of ferritin storage.
  - minute quantities are present in plasma in equilibrium with the intracellular ferritin.
- Hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is the main source of hemosiderin.
IRON METABOLISM

The diagram illustrates the iron metabolism cycle, showing the following steps:
- **Intestine**: Iron is absorbed from the diet.
- **Liver**: Processes iron for storage or release.
- **Macrophages**: Recycles iron from old red blood cells.
- **Bone marrow erythroid precursors**: Uses iron for new red blood cell formation.
- **Erythrocytes**: Release iron into the circulation.

The cycle is completed through the transport of iron by the complex Fe₂-Tf.
Causes of IDA

**PHYSIOLOGIC CAUSES**
- Increased need for iron in the body.
- Infancy.
- Adolescence, menstruation.
- Pregnancy, lactation.

**PATHOLOGIC CAUSES**
- In adult males and post-menopausal females, Fe deficiency is usually related to chronic blood loss mainly from GIT.
- Dietary deficiencies (rarely the only etiology)
  - cow’s milk (infant diet)
  - poor dietary iron intake (elderly)
- Absorption imbalances
  - post-gastrectomy
  - malabsorption
- Hemorrhage
  - obvious causes - menorrhagia
  - occult - peptic ulcer disease, aspirin, GI tract cancer, ankylostoma.
- Intravascular hemolysis; iron will be lost in the urine.
CLINICAL PRESENTATION of IDA

- Iron deficiency may cause fatigue before clinical anemia develops
- Brittle hair
- Dry skin
- Dysphagia (esophageal web, Plummer-Vinson ring)
- Nail changes
  - brittle
  - koilonychia
- Glossitis
- Angular stomatitis
- Pica (appetite for bizarre substances e.g. ice, paint, clay)
IRON INDICES

* Bone marrow biopsy is the gold standard test for iron stores.

- **Serum ferritin**
  - Single most important blood test for iron stores.
  - Falsely elevated in inflammatory disease, liver disease (from necrotic hepatocytes), neoplasm and hyperthyroidism.

- **Serum iron**
  - A measure of Fe present in blood.
  - Virtually all serum iron is bound to transferrin.
  - Only a trace of serum Fe is free or complexed in ferritin.

- **Total iron binding capacity (TIBC)**
  - Measure of total amount of transferrin present in blood.
  - Normally, one third of the TIBC is saturated with Fe, the remainder is unsaturated.

- **Transferrin Saturation**
  - Serum Fe divided by TIBC, expressed as a proportion or a percentage.
Diagnosis of IDA

*Laboratory Investigations*

1- *Peripheral blood film*
   - Hypochromic microcytic RBC.
   - Pencil forms.
   - Target cells (thin).
   - Platelet count may be elevated.

2- *Serum Iron Studies*
   - low s.iron, high TIBC, low Fe saturation
   - S. ferritin < 20 ug/l is diagnostic of iron deficiency anemia, Iron deficiency anemia unlikely if ferritin > 100 ug/l.
   - Increased plasma level of soluble transferrin receptors.

3- *Hemoglobin Electrophoresis* decreased Hb A2 percentage.

4- *Bone marrow study*  *(Needed in difficult cases)*
   - Predominence of intermediate and late erythroblasts.
   - Micronormoblastic maturation of erythroid precursors.
   - Fe stain (Prussian blue) shows decreased iron in macrophages.
   - Decreased sideroblasts.
## Differential Diagnosis OF IDA

<table>
<thead>
<tr>
<th></th>
<th>S.Ferritin</th>
<th>Serum iron</th>
<th>TIBC</th>
<th>%Saturation</th>
<th>Hb A2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>L</td>
<td>L</td>
<td>H</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>H/N</td>
<td>L/N</td>
<td>L/N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Sideroblastic anemia</td>
<td>H</td>
<td>H</td>
<td>N</td>
<td>H</td>
<td>N</td>
</tr>
<tr>
<td>Thalassemia minor</td>
<td>H/N</td>
<td>H/N</td>
<td>L/N</td>
<td>-</td>
<td>H</td>
</tr>
</tbody>
</table>
Treatment of IDA

1- **TREAT THE UNDERLYING CAUSE**: to control the site of blood loss, correct malabsorption, improve oral iron intake etc…

