Blood loss – acute and chronic

Increased rate of destruction (hemolytic anemias)

Impaired red cell production (diminished erythropoiesis)

Classification of Anemia

- Blood loss – acute and chronic
- Increased rate of destruction (hemolytic anemias)
- Impaired red cell production (diminished erythropoiesis)

Classification of Anemia

Increased Rate of Destruction

Intrinsic abnormalities of RBCs
- Hereditary
  - Red cell membrane disorders
  - Red cell enzyme deficiencies
  - Disorders of hemoglobin synthesis
    - structurally abnormal globin synthesis
    - deficient globin synthesis (thalassemia)
  - Acquired (PNH)

Extrinsic abnormalities of RBCs
Thalassemias

- Group of genetic disorders characterized by the lack, or decreased synthesis, of either alpha or beta-globin chains of hemoglobin A
  - alpha-thalassemia - α-globin chain synthesis is reduced
  - beta-thalassemia - β-globin chain synthesis is absent (β₀-thalassemia) or deficient (β⁺-thalassemia)

Thalassemias

- Hematologic consequences of diminished synthesis of one globin chain derive from:
  - low intracellular hemoglobin (hypochromia)
  - relative excess of other chain

α-thalassemias

- α-globin chains are coded by two α-genes on each chromosome 16
- Most α-thalassemias are due to deletion(s) of an α-globin locus (or loci)
  - 4 degrees of α-thalassemia may result
**α-thalassemias**

<table>
<thead>
<tr>
<th>Silent carrier</th>
<th>α / αα</th>
</tr>
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<tbody>
<tr>
<td>α-thalassemia trait</td>
<td>-- / αα (Asian)</td>
</tr>
<tr>
<td></td>
<td>-α / -α (black African)</td>
</tr>
<tr>
<td>HbH disease</td>
<td>-- / -α</td>
</tr>
<tr>
<td>Hydrops fetalis</td>
<td>-- / --</td>
</tr>
</tbody>
</table>

**β-thalassemias**

- β-chains are coded by one β-globin genes on each chromosome 11
- β-thalassemia refers to lack of β-globin expression,
  β+-thalassemia refers to decreased β-globin expression
- Common forms of β-thalassemia are due to point mutations or small insertions or deletions within the β-globin gene
  - errors in transcription, RNA processing, or translation

**β-thalassemias**

- Anemia is due to
  - reduced synthesis of β-globin leading to inadequate Hgb A formation
  - hemolytic component of the disease due to relative excess of α-globin chains
  - form insoluble aggregates which damage cell membranes, reduce membrane plasticity, and allow RBCs to be susceptible to phagocytosis
β-thalassemias

- Thalassemia major - clinical term to describe severe disease, reliance on transfusions
- Thalassemia minor - clinical term to describe patients with asymptomatic, mild or absent anemia, some RBC abnormalities

- Thalassemia major
  - Marrow space is expanded, causing skeletal deformities
  - Hepatosplenomegaly from extramedullary hematopoiesis causes abdominal distension
  - Multiple transfusions necessary, leading to excessive deposition of iron—death may result from cardiac failure

- Thalassemia minor
  - Clinical term to describe patients with asymptomatic, mild or absent anemia, some RBC abnormalities

Robbins Pathologic Basis of Disease (8th Edition)
**β-thalassemias**

**Thalassemia minor**
- Usually associated with a minor microcytic hypochromic anemia
  - must be distinguished from iron deficiency
- Hemoglobin electrophoresis and iron studies are used to make diagnosis
  - Hgb A \( (\alpha_2\beta_2) \) is reduced
  - Hgb A\(_2\) \( (\alpha_2\delta_2) \) is increased

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**Beta-thalassemia minor**

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**Classification of Anemia**

**Increased Rate of Destruction**

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  - Red cell enzyme deficiencies
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    - structurally abnormal globin synthesis
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Extrinsic abnormalities of RBCs
Paroxysmal Nocturnal Hemoglobinuria (PNH)

