Pathophysiology of the diseases of the blood:

Anemias and haemorrhagic diatheses

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Haemopietic system

Blood production

Blood wasting
Haemopoiesis

Blood - structure

≈ 4-5 L
Characteristics of normal Er

- Highly elastic bi concave discs ($\sim 5 \times 10^{12}$).
- Without nucleus and mitochondria (anaerobic metabolism).
- Contain large quantities of enzyme carbonic anhydrase.
- Lifecycle $\sim 120$ days.

Structure and function of Hb

90% of the protein content of Er is haemoglobin.

- Transports $O_2$ and part of the $CO_2$.
- Represents mighty buffer system.
Definition

Anemias are diseases of the blood having less than the normal number of red blood cells or less than the normal quantity of hemoglobin in the blood. The oxygen-carrying capacity of the blood is, therefore, substantially decreased.

Classifications

- Clinical
  - Acute
  - Subacute
  - Chronic
- Erythrocytes morphology
  - Microcytic
  - Macrocytic (megaloblastic)
  - Spherocytic
- Haemoglobin content
  - Hypochromic
  - Hyperchromic
Pathogenetic classification of anemias

- Haemorrhagic anemias
  - Impaired erythroproduction (depressed erythropoiesis)
  - Increased erythrodestruction (pathologic haemolysis)

Lab tests to consider in anemic states

<table>
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<tr>
<th>I. Complete blood count (CBC)</th>
<th>II. Iron supply studies</th>
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<tr>
<td>A. Red blood cell count</td>
<td>A. Serum iron</td>
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<tr>
<td>1. Hemoglobin</td>
<td>B. Total iron-binding capacity</td>
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<tr>
<td>2. Hematocrit</td>
<td>C. Serum ferritin, marrow iron stain</td>
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<td>3. Reticulocyte count</td>
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<tr>
<td>B. Red blood cell indices</td>
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</tr>
<tr>
<td>1. Mean cell volume (MCV)</td>
<td></td>
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<tr>
<td>2. Mean cell hemoglobin (MCH)</td>
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<tr>
<td>3. Mean cell hemoglobin concentration (MCHC)</td>
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<tr>
<td>4. Red cell distribution width (RDW)</td>
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<tr>
<td>C. White blood cell count</td>
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<tr>
<td>1. Cell differential</td>
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<td>2. Nuclear segmentation of neutrophils</td>
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<td>D. Platelet count</td>
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<td>E. Cell morphology</td>
<td></td>
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<tr>
<td>1. Cell size</td>
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<tr>
<td>2. Hemoglobin content</td>
<td></td>
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<tr>
<td>3. Anisocytosis</td>
<td></td>
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<tr>
<td>4. Poikilocytosis</td>
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<td>5. Polychromasia</td>
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<th>III. Marrow examination</th>
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</thead>
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<tr>
<td>A. Aspirate</td>
</tr>
<tr>
<td>1. M/E ratio*</td>
</tr>
<tr>
<td>2. Cell morphology</td>
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<tr>
<td>3. Iron stain</td>
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<tr>
<td>B. Biopsy</td>
</tr>
<tr>
<td>1. Cellularity</td>
</tr>
<tr>
<td>2. Morphology</td>
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</tbody>
</table>
Hemorrhagic anemias

Anemias due to impaired erythrophoioesis

- Impaired synthesis of haemoglobin
  - Fe deficit
- Altered DNA synthesis
  - B₁₂ defect
  - Folate deficit
- Hypo- and aplastic anemias
  - Idiopathic (EPO* insensitive)
  - Erythropoietin deficit

*EPO - Erythropoietin
Iron metabolism

Iron metabolism

**Iron metabolism**

- Chronic haemorrhages
- Increased physiologic requirements
- Decreased Fe-uptake
- Altered Fe-transformation
- Decreased Fe-absorption
- Improper Fe-transport to hemopoietic organs
Fe-deficient anemias - etiology