2- **IRON REPLACEMENT**
- Different preparations available: tablets, syrup, parenteral
- Dose: ferrous sulphate 325 mg PO TID or ferrous gluconate 300 mg PO TID until anemia corrects and then for 3 months after to replenish the stores.
- Reticulocytes begin to increase after one week indicating response.
- Ensure that the hemoglobin returns completely to normal.
- If serum ferritin returns normal discontinue iron therapy.
- Treatment of iron deficiency anemia is made somewhat difficult by the frequent induction of nausea, dyspepsia, constipation, and diarrhea by oral iron preparations.
- Blood is given for severely symptomatic anemia.
- In the rare patient who cannot tolerate or cannot absorb iron from the gastrointestinal tract and in individuals who require large iron boluses to compensate for chronic blood loss, parenteral iron is available as an iron-dextran complex (Imferon) and iron sorbitol; they should be used with caution because of the threat of acute anaphylaxis and subacute (arthralgias, myalgias, and adenopathy) side effects.
Treatment of IDA

**ANEMIA REFRACTORY TO ORAL IRON**

- **Medication Problem:**
  - Poor preparation (e.g. expired).
  - Drug interactions.

- **Patient Problem:**
  - Poor compliance.
  - Bleeding continues.
  - Malabsorption (rare).

- **Physician Problem:**
  - Misdiagnosis.
Megaloblastic Anemias

**DEFINITION:**

Megaloblastic anemias are caused by various defects in **DNA synthesis** that lead to a common set of hematologic abnormalities of **bone marrow and peripheral blood cells**. The term **megaloblastic** refers to a **morphologic abnormality (mainly affecting the size and morphology) of the cell and its nucleus**. The erythrocytic, granulocytic, and megakaryocytic cell lines are all involved, and pancytopenia may result.
Causes of Megaloblastic Anemia

I. Cobalamin (vit B12) deficiency
   A. Decreased ingestion: vegetarians.
   B. Impaired absorption: small intestinal disease.
   C. Impaired utilization.

II. Folate deficiency
   A. Decreased ingestion: prolonged parenteral feeding, alcoholism.
   B. Impaired absorption: small intestinal disease.
   C. Impaired utilization: drug induced eg; sulfa drugs, methotrexate, phenytoin…
   D. Increased requirement: pregnancy, hemolysis.
   E. Increased loss: through urine.

III. Drugs — metabolic inhibitors

IV. Miscellaneous
   A. Inborn errors
   B. Unexplained disorders
Cobalamine Metabolism

- Cobalamine is an animal product. Daily need = 1 microgram
- Under normal conditions of gastric acidity, dietary cobalamin enters the duodenum bound to R protein. Additional cobalamin bound to R protein enters the duodenum after secretion into bile by the liver (the only significant route by which cobalamin is lost from the body). Pancreatic proteases partially degrade salivary and biliary R protein–cobalamin complexes in the jejunum; cobalamin is bound to intrinsic factor only after this process occurs. The intrinsic factor–cobalamin complex remains intact until it reaches the distal end of the ileum, where it binds with high affinity to specific receptors located on ileal mucosal cells. Cobalamin then enters these cells and reaches the portal plasma, which contains three cobalamin binding proteins known as transcobalamin I, II, and III).
Folate Metabolism

- Folate is widely distributed in plants and in products of animal origin; green vegetables are particularly rich sources of folate. Daily need = 50 microgram.

- Folates in natural foods are conjugated to chains of polyglutamic acid. Enzymes in the lumen of the small intestine convert the polyglutamate forms of folate to the monoglutamate and diglutamate forms, which are readily absorbed in the proximal portion of the jejunum. Most of the folate in plasma is present as 5-methyltetrahydrofolate in the monoglutamate form. The majority is loosely bound to albumin, from which it is readily taken up by the high-affinity folate receptors present on cells throughout the body. Once it enters the cell, 5-methyltetrahydrofolate must be converted to tetrahydrofolate by the cobalamin-dependent enzyme methionine synthase before it can be converted to the polyglutamate form and take part in the other folate-dependent enzymatic reactions. In addition to being secreted into bile and reabsorbed in the small intestine, folates are also degraded and excreted in the urine.
Folate and Cobalamine metabolism

CH$_3$-Tetrahydrofolate  $ightarrow$ Methyl-Cbl  $ightarrow$ Tetrahydrofolate

Methyl-Cbl  $ightarrow$ Synthase  $ightarrow$ Homocysteine

CH$_3$-S-C-C-C-COOH  $ightarrow$ Methionine
Clinical Manifestations of Megaloblastic Anemia

1. Symptoms of slowly progressive anaemia
2. Jaundice (Cobalamin deficiency).
3. Glossitis
4. Stomatitis
5. Gastrointestinal symptoms
6. Orthostatic hypotension
7. Weight loss
8. Neuropsychiatric: in Cobalamin deficiency
   - Paresthesia, Abnormal gait, Memory loss.
   - Disorientation, Decreased or Increased reflexes, Romberg's sign.
   - Spasticity, Babinski's sign, Psychosis, Slow Mentation.
Laboratory Investigations

1- Complete Blood Count & Blood Film:
   Macrocytosis (increased MCV), Neutropenia, Thrombocytopenia, Neutrophil hypersegmentation, Reticulocytopenia

2- Bone Marrow Aspirate & Biopsy:
   Hypercellular, Megaloblastic morphology, Giant bands & metamyelocytes.