- The only acquired (rather than inherited) defect in the red cell membrane

PNH

- Stem cell disorder that results from a mutation in the phosphatidylinositol glycan A (PIGA) gene
- Deficiency of GPI anchor
- Lack of expression of GPI-linked proteins
Important GPI-linked proteins
- CD55 (decay-accelerating factor)
- CD59 (membrane inhibitor of reactive lysis)
- C8 binding protein

These proteins are involved in inactivating or the complement pathway

Patients have classic intravascular hemolysis
- Paroxysmal and nocturnal in only 25% of cases
- Infections and venous thromboses
- Occasional evolution to aplastic anemia or acute leukemia
Classification of Anemia

Increased Rate of Destruction

- Intrinsic abnormalities of RBCs
- Extrinsic abnormalities of RBCs
  - Antibody-mediated
  - Mechanical trauma
  - Infections
  - Chemical injury
  - Sequestration

Anemia due to mechanical trauma to RBCs

- Anemia due to prosthetic cardiac valves
- Anemia due to narrowing of small vessels and fibrin deposition (Microangiopathic hemolytic anemia)

Microangiopathic hemolytic anemia

- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Disseminated intravascular coagulation (DIC)

Presence of schistocytes in peripheral blood
Schistocytes

Blood loss – acute and chronic
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Classification of Anemia

Impaired red cell production

- Disordered proliferation and maturation of erythroblasts
  - Deficient heme synthesis (iron deficiency)
  - Deficient DNA synthesis (megaloblastic anemia)
  - Multiple mechanisms (anemia of chronic disease)

- Disordered proliferation and maturation of stem cells
  - Aplastic anemia
Classification of Anemia

Impaired red cell production

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Iron Deficiency Anemia

- Low dietary intake alone is not often the cause of iron deficiency in the U.S.
- Some disorders result in malabsorption of iron (sprue, gastrectomy)
- Adequate diet under usual circumstances may not meet demand for iron during pregnancy and infancy
- Most important cause of iron deficiency in the Western world is chronic blood loss

Iron Deficiency Anemia

- Stored iron first depleted
  - serum ferritin declines, bone marrow iron depleted

- Circulating iron then decreases
  - measured serum iron low

- Increased total iron binding capacity (TIBC)
Iron Deficiency Anemia

- Hemoglobin eventually decreases
- Red cells become small (microcytic) with reduced hemoglobin concentration

Iron Deficiency Anemia

- Nails may develop ridges and become spoon-shaped
- Tongue may become smooth
- Intestinal malabsorption may develop
- Esophageal webs may appear (rare today)
Classification of Anemia

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Megaloblastic Anemias

- Disturbances of proliferation and maturation of erythroblasts due to defective DNA synthesis

- Two principal types
  - vitamin B₁₂ deficiency
  - folate deficiency

Megaloblastic Anemias

- Both B₁₂ and folate are coenzymes in the DNA biosynthetic pathway

- Enlargement of proliferating cells, particularly in erythroid precursors, is seen
  - enlarged red cell precursors are called megaloblasts
  - enlarged red cells are called macrocytes or macro-ovalocytes
Megaloblastic Anemias

- Impairment of DNA synthesis underlies enlargement
  - due to abnormal cell maturation and division
  - RNA and protein synthesis proceeds normally
- Cellular nuclei are immature and cytoplasm is fully mature: nuclear-cytoplasmic asynchrony

Megaloblastic Anemias

Vitamin B₁₂ deficiency

- Many potential causes
  - Inadequate diet
  - Increased requirements
  - Impaired absorption
Megaloblastic Anemias
Vitamin B₁₂ deficiency - Impaired absorption

- Intrinsic factor deficiency
- Pancreatitis
- Gastrectomy
- Ileal resection, regional enteritis
- Parasites (Fish tapeworm)

