ORAL MANIFESTATIONS OF BLOOD DISORDERS

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Physiology of Blood: Functions

- Transportation:
  - oxygen & carbon dioxide (in the form of HCO_3^-)
  - nutrients & electrolytes
  - waste products (metabolic wastes, excessive water, & ions)
- Regulation - hormones & heat (to regulate body temperature)
- Protection
  - Clotting - protects against blood loss
  - Leucocytes - immunity against infections

Physiology of Blood: Components

- 22% solids and 78% water
- Formed elements:
  - Red blood cells (or erythrocytes)
  - White blood cells (or leucocytes)
  - Platelets (or thrombocytes)
- Plasma = water + dissolved solutes

Physiology of Blood: RBCs (erythrocytes)

- Biconcave discs
- Lack a nucleus
- Lifespan = about 120 days
- Conc. \( \geq 4.6 \text{ million/ mm}^3 \)
- Haemoglobin (Average 14-16g/100ml)
- Haematocrit [packed cell volume] of about 42% for females & 45% for males
- Contain carbonic anhydrase (critical for transport of carbon dioxide)

Physiology of Blood: WBCs (leucocytes)

- have nuclei
- do not contain hemoglobin
- 5,000 - 9,000 / mm^3
- Types:
  - granular WBCs:
    - neutrophils (50 - 70%)
    - eosinophils (1 - 4%)
    - basophils (less than 1%)
  - agranular WBCs:
    - lymphocytes (25 - 40%)
    - monocytes (2 - 8%)

Physiology of Blood: Functions WBCs

- Neutrophils
  - phagocytosis (bacteria & cellular debris); very important in inflammation
- Eosinophils
  - help break down blood clots & kill parasites
- Basophils
  - synthesize & store histamine (a substance released during inflammation) & heparin (an anticoagulant)
- Monocytes
  - phagocytosis (typically as macrophages in tissues of the liver, spleen, lungs, & lymph nodes)
- Lymphocytes
  - immune response (including production of antibodies)
Physiology of Blood: Platelets (thrombocytes)

- Formed in bone marrow-from megakaryocytes
- Have no nucleus, but can secrete a variety of substances & can also contract (because they contain actin & myosin)
- Normal concentration – 1,50,000-3,00,000/mm³
- Half life – 8 to 12 days
- Later removed from the blood by macrophages in the spleen & liver
- play an important role in haemostasis

Physiology of Blood: Plasma

- Water - serves as transport medium; carries heat
- Albumins
- Globulins
  - α β γ globulins
- Fibrinogen - produced by liver
- Inorganic constituents
- Nutrients
- Waste products
- Dissolved gases
- Hormones

Haemopoiesis

Haemostasis

Coagulation cascade

RED BLOOD CELL DISORDERS

- ANAEMIA
- POLYCYTHAEMIA
ANAEMIA
- Deficiency in the transport of oxygen by blood; Reduction in Haemoglobin concentration
- Classification based on cell size & colour
  - Microcytic: small cells
  - Hypochromic: ↓ haemoglobin
  - Macrocytic-hyperchromic: Total number of RBC ↓, bone marrow produces larger cells with increased concentration of hemoglobin

Peripheral blood smear

Reticulocyte
- Supravital staining
- Normal (top)
- Elevated (bottom)

Erythrocyte Inclusions

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Composition</th>
<th>Appearance</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophilic stippling</td>
<td>Precipitated ribosomes</td>
<td>Evenly dispersed fins of coarse granules</td>
<td>Lead poisoning, thalassemia</td>
</tr>
<tr>
<td>Howell-Jolly bodies</td>
<td>Nuclear fragment</td>
<td>Dense, round blue granule</td>
<td>Post-splenectomy</td>
</tr>
<tr>
<td>Heinz bodies</td>
<td>Denatured Haemoglobin</td>
<td>Small round inclusions may project</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Pappenheimer bodies</td>
<td>Iron-containing granules</td>
<td>Small blue granules in clusters</td>
<td>Anaemias</td>
</tr>
<tr>
<td>Organism</td>
<td></td>
<td>Small blue inclusions</td>
<td>Malaria</td>
</tr>
</tbody>
</table>