3- Indirect Hyperbilirubinemia, elevated s.LDH.

4- Serum cobalamin: in cobalamine deficiency (normal, 200–900 pg/mL).

5- Serum folate: in folate deficiency (normal, 2.5–20 ng/mL).

6- Schilling Test for diagnosing the cause of Cobalamine malabsorption.

7- Gastric biopsy for pernicious anemia (cobalamine deficiency) and/or Small Intestinal Biopsy for malabsorption.

8- Anti-Intrinsic factor Ab & Anti-Parietal cell Ab in Pernicious anemia (Cobalamine deficiency).

9- Elevated serum Methylmalonic acid in Cobalamine deficiency.
PERNICIOUS ANEMIA

The most common cause of cobalamin malabsorption is pernicious anemia, a disease of unknown origin in which the fundamental defect is atrophy of the gastric (parietal cell) oxyntic mucosa eventually leading to the absence of IF and HCl secretion. Because cobalamin is only absorbed by binding to IF and uptake by ileal IF-cobalamin receptors, the net consequence is severe cobalamin malabsorption leading to cobalamin deficiency.

There is a significant association of pernicious anemia with other autoimmune diseases. There is a positive family history for about 30% of patients, among whom the risk of familial pernicious anemia is 20 times as high as in the general population. The histologic appearance of the gastric mucosa (infiltration with plasma cells and lymphocytes) is also strongly reminiscent of autoimmune-type lesions. There is also a high incidence of anti-parietal cell IgG antibodies in the serum of 90% of patients with pernicious anemia.
Treatment of Megaloblastic Anemia

**Cobalamine Deficiency:**

Hydroxycobalamine 1 mg i.m. daily for 10 days, then once every one month for life. Iron is added for slow response. Hypokalemia may develop during therapy. Reticulocytosis at day 7 will indicate response.

Blood is given for severly symptomatic patients.

**Folate Deficiency:**

Oral Folic acid 5 mg/day for 3 weeks then weekly as maintenance.
Anemia of Chronic Disease

Etiology

- Infections, cancer, endocrine disorders (e.g. thyroid).
- Inflammatory and rheumatologic disease.
- Renal disease.

Pathophysiology

- A mild hemolytic component is often present, red blood cell survival is moderately decreased.
- Erythropoietin levels are normal or slightly elevated but are inappropriately low for the degree of anemia, erythropoietin level is low in renal failure.
- Iron cannot be removed from its storage pool in hepatocytes and RES cells.
Anemia of Chronic Disease

Diagnosis

- RBC are usually normocytic and normochromic if the anemia is mild, may be microcytic and normochromic if the anemia is moderate, may be microcytic and hypochromic if the anemia is severe, Hb rarely < 9 g/dL except in renal failure.
- Serum iron, TIBC, and % saturation all normal or slightly reduced, serum ferritin is normal or increased.
- Normal or increased iron stores in bone marrow, decreased “normal” sideroblasts.

Management

- Resolves if underlying disease is treated.
- Erythropoietin may normalize the hemoglobin value especially in chronic renal failure. Dose of erythropoietin required is lower for patients with renal disease.
Aplastic Anemia

Etiology

- Radiation
- Drugs
  - anticipated (chemotherapy)
  - idiosyncratic (chloramphenicol, phenylbutazone)
- Chemicals
  - benzene and other organic solvents
  - DDT and insecticides
- Post viral e.g. hepatitis B, parvovirus, HIV.
- Idiopathic
  - often immune (cell mediated)
- Paroxysmal nocturnal hemoglobinuria
- Marrow replacement
- Congenital: Fanconi anemia, associated with dysmorphic features.
Abnormal Thumbs in Fanconi Anemia
Clinical Presentation of Aplastic Anemia

- Occurs at any age
- Slightly more common in males.
- Can present acutely or insidiously.
- Features of anemia or neutropenia or thrombocytopenia (any combination).
  1. Thrombocytopenia as bruising, bleeding gums, epistaxis.
  2. Anemia as SOB, pallor and fatigue.
  3. Presentation of neutropenia ranges from infection in the mouth to septicemia.
Aplastic Anemia

**Diagnosis**
1- CBC: Pancytopenia
   - normochromic normocytic anemia.
   - neutrophil count < 1.5 x 10⁹/L.
   - platelet count < 20 x 10⁹/L.
   - corrected reticulocyte count < 1%.
2- Bone marrow aspirate and biopsy
   - aplasia or hypoplasia of marrow cells with fat replacement.