Megaloblastic Anemias
Vitamin B₁₂ deficiency

- “Pernicious anemia” applies to vitamin B₁₂ deficiency secondary to atrophic gastritis with failure of production of intrinsic factor (IF)

Megaloblastic Anemias
Vitamin B₁₂ deficiency

- IF is necessary for absorption of B₁₂ in the distal ileum
- Deranged synthesis of IF appears to be secondary to an autoimmune phenomenon
  - destruction of gastric mucosa
  - chronic atrophic gastritis
  - loss of parietal cells
Vitamin B₁₂ deficiency is important in 2 reactions:

- Essential cofactor for 5-methyltetrahydrofolate homocysteine methyltransferase (methionine synthase)
  - Deficiency leads to decreased availability of tetrahydrofolate (THF)
  - THF accepts/donates one carbon units, which is critical in DNA synthesis

- Isomerization of methylmalonyl coenzyme A to succinyl coenzyme A
  - Deficiency leads to increased methylmalonate

Megaloblastic Anemias

- Clinical findings found mainly in alimentary tract, blood, bone marrow, and in CNS
  - Alimentary tract: atrophic glossitis, chronic gastritis
  - Blood and bone marrow: megaloblastic anemia, leukopenia with hypersegmented granulocytes, mild to moderate thrombocytopenia
Megaloblastic Anemias

Vitamin B₁₂ deficiency

- Clinical findings: CNS
  - Involvement of posterolateral spinal tracts, leading to sensory and motor abnormalities
    - “subacute combined degeneration”: spastic paraparesis, sensory ataxia, lower limb paresthesias

Folate deficiency

- Widely prevalent in raw foods, quickly destroyed by cooking
- Reserves are modest
  - deficiency still does not appear for months, unless demand increased
- Deficiency results from inadequate intake (absolute or relative) or impaired absorption
Megaloblastic Anemias
Folate deficiency
- Clinical findings
  - megaloblastic anemia identical to vitamin B₁₂ deficiency
  - no CNS abnormalities
  - prompt response following administration of folic acid
  - may also occur with vitamin B₁₂ deficiency, but no reversal of CNS abnormalities

Classification of Anemia
Impaired red cell production
- Disordered proliferation and maturation of erythroblasts
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- Disordered proliferation and maturation of stem cells
  - Aplastic anemia

Anemia of chronic disease
Most common form of anemia in hospitalized patients
- Associated with
  - Chronic infections
  - Chronic immune disorders
  - Malignancies

Caused by high levels of plasma hepcidin that blocks transfer of iron from macrophages to erythroid precursors

Microcytic anemia with low serum iron (like iron deficiency) but:
  - High ferritin
  - Decreased total iron binding capacity
  - Increased bone marrow iron stores
Classification of Anemia

Impaired red cell production

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  - Aplastic anemia

Aplastic Anemia

Failure or suppression of stem cells leads to a hypocellular marrow

Peripheral blood findings:
- anemia
- granulocytopenia
- thrombocytopenia

Pancytopenia

Aplastic Anemia-Proximate causes

- Aplastic anemia is frequently idiopathic, but may result from a known toxic agent:
  - Whole body irradiation
  - Myelotoxic drugs / chemicals
  - Viral infections
Aplastic Anemia-Basic Mechanisms

- Aplastic anemia is likely secondary to heterogeneous group of distinct disorders:
  - defective or deficient hematopoietic stem cells
  - defect in bone marrow stroma ("hematopoietic microenvironment")
  - suppression of marrow stem cells by T-cell mediated immune mechanisms

Aplastic Anemia

- Bone marrow typically is hypocellular with increased fat and small foci of lymphocytes and plasma cells
Aplastic Anemia

Clinically, the signs and symptoms may develop insidiously and reflect the effects of anemia, neutropenia, and thrombocytopenia.

Must be distinguished from other syndromes causing pancytopenia.

Prognosis is unpredictable.

Pathology of Anemia

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Thank you!