Stages of Fe deficiency

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Negative iron balance</th>
<th>Iron-deficient erythropoiesis</th>
<th>Iron-deficiency anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron stores</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Marrow iron stores (µg/dL)</td>
<td>1-3+</td>
<td>0-1+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum ferritin (µg/dL)</td>
<td>50-200</td>
<td>&lt;20</td>
<td>&lt;15</td>
<td>&lt;15</td>
</tr>
<tr>
<td>TIBC (µg/dL)</td>
<td>300-360</td>
<td>&gt;350</td>
<td>&gt;350</td>
<td>&gt;450</td>
</tr>
<tr>
<td>SI (µg/dL)</td>
<td>50-150</td>
<td>NL</td>
<td>&lt;50</td>
<td>&lt;90</td>
</tr>
<tr>
<td>Saturation (%)</td>
<td>20-50</td>
<td>NL</td>
<td>&lt;20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Marrow sideroblasts (%)</td>
<td>4-60</td>
<td>NL</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>RBC protoporphyrin (µg/dL)</td>
<td>30-50</td>
<td>NL</td>
<td>&gt;100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>RBC morphology</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>Microcytic/ hypochromic</td>
</tr>
</tbody>
</table>
Fe-deficient anemias - pathogenesis

Decrease of the Fe stores in the organism

- Prelatent Fe-deficit
  - Feritin ↑
  - Intestinal absorption ↑

- Latent Fe-deficit
  - Serum Fe ↓
  - Feritin ↓
  - total iron binding capability (TIBC) ↑

- Manifest Fe-deficient anemia
  - Ers ↓; Hb ↓; MCV ↓;

Fe-deficient anemia: Ers morphology

Fe-deficient anemia is microcytic and hypochromic !!!
Fe-deficient anemias - signs and symptoms

Megaloblastic anemia - etiology

Autosomal-recessive inheritance (Addison-Biermer anemia)

- Genetic predisposition – HLA-A3, HLA-B7
- Auto AB against:
  - Parietal cells in the gastric mucosa
  - Gastromucoprotein
Vit B$_{12}$ metabolism

Megaloblastic anemia - pathogenesis
Erythrocyte profile in megaloblastic anemia

- Anisocytosis
- poikilocytosis
- Macrocytes
- Ovalocytes
- Howell-Jolly bodies

Megaloblastic anemia – signs and symptoms

GI symptoms – Hunter glossitis

Subacute combined degeneration of spinal cord, due to demyelination secondary to deficiency of vitamin B12.
Secondary megaloblastic anemias

- Primary liver disease
- Surgical interventions on the stomach and intestines
- Neoplastic processes
- Parasitic diseases
- Medications (cytostatics, immunosuppressors, antiepileptics)

Hypo- and aplastic anemias

- Radiation
- Cytostatics
- Antibiotics
- Antithyroid drugs
- Henni derivatives
- Viral infections
- Metastases
- Genetic defects

Pluripotent stem cell

- Replication defects
- Stimulatory deficit
- Inhibitory effect
- T-suppressor mechanism
- Apoptosis mechanism

STEM CELLS

- Leukopoesis
- Erythropoesis
- Thrombopoiesis

Bone marrow insufficiency (PANCYTOPENIA)
Anemias due to increased erythrodestruction

- **Inborn (inherited)**
  - Disorders in the structure of Er membrane
  - Disorders in Er's enzymatic content
  - Disorders in the synthesis of the globin molecule
    - Haemoglobinoses
    - Thalassemias

- **Acquired**
  - Immunologic mechanisms
    - Isoimmune
    - Drug induced (haptens)
    - Autoimmune
  - Symptomatic (secondary)

Anemias due to disorders in the structure of Er membrane

- Microspherocytosis (M. Minkowski-Chauffard)
  - Quantitative and qualitative changes of membrane protein *spectrin* (autosomal dominant trait)
  - Disturbance in ATP metabolism
  - Decreased activity of the enzyme *protein kinase*

- Spectrin deficit
- Increased permeability
- Shortened life cycle
- Haemolytic anemia
Anemias due to disorders in Ers enzymatic content

- Glucose-6-phosphate dehydrogenase deficient anemia
  - Sex-linked recessive inheritance.
  - The most common enzymopathy
- Pyruvatekinase deficient anemia
  - Autosomal-recessive inheritance

Anomalies in Ers enzymes

Defect in G6PDH
- ?? \( \downarrow \)
- NADP \( H_2 \) \( \downarrow \)

Glutation Reductase

Glutation Oxydase

Erythrocytic Reductases

Hb-Fe \( ^{3+} \)

Broad Beans

Medicaments

Defect in PK
- Glycolysis \( \downarrow \)
- NAD \( H_2 \) \( \downarrow \)
- ATP \( \downarrow \)