**Management**
- Removal of offending agents.
- Supportive care (red cell and platelet transfusions, antibiotics).
- Antithymocyte globulin (50-60% of patients respond) for patients who are >45 years of age and those who have no donor for bone marrow transplant
- Cyclosporin A, mainly useful for mild cases.
- Allogeneic bone marrow transplantation for patients <45 y
  - minimize blood products on presentation.
  - only irradiated, leuko-depleted blood products should be used to minimize CMV transmission.
  - CMV negative blood for CMV negative patients.
MYELODYSPLASTIC SYNDROMES (MDS)

Pathophysiology

- A group of clonal bone marrow stem cell disorders characterized by one or more cytopenias with anemia present.
- Ineffective hematopoiesis despite presence of adequate numbers of progenitor cells (bone marrow is usually hyper-cellular).
- Dysplastic changes affect all the hematopoietic cell lines due to abnormal maturation and differentiation which include abnormal size, nuclear shape and cytoplasmic granules.
- The blood elements are dysfunctional.
- There is increased liability for transformation to AML.
Dysplastic nuclear features in circulating cells. Composite image taken from several cases of myelodysplastic syndrome showing dysplastic nuclear features seen in circulating granulocytes and nucleated RBCs. The right lower figure shows numerous Pappenheimer bodies.
MDS

Types

- Refractory anemia (RA).
- Refractory anemia with ring sideroblasts (RARS).
- Refractory anemia with excess blasts (RAEB).
- Refractory anemia with excess blasts in transformation (RAEB-T).
- Chronic myelomonocytic leukemia (CMML).
MDS

Clinical Presentation
- Related to bone marrow failure, most common in elderly, usually > 70 and post-chemotherapy or radiation
- Usually insidious in onset: fatigue, weakness, pallor, infections, bruising and rarely weight loss, and hepatosplenomegaly

Diagnosis
1- Anemia ± thrombocytopenia ± neutropenia
   - RBC: variable morphology with decreased reticulocyte count,
   - WBC: decrease in granulocytes and abnormal function,
   - Platelet: either too large or too small and thrombocytopenia
2- Bone marrow: dysmyelopoiesis in bone marrow precursors
3- Chromosomal Abnormalities: 5, 7, 8, others
MDS

Management

1- Symptomatic (transfusion, antibiotics)

2- Growth factors: Erythropoietin, G-CSF.

3- Cytotoxics for RAEB & RAEB-T & CMML

4- Bone marrow transplant for young patients with advanced disease.

5- Immune modulating and differentiating agents.
Hemolytic anemias

Definition: Anemias that result from shortening of RBC life span, RBC destruction could be extravascular or intravascular

Etiology

**Congenital**
1. Membrane abnormalities
   • Hereditary spherocytosis
   • Hereditary elliptocytosis
2. Haemoglobinopathies
   • Lack of haemoglobin chain synthesis Thalassaemias
   • Amino acid substitution on the haemoglobin chain Haemoglobin S, C, D
3. Red cell enzyme detects
   • Glucose-B-phosphate dehydrogenase deficiency

**Acquired**
1. Immune
   • Isoimmune
   • Autoimmune Warm antibody Cold antibody
   • Alloimmune
2. Non-immune
   • Mechanical
     - Artificial cardiac valves
     - Burns
     - Microangiopattlic
     - March haemoglobinuria
   • Infections
     • Clostridium perfringens, malaria
   • Drugs, chemicals
3. Paroxysmal nocturnal haemoglobinuria (PNH).
Approach To Hemolytic anemia

A- Prove The Presence of Hemolysis *(Evidence of hemolysis)*:

- Clinical Features: anemia + jaundice.
- Laboratory Tests
  1. Low Hb, Increased *reticulocyte* count and percentage.
  2. *Indirect hyperbilirubinemia*, raised s.LDH, increased urinary urobilinogen.
  3. Low serum *haptoglobin*.
  4. Hemosiderinurea, hemoglobinurea in cases of *intravascular hemolysis*.