Basophilic stippling & Howell-Jolly body

Malarial trophozoites & Heinz bodies
Erythrocyte Distribution Abnormalities

- **Rouleaux formation**: Stacking of RBCs due to increased plasma proteins coating RBCs
- **Agglutination**: Antibody-mediated clumping; temperature dependent

Variations in RBC Size and Shape

- **Anisocytosis**: Variations in size (e.g. microcytes)
- **Poikilocytosis**: Variations in shape (e.g. target cells)
- **Hypochromia**: Increased central pallor due to ↓ Hb

RBCs: Shape Abnormalities

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target cells</td>
<td>Central hemoglobin, target-shaped</td>
<td>Liver disease, thalassemia</td>
</tr>
<tr>
<td>Echinocyte</td>
<td>Short spicules, equidy-spaced</td>
<td>Uremia, hypokalemia</td>
</tr>
<tr>
<td>Acanthocyte</td>
<td>Spiculated, irregular</td>
<td>Liver disease, Post-splenectomy</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Spherical, no central pallor</td>
<td>Autoimmune Haemolytic anaemia</td>
</tr>
<tr>
<td>Schistocyte</td>
<td>Fragmented RBC, helmet cells</td>
<td>MHA, burns</td>
</tr>
<tr>
<td>Ovalocyte</td>
<td>Oval or elliptical shaped</td>
<td>Megaloblastic anaemia</td>
</tr>
<tr>
<td>Sickled cell</td>
<td>Bipolar spiculated (banana) shaped</td>
<td>Sickle-cell anaemia</td>
</tr>
<tr>
<td>Teardrop cell</td>
<td>Single elongated extremity</td>
<td>Myelophthistic changes</td>
</tr>
<tr>
<td>Bite cells</td>
<td>Irregular gap in membrane</td>
<td>G6PD deficiency</td>
</tr>
</tbody>
</table>

Target cells & Ecchinocytes (Burr cells)
Acanthocytes (spur cells) & Spherocytes

Schistocytes & Elliptocytes

Sickle, Tear drop & Bite cells

ANAEMIA: Basic causes
1. ↑ed RBC Loss without RBC destruction
2. ↓ed RBC production
3. ↑ed RBC destruction over production

• Laboratory tests: RBC count, haematocrit, Hb evaluation
• Remember, Anemia is a symptom of an underlying disease… not a disease itself!

Anaemia: ↑RBC loss without RBC destruction
• Haemorrhage
• Due to trauma
• Due to disorders: e.g. cancer, ulcers, tuberculosis, diverticular disease, and irritable bowel syndrome (including ulcerative colitis and Crohn’s disease)
• Menstrual flow
• Gynecological disorders (e.g. endometriosis, fibroids)
• Pregnancy, especially at gestation
• Parasitism e.g. Hookworms

Anaemia: ↓RBC production
• Neoplasia
  • Leukemia
  • Metastasis to bone marrow
  • Osteogenic sarcoma
• Myelofibrosis
• Pernicious anaemia
• Iron Deficiency anaemia
• Aplastic anaemia
  • Chloramphenicol administration
• Renal disease (lack of erythropoietin production)
Anaemia: Ed RBC destruction over production

- Intrinsic Abnormalities
  - Thalassemia
  - G6PD
  - Sickle Cell Anemia
  - Hereditary Spherocytosis
- Extrinsic Abnormalities
  - Infections
    - Malaria (Plasmodium species)
    - Mycoplasma
  - Disseminated Intravascular Coagulation
  - Lead poisoning

Anaemia: Classification

- Microcytic
  - Small size of RBCs
  - E.g. Fe def Anaemia, Thalassemia
- Macrocytic
  - Large size of RBCs
  - E.g. Vit B12 or Folate deficiency, Pregnancy, Malignancy, Drugs
- Normocytic
  - Normal size of RBCs
  - E.g. Leukemia, Liver disorders, Renal failure, Sickle cell anaemia