Glutation SH

Hb-Fe \( ^{3+} \)
G6PD

- Genetic defects
- Deficit of G6PD
- Impaired glutathione synthesis
- Oxygen stress
- Denaturation of hemoglobin
- Hemolysis of Ers with enzyme defects

Thalassemias

- Beta thalassemias
  - Homozygotic form (β-thalassemia major, Morbus Cooley)
  - Heterozygotic forms (β-thalassemia minor)

- Alpha thalassemias
  - Homozygotic form
  - Heterozygotic forms
Thalassemia mayor (M. Cooley)

- Abnormally high quantity of Hb F and Hb A₂ is synthesised
- Due to deficit or inappropriate synthesis of β-chains in Ers there is an excess of uncoupled α-chains
- The uncoupled α-chains precipitate
- The permeability of Ers is increased
- Hemolysis

Sickle cell anemia

Impaired β-chain synthesis, with formation of pathologic haemoglobin S

Homozygote

Hardly soluble in liquids

Haemoglobin crystals in hypoxic environment

Heterozygote

OXY-state ↔ DEOXY- state
Sickle cell anemia - distribution

Hemolytic disease of the newborn

Isoimmune conflict between the mother and the foetus due to antigen incompatibility in Rh or ABO systems

- Rh - mother
- Incomplete anti-Rh AB
- Rh+ foetus
- HEMOLYSIS

FORMS
- Hemolytic disease of the newborn
- Icterus gravis
- Foetoplacentar anasarca
- Nuclear icterus (Kernicterus)
Acquired autoimmune anemias

Autoimmune conflict between specific AB and body’s own unchanged erythrocyte antigens

Types of antibodies

- Incomplete heat agglutinins
- Heat hemolysins
- Complete cold agglutinins
- Bi-phase hemolysins

Bone marow transplantation

[Diagram of bone marrow transplantation process]
Hemorrhagic diatheses

Blood Coagulation

- Tissue Factor Pathway
  - Factor VII
  - Factor VIII

- Contact Pathway
  - Factor X
  - Factor V

- Intrinsic Pathway
  - Factor XI
  - Factor IX

- Extrinsic Pathway
  - Factor VIIa (Prothrombinase Complex)

- Common Pathway
  - Prothrombin
  - Thrombin
  - Fibrinogen
  - Fibrin (Blood Clot)
Hemorrhagic diatheses

- Coagulation abnormalities
- Quantitative and qualitative platelet abnormalities (thrombocitopenias & thrombocitopathias)
- Damage to the vascular wall (vasopathies)

Hemophilia

- Disorder of hemostasis, a coagulopathy
- Hemophilia A - Factor VIII deficiency
- Hemophilia B - Factor IX deficiency
- Hemophilia C - Factor XI, XII

- Prevalence: 13.4 cases per 100,000 males
- Incidence: 1 in 5032 live male births
How do you get it?

- Hemophilia is a genetic disease and is passed on by the X chromosome (the chromosome that carries the clotting factor).
- If a boy gets the X chromosome that carries the hemophilia gene he will become a hemophiliac.
- If a girl get the gene, she will become the carrier of the gene,
Severity of Factor Deficiencies

- Severe: <1%
  - Hemarthrosis with minimal trauma or ADLs
- Moderate: 1 to 5%
  - Intermediate symptoms with fewer hemarthroses
- Mild: >5%
  - Joint bleeds rarely develop except with significant trauma

Hemophilic Arthropathy

- As blood is catabolized, it is absorbed by synovium
- Iron is toxic to cells – synovial cells disintegrate releasing lysosomes which destroy cartilage and inflame synovium
- Chondrocytes also affected
- FIBROSIS
Thrombocitopenia

- 1/3 of all Hospital Hematology Consults are for thrombocytopenia
- 5 to 10% of all hospitalized patients are thrombocytopenic in the ICU the number increases to 35%
- Thrombocytopenic patients in the hospital suffer a twofold greater mortality rate than those who are not

Echymoses
Thrombocytopenia

<table>
<thead>
<tr>
<th>Platelet count</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>50-100,000</td>
<td>Prolonged bleeding following trauma</td>
</tr>
<tr>
<td>&lt; 50,000</td>
<td>Easy bruising</td>
</tr>
<tr>
<td></td>
<td>Purpura following minor trauma</td>
</tr>
<tr>
<td>&lt; 20,000</td>
<td>Spontaneous bleeding</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
</tr>
<tr>
<td></td>
<td>May suffer spontaneous internal and intracranial bleeding</td>
</tr>
</tbody>
</table>