B- Find The Cause Of Hemolysis:

  1. Blood Film Morphology: Target Cells, Sickle Cells, Heinz Bodies, Blister Cells, Fragmented RBC, Spherocytes.
  3. Osmotic Fragility test for Spherocytosis
  4. Enzyme assay for Enzymopathies.
  5. Coomb’s test for immune hemolysis.
  6. Ham’s test for PNH.
Hereditary spherocytosis

This is an autosomal dominant disorder in which the principal abnormality appears to be a deficiency of spectrin, a red cell membrane protein. Approximately 25% of patients have no family history. The erythrocyte envelope is abnormally permeable and the sodium pumps are overworked. The exact nature of the red blood cell defect may vary from family to family. The erythrocytes lose their biconcave shape, become spherical and are more susceptible to osmotic lysis. These spherocytes are destroyed almost exclusively by the spleen. The severity of the disorder is very variable even within an affected family. Haemolysis is mainly extravascular.
Diagnosis & Treatment

Clinical Features:
- The severity of anemia is variable from asymptomatic to transfusion dependent anemia. Jaundice is also variable, as well as splenomegaly.
- Complications include
  1. Crises (hemolytic, megaloblastic, and aplastic).
  2. Pigment Gall stones.

Lab Tests:
- Evidence of Hemolysis: Anemia, Reticulocytosis, raised S.LDH…
- Spherocytes on blood film.
- +ve Osmotic Fragility Test.
- -ve Coombs Test.

Treatment:
1. Blood Transfusion.
2. Folic acid.
3. Splenectomy for moderate to severe cases.
OSMOTIC FRAGILITY TEST

The graph shows the percentage of hemolysis of red blood cells (RBCs) as a function of sodium chloride (NaCl) concentration (gm/dL).

- **Normal Range**:
  - Fresh: The curve for normal RBCs is shown, indicating the range of NaCl concentration at which hemolysis occurs.
  - Incubated: The curve for incubated RBCs is also shown, showing a different range of hemolysis compared to the fresh state.

- **Hereditary Spherocytosis**:
  - Fresh: The graph indicates a higher susceptibility to hemolysis, with a steeper curve, suggesting more rapid hemolysis at lower NaCl concentrations.
  - Incubated: The incubated state also shows a steeper curve, with a marked increase in hemolysis at lower NaCl concentrations.
Glucose 6 Phosphate Dehydrogenase Deficiency

- G6PD Enzyme is the first one in the hexosmonophosphate shunt, the function of this shunt is to service the enzymes glutathione reductase and glutathione peroxidase, which protect the red cells against damage due to oxidation.

- The deficiency is inherited as an X-linked disorder with a high frequency among Black Africans who possess an electrophoretic enzyme polymorphism with A and B type enzymes. The enzyme is A type (A-) in deficient Black Africans. In Caucasians only the normal B type enzyme is found and the deficient type is also B (B-).
G6PD deficiency

- Oxidant damage of RBC followed by intravascular hemolysis is induced by:
  1. Infections.
  2. Ingestion of Fava Beans.
  3. Oxidant drugs like: sulfa, dapsone, antimalarial, chloramphenicol....,

**Clinical manifestations:**

1. Most cases present with episodic intravascular hemolysis with fever, rapid anemia, jaundice and deep colored urine.
2. Rarely the hemolysis is chronic.
**G6PD deficiency**

**Lab Tests:**
1- Anemia, reticulocytosis, indirect hyperbilirubinemia...
2- Blister RBC on blood film, and Heinz bodies.
3- Hemoglobininurea and later hemosideriurea.
4- Enzyme assay is useful after recovery.

**Treatment:**
1- Avoid fava beans and oxidant drugs.
2- For the hemolytic episode: stop the offending factor, blood transfusion, folic acid.
The haemoglobinopathies can be classified into two subgroups:

1- Where there is an alteration in the amino acid structure of the polypeptide chains of the globin fraction of haemoglobin, commonly called the abnormal haemoglobins: the best-known example is haemoglobin S found in sickle-cell anaemia.

2- Where the amino acid sequence is normal but polypeptide chain production is impaired or absent for a variety of reasons: these are the Thalassemias.
Hemoglobin Structure and Production

- Fetal hemoglobin, HbF (α2γ2) switches to adult forms HbA (α2β2) and HbA2 (α2δ2) at 3-6 months of life.
- HbA constitutes 97% of adult hemoglobin.
- HbA2 constitutes 3% of adult hemoglobin.
- 4 α genes are located on chromosome 16.
- 2 β genes are located on chromosome 11.
- There is the possibility of mixed defects e.g. β-thalassemia minor and sickle cell (HbS) trait.
Hemoglobin Structure
THALASSEMIAS

HETEROZYGOU \(\beta\) THALASSEMIA : \(\beta\)-Thalassemia Minor

- Common condition in Mediterranean Basin, Africa, Asia

Clinical Presentation

- Mild or no anemia.
- Spleen sometimes is palpable.
- May be masked by Fe deficiency and sometimes confused with iron deficiency anemia.