ANAEMIA: Symptoms

- Tiredness
- Dyspnoea
- Malaise
- Tachycardia, palpitations
- Headache
- Pallor – conjunctiva, oral mucosa, palmar creases
- Spoon-shaped nails – koilonychia (Fe def )
- Angular stomatitis, glossitis, BMS
- Oral Ulcers

Lab investigations in Anaemia

- RBC count: 4 - 5 ×10⁶/ml
- Hb: Males: 14-18 g/dL, Women: 12-16 g/dL.
  - Anaemia if
    - < 11.0g/dl in persons upto puberty
    - < 11.5g/dl in adult females
    - < 13.5g/dl in adult males
- Haematocrit: Male: 42-52%, Female: 37-48%.
- MCV – for detection of macro/microcytosis
  - Increase/decrease in RBC volume.
- MCH – Detection of defects in Hb production (hypochromia).
- RDW (red cell distribution width) – Detection of early iron/ folate def.
- Reticulocyte count: Normal < 2%; ↓ in ineffective erythropoiesis; ↑ anaemia Rx, polycythaemia, metastatic bone marrow carcinoma
- Peripheral smear

Dental Aspects of Anaemia

- LA recommended
- GA problem b’cos of impaired oxygenation; Nitrous oxide contraindicated in Vit B12 def; GA contraindicated in sickle cell anaemia
- Depapillation of tongue – atrophic glossitis
- Candidosis aggravated or precipitated – angular stomatitis
ANAEMIA: Types

- Iron deficiency anaemia
- Pernicious anaemia
- Aplastic anaemia
- Sickle cell anaemia
- Thalassemia

ANAEMIA: Fe deficiency

Iron (Fe) is used in:
- Haemoglobin
- Haeme enzymes, e.g., cytochromes, catalase, peroxidase
- Myoglobin
- Metalloflavoprotein enzymes such as xanthine oxidase
- The mitochondrial enzyme alpha-glycerophosphate oxidase and other mitochondrial enzymes
- Other enzymes and processes

Iron (Fe) deficiency causes

- Inadequate dietary intake of iron
- Infants in the postnatal period
- Young females after menarche
- Adolescents of both sexes
- During pregnancy
- Partial gastrectomy due to ulcers
- Blood loss due to:
  - Bleeding peptic ulcers
  - Malignancy
  - Trauma in which there is excessive bleeding
- Malabsorption syndromes
  - Cystic fibrosis
  - Celiac Disease (nontropical sprue)

Body Iron Distribution and Storage

- Dietary iron
  - Duodenum
    - (average, 1 - 2 mg per day)
- Muscle (myoglobin)
  - (300 mg)
- Liver
  - (1,000 mg)
- Bone marrow
  - (300 mg)
- Circulating erythrocytes (haemoglobin)
  - (1,800 mg)
- Reticuloendothelial macrophages
  - (600 mg)
- Plasma transferrin
  - (3 mg)
- Storage iron
  - (Ferritin)
- Iron loss
  - (Ferritin, TIBC)

ANAEMIA: Fe deficiency causes in children

- Hypochromic, microcytic, ↓ RBC
- Symptoms of anaemia
- Behavioural disorders in children
- Oral findings
  - Bald tongue, atrophic mucosa, angular cheilitis, aphthous stomatitis
  - Plummer-Vinson (Patterson-Kelly) syndrome
- Dental aspects
  - LA advised for pain control; GA avoided
  - Staining of teeth by iron preparations
Fe deficiency Anaemia

Fe def Anaemia: Lab Evaluation
- Serum iron.
- Serum ferritin (apoferitin + iron) – for body iron stores.
  - Low levels ➔ depletion of iron stores ➔ Fe deficiency.
  - Fe overload (haemachromatosis, haemosiderosis) – high serum ferritin levels.
- TIBC—total iron binding capacity (transferrin)
  - Increased in iron def.
  - Decreased in thalassemia, hemachromatosis, anaemia of infection and chronic diseases (e.g. uremia).