Mechanisms of Thrombocytopenia

- Decreased platelet production
- Increased platelet destruction
- Dilutional Thrombocytopenia
- Splenomegaly or splenic sequestration
- Pseudothrombocytopenia

The primary reason for evaluating thrombocytopenia is to assess the risk of bleeding and assess the presence of underlying disorders.
**Decreased Platelet Production**

- Factors causing bone marrow suppression or damage
- Viral illness
- HIV (direct damage to Megakaryocytes)
- Chemo- or radiation therapy
- Congenital or acquired bone marrow aplasia or hypoplasia
- Vit. B12 or Folate deficiency

**Increased Platelet Destruction**

- Idiopathic (Immune) Thrombocytopenic Purpura
- Alloimmune destruction—Posttransfusion, Post-transplantation
- Disseminated Intravascular Coagulation
- Thrombotic Thrombocytopenic Purpura
- Antiphospholipid Antibody Syndrome
- Certain drugs—Heparin, quinidine, valproate
Splenic Sequestration

- Normally, ~1/3 of platelets are sequestered in the spleen in any given time
- In extreme splenomegaly, up to 90% of platelets can be trapped in the spleen
- Cirrhosis, Portal HTN, splenomegaly can all present with apparent thrombocytopenia, although these pts are not usually at risk for clinical bleeding

Qualitative platelet disorders - thrombocytopenia

- Hereditary
  - Glanzmann Thrombasthenia
  - Bernard Soulier disease
  - Plt granules deficiency
- Acquired
  - Drugs (aspirin)
  - Inhibitors (Ab)
Vasopathias

- Schönlein-Henoch Purpura

- Symptomatic hemorrhagic vasculites
  - Krimean hemorrhagic fever
  - Measels

- Hereditary vasopathias
  - Rendu-Osler-Weber

Schönlein-Henoch Purpura

anaphylactoid purpura

- Schönlein-Henoch Purpura is a common vasculitis with *cutaneous and systemic complications*.

- The usual location of the *acute small vessel damage* is primarily in the skin, GI tract, and kidneys

- It is the most common cause of nonthrombocytopenic purpura in children.
History

- First described in 1801 by William Heberden, a physician in London, who wrote about a case of a 5 year old boy with hematuria, abdominal pain, joint pains and a skin rash.

- In 1837, Johann Schönlein and later in 1874, Edouard Henoch described multiple case reports of similar cases. They also showed an association of an upper respiratory infection preceding development of symptoms.

Pathogenesis

- Likely mechanism thought to be an immune-complex mediated disease with deposits in the glomerular capillaries, dermal capillaries and GI tract.

- Mesangial deposits of IgA are the same as those seen in IgA nephropathy
**Epidemiology**

- More frequent in children than adults, with most cases occurring between 2 and 8 yr of age,
- Most frequently in the winter months.
- The overall incidence is estimated to be 9/100,000 population.
- Males are affected twice as frequently as females.

**Clinical manifestations**

- Rash (95-100%), especially involving the legs, may not be present on initial presentation
- Subcutaneous edema (20-50%)
- Abdominal pain and vomiting (85%)
- Joint pain (60-80%), especially involving the knees and ankles
- Scrotal edema (2-35%)
- Bloody stools
Clinical Presentation

- Petechiae
- Purpura
- Ecchymoses

Arthritis

- Present in more than ⅔ of children with HSP,
- Is usually localized to the knees and ankles and appears to be concomitant with edema.
- The effusions are serous, not hemorrhagic,
- Resolve after a few days without residual deformity or articular damage.
- They may recur during a subsequent reactive phase of the disease.
Gastrointestinal tract

- Intermittent abdominal pain that is often colicky in nature.
- There may be peritoneal exudate, enlarged mesenteric lymph nodes, segmental edema, and hemorrhage into the bowel.
- More than half of patients have occult heme-positive stools.
- Diarrhea (with or without visible blood), or hematemesis.
- Complete bowel obstruction or infarction with bowel perforation.

Renal involvement

- occurs in 25-50% of children

**may manifest with:**
- hematuria,
- proteinuria, or both;
- nephritis or nephrosis;
- acute renal failure.

- Renal involvement at presentation may lead to chronic hypertension or end-stage renal disease in the future
The END

Have a wonderful day!