Diagnosis

1- Hb 9-12 g/dL, MCV < 70
2- Microcytosis +/- hypochromia, target cells present, basophilic stippling usually present.
3- Hb electrophoresis: Hb A2 increased to 3.5-5% (normal 1.5 - 3.5%), 50% of individuals have slight increase in HbF.

Management

- Add folic acid.
- Patient and family should receive genetic counseling.
HOMOZYGOUS β THALASSEMIA (β-Thalassemia Major)

Pathophysiology

Ineffective beta chain synthesis due to point mutation in the beta gene promoter or enhancer on chromosome 11, excess alpha chains relative to beta chain leading to ineffective erythropoiesis and hemolysis of RBC, compensatory increase in HbF

Clinical Presentation

- Start presenting at 3-6 months because of replacement of HbF by HbA
- Severe anemia developing in the first year of life
- Jaundice
- Stunted growth and development (hypogonadal dwarf)
- Gross hepatosplenomegaly (extramedullary hematopoiesis)
- Skeletal changes (expanded marrow cavity)
  - Skull x-ray has “hair-on-end” appearance
  - Pathological fractures common
- Evidence of increased Hb catabolism (e.g. gallstones)
- Death from
  - Untreated anemia.
  - Infection (early).
  - Iron overload (late, secondary to transfusions), usually 20-30 years old.
PATHOPHYSIOLOGY OF B-THALASSEMIA MAJOR

- **α-Gene** → α mRNA
- **β-Gene** → β mRNA

**α**-globin

- α2β2 + α precipitates
- Inclusion bodies in RBC precursors

**Membrane damage**
**Abnormal metabolism**

1. ↓Hb per cell produced (hypochromia)
2. Massive ↓mature RBC production
3. Shortened RBC survival

**Sequestration in spleen**

- Massive death of RBC precursors in bone marrow (ineffective erythropoiesis)
- Few surviving RBCs are highly abnormal, carry inclusions
- Bizarre morphology

**Splenomegaly** → hypersplenism
- ↑Hb catabolism → ↑bilirubin

**Erythropoietin released by kidney**

**Tissue hypoxia**

**Massive expansion of bone marrow**

**Profound anemia**

- Transfusion

- High output heart failure, infection, leg ulcers, pallor, growth retardation

**Bony deformities, fractures, extramedullary hematopoiesis**
- Increased gastrointestinal iron absorption
- Iron overload and Parenchymal iron deposition (hemochromatosis)

**Increased blood volume, secondary folate deficiency, pathologic bone fractures**

**Jaundice**
**Gallstones**
**Leg ulcers**

**Cirrhosis**
**Endocrine dysfunction**
**Cardiomyopathy**
**ß-Thalassemia Major**

**Diagnosis**

1- Hemoglobin 4-6 g/dL.

2- Peripheral blood: hypochromic microcytotic, increased reticulocytes, basophilic stippling, target cells.

   - Postsplenectomy blood film shows Howell Jolly bodies, Nuleated RBC, and thrombocytosis.

3- Hb electrophoresis

   • Hb A: 0-10% (normal > 95%)

   • Hb F: 90-100%

4-DNA analysis.
**Management**

1. Blood transfusions to ensure growth and decrease skeletal deformities, try to keep Hb > 10 gm/dL, add folic acid.

2. Fe chelators to prevent iron overload like desferrioxamine, deferiprone.

3. Ensure good nutrition and try to minimize the frequency of infectious episodes by vaccination. Infections should be treated adequately.

4. Allogeneic Bone marrow transplant (if suitable donor).

5. Splenectomy for mechanical problems and hypersplenism.

**ALPHA THALASSEMIAS**

**Pathophysiology**
- Autosomal recessive
- Deficit of alpha chains
- 4 grades of severity depending on the number of defective alpha genes
  1. Silent: αα/ α-
  2. Trait: αα/ -- or α-/ α-
  3. Hb H Disease (presents in adults): α-/--
  4. Hb Bart’s (hydrops fetalis): --/--
- Hb Bart’s made of 4 gamma chains; not compatible with life
- Hb H made of 4 beta chains, is unstable, and leads to inclusion bodies

**Diagnosis**
1. Peripheral blood film: microcytes, hypochromia, occasional target cells, screen for Hb H inclusion bodies.
2. Hb electrophoresis not diagnostic.
3. DNA analysis using alpha gene probe.

**Management:** same as beta thalassemia.
PATHOPHYSIOLOGY OF ALPHA THALASSEMIA

A. Hydrops Fetalis with Hb Bart’s in Fetus

- α Genes absent
- γ Genes
- α mRNA absent
- γ mRNA
- α Globin absent
- γ₄ (Hb Bart’s)
- No Hb F

Extremely high O₂ affinity
Profound tissue hypoxia
Heart failure
Liver failure (↓ Albumin)

Mildly unstable
Hemolysis
Anemia

Massive edema (hydrops)
Hypoxic death in utero

B. Hb H Disease in Adult

- 1 of 4 α Gene loci present
- β Gene
- ↓ α mRNA
- β mRNA
- ↓ α Globin
- β Globin
- ↓ Hb A

Moderate hypochromic hemolytic anemia with splenomegaly, bizarre morphology
Excess β Globin
β₄ (Hb H)

Moderately unstable

N.B.: During fetal life, similar syndrome but with accumulation of Hb Bart’s
Sickle Cell anemia

- Autosomal recessive
- Amino acid substitution of valine for glutamate in position 6 of beta globin chain.

*It has a wide geographical distribution.*
Sickle Cell anemia

Mechanisms of Sickling

- At low PO2, deoxy Hb S polymerizes, leading to rigid crystal-like rods that distort membrane = SICKLES
- The PO2 level at which sickling occurs is related to the % of Hb S present
  - If the patient is heterozygous (Hb AS), the sickling phenomenon occurs at a PO2 of 40 mmHg
  - If the patient is homozygous (Hb SS), sickling occurs at 80 mmHg
- Sickling is also aggravated by
  - Acidosis.
  - Increased CO2.
  - Increased 2,3-DPG.
  - Increased temperature and osmolality.
Clinical Consequences Of SCA

- Increased mechanical fragility
- Increased blood viscosity
- Loss of plasticity
  
  - Sludging in microvasculature

- Haemolysis

- Anaemia
  
  - Splenomegaly
  - Hepatomegaly

  - Leg ulcers

  - Bone marrow hyperplasia

  - Cholelithiasis

  - Icterus

  - Ischaemia

  - Infarction

- Cardiomegaly

- Folic acid deficiency

- Skull bossing

- Hyposplenism

- Osteomyelitis

- Heart failure

- Stunted growth
Heterozygous SCA: Hb S Trait

**Clinical presentation:**
- the patient will appear normal except at times of extreme hypoxia and infection, elderly patients may suffer from loss of renal concentration ability.

**Diagnosis:**
1- Hb level is normal
2- Peripheral blood: normal except for a few target cells
3- Hb electrophoresis (confirmatory test): Hb A fraction of 65% ; Hb S fraction of 35%

**Treatment:**
1- Avoid hypoxia during flying and surgery.
2- Folic acid for pregnant.
3- Genetic counseling.
HEMOGLOBIN ELECTROPHORESIS IN SCA

![Graph showing hemoglobin electrophoresis in SCA trait and disease.](image-url)
Homozygous SCA: Hb SS Disease

Clinical presentation
1- Chronic hemolytic anemia with jaundice in the first year of life.
2- Retarded growth and development +/- skeletal changes.
3- Susceptibility to infections by encapsulated organisms due to hyposplenism.
4- Spleen enlarged in children and atrophic in adults.
5- Crises:
   - Vaso-occlusive crises (infarction) leading to pain, fever, leukocytosis, acidosis & dehydration. Any organ or tissue can be involved.
   - Hyperhemolytic crises associated malaria.
   - Sequestration crises presenting with anemia and rapidly enlarging spleen or liver.
   - Aplastic crisis due to parvovirus infection or folate deficiency, leading to rapid anemia and reticulocytopenia.
   - Acute Chest Syndrome presenting as fever, chest pain, cough and hypoxia.
6- Iron overload due to repeated blood transfusion (less likely compared to Thalassemia).
7- Gall stones, leg ulcers.
Diagnosis

1. Peripheral blood: sickled cells, target cells, reticulocytosis.
2. Indirect hyperbilirubinemia, raised s.LDH
4. Hb electrophoresis (confirmatory test): Hb S fraction > 80%, the rest is Hb F.
Homozygous SCA: Hb SS Disease

Management

1- Prevention Of Sickling Attacks:
   • Avoid conditions that favor sickling (hypoxia, acidosis, dehydration, fever).
   • Vaccination in childhood e.g. pneumococcus, meningococcus.
   • Good hygiene and nutrition.

2- Genetic counseling.

3- Blood transfusion to keep Hb>8 g/dl + Iron chelation for frequent transfusions.

4- Folic acid to avoid folate deficiency.

5- Hydroxyurea to enhance production of Hb F, presence of Hb F in the SS cells decreases polymerization and precipitation of Hb S.

   Note: Hydroxyurea is cytotoxic and may cause bone marrow suppression it is indicated in severe cases.

6- Experimental anti-sickling agents.

7- Allogeneic Bone marrow transplant for selected patients.
Homozygous SCA: Hb SS Disease

*Treatment of Vaso-Occlusive Crisis*

- Oxygen.
- Good Hydration (reduces viscosity).
- Antimicrobials.
- Correct acidosis if severe.
- Analgesics/narcotics (give enough to relieve pain).
- Exchange transfusion for CNS crisis.
AUTOIMMUNE HEMOLYTIC ANEMIA

Types:
1- Warm Antibody type: usually IgG.
2- Cold Antibody type: usually IgM.

AUTOIMMUNE HEMOLYTIC ANEMIA (Warm Antibody type)

Pathophysiology: RBC are coated with IgG or complement (C3d) or both leading to extravascular hemolysis in RES (mainly spleen).

Classification:
1- idiopathic
2- secondary to
   • Lymphoproliferative disorders (CLL, Hodgkin’s disease, Non - Hodgkin’s lymphoma)
   • Autoimmune (SLE)
3- Drug induced (penicillin, quinine/quinidine, alpha methyl dopa)

Clinical Features:
Usually insidious: anemia, jaundice and splenomegaly.
Mechanism of extravascular hemolysis in autoimmune hemolytic anemia. (A) Macrophage encounters an IgG-coated erythrocyte and binds to it via its Fc receptors. Thus entrapped, the RBC loses bits of its membrane as a result of digestion by the macrophage. The discoid erythrocyte transforms into a sphere. (B) RBC lightly coated with IgG (and therefore incapable of activating the complement cascade) is preferentially removed in the sluggish circulation of the spleen. (C) RBC with a heavy coat of IgG; thus, C3b (black circles) can be removed both by the spleen and the liver.
AUTOIMMUNE HEMOLYTIC ANEMIA
(Warm Antibody type)

**Diagnosis**
1- Spherocytes in blood film, reticulocytosis.
2- Indirect hyperbilirubinemia, raised s.LDH.
3- Positive direct antiglobulin test (direct Coombs’) best detected at 37ºC (hence “warm-reacting antibodies”)
4- Exclude delayed transfusion reaction.

**Management**
- Treat underlying cause
- Corticosteroids: prednisolone 1mg/Kg until response then taper over 2-3 months.
- Splenectomy for relapsed and corticosteroid resistant cases.
- Immunosuppressives like azathioprine for relapses after splenectomy
- Blood transfusion is used with caution.
- Add folic acid.
Autoimmune Hemolytic Anemia with Cold-Reacting Antibodies

Pathophysiology
- Either monoclonal or polyclonal IgM Antibodies attach to RBC surface antigens in peripheral circulation where $T < 37^\circ C$.
- Antibodies will detach from the surface antigen if $T >$ thermal amplitude.
- Thermal amplitude is the temperature at which IgM is attached to RBC surface.
- Associated with intravascular hemolysis.

Classification
- Idiopathic
- Secondary to
  - Lymphoproliferative disorders (CLL, Hodgkin’s disease, non-Hodgkin’s lymphoma)
  - Infections (Mycoplasma pneumoniae, EBV).

Clinical Features:
Anemia, acrocyanosis, joint pain, vasculitic rash, Raynaud phenomena, and rarely splenomegaly.
COLD AGGLUTININ
Autoimmune Hemolytic Anemia with Cold-Reacting Antibodies (IgM)

**Diagnosis**
1- Anemia, mild reticulocytosis, RBC agglutination in blood film.
2- Positive cold agglutinin test best at 4ºC.
3- Positive direct Coombs’ for complement at any temperature.

**Management**
- Treat underlying cause
- Warm the patient above the thermal amplitude of the antibody
- Plasmapheresis.
- Immunosuppressives like chlorambucil.
Non Immune Hemolysis

1- Infections:
   Bacterial, Malaria, Babesia.

2- Mechanical:
   - Microangiopathic Hemolysis (MAHA): TTP, HUS, DIC.
   - March Hemoglobinurea.
   - Mechanical Cardiac Valves.

3- Snake bite.
4- Burns.
Drug Induced Hemolysis

1- Hapten Mechanism: high dose Penicillin
2- Complement Fixation : quinidine , phenacetin.
3- Autoantibody production: L-dopa, methyldopa.
4- Nonspecific: cephalothin.
5- Metabolic: sulfa drugs.
Hypersplenism

It is a state of sequestration of one or more of blood elements in an enlarged spleen.

**Causes**
1- Portal hypertension
2- Myeloproliferative disorders.
3- Thalassemia major.
4- Others.

**Diagnosis**
1- Reduction of one or more of blood elements.
2- Normal cellularity of bone marrow.

**Treatment**

Treat the underlying condition, splenectomy may be indicated for increased transfusion requirements.