Fe def Anaemia: Treatment
- Ferrous sulphate 200mg t.i.d
- Ferrous gluconate 250mg/day
  Oral Iron at least for 3 months

ANAEMIA: Megaloblastic (Macrocytic)
- Due to lack of folic acid or vitamin B12
- Folate (folic acid) interacts with vitamin B12
- To synthesize DNA/RNA – formation of new cells
- Essential for normal blood and nerve function
- Vit B12
  - Also called the extrinsic factor
  - Combining with intrinsic factor from parietal glands (stomach).
  - Lack of vitamin B12 - pernicious anemia – due to autoimmune disease that destroys the parietal cells.
  - Patients also have achlorohydria ➔ halitosis.
- Sources: Meat, Eggs, Dairy products

ANAEMIA: Megaloblastic (Folic Acid def)
- Causes:
  - Inadequate folate intake – Alcoholics, Teenagers, Some infants
  - Malabsorption – Drugs (barbiturates, phenytoin, oral contraceptives), sprue, Crohn’s disease
  - Impaired metabolism – may be due to methotrexate or rare enzyme deficiencies
  - Increased req – pregnancy
- Natural folate sources: Green vegetables, Nuts, Cereals, Fruits
- Therapy: Folic acid, 5mg tabs; Multivit tabs
ANAEMIA: Pernicious

- Impaired RBC maturation secondary to insufficient vitamin B12 (cobalamin)
- Autoimmune destruction of parietal cells in the stomach
- GIT by-pass operations
- General findings: Symptoms of anaemia; paraesthesia of limbs; neurological changes paraplegia and “megaloblastic madness”; premature greying of hair
- Schilling test

ANAEMIA: Pernicious

- Oral findings
  - Burning mouth
  - Atrophic glossitis (Hunter’s glossitis)
  - Angular cheilitis
  - Aphthous ulcers
- Dental aspects
  - LA advised; Nitrous oxide contraindicated; GA not advised
- Treatment: cyanocobalamin injections

ANAEMIA: Haemolytic

- Inherited abnormalities of Hb formation
  - Haemoglobinopathies
- Inherited abnormal structure / function of RBCs
  - Spherocytosis
  - G6PD deficiency
- Extrinsic damage
  - Autoimmune
  - Infections (Malaria)
  - Drugs & heavy metals

Haemolytic Anaemia: General aspects

- Jaundice – from bilirubin overproduction
- Enlarged spleen
- Increased reticulocyte count
- Expansion of marrow cavity – due to compensatory hypertrophy

Glossitis

Angular cheilitis
ANAEMIA: Sickle-cell
- Amino acid substitution valine instead of glutamic acid in Hb β chain
- RBCs have sickle-shape
- Trait is AD; disease is AR
- Clinical Features
  - Tissue ischemia, infarction and tissue death
  - Sickle cell crisis: long bones, lungs, abdomen
  - Infections: Haem. influenza, Strep.pneumoniae, Salmonella (osteomyelitis)
  - Hyperbilirubinaemia – gall stones

Sickle cell crisis
- Deoxygenation
- Sludging
- Stasis
- Spleen
- Anoemia
- Painful Crisis
- Haemolytic Anaemia

Pathophysiology of Sickle cell disease

Sickle-cell Anaemia: Oral & Dental aspects
- GA contraindicated
- Radiographic findings
  - Reduced trabeculation of mandible
  - “Hair-on-end” appearance of calvaria
  - Hypercementosis
  - Haemopoietic maxilla - ↑ overjet/overbite
  - Osteomyelitis
  - Hypomineralization of teeth
  - Avoid aspirin – can precipitate crisis

ANAEMIA: Thalassemia
- Alpha and Beta types
- 2 genes for β; 4 genes for α
- Haemolytic disorder: spleen haemolysis

Haemoglobin structure
Thalassemias
- Heterogenous group of disorders due to an imbalance of α and β globin chain synthesis
  - α thalassemia: α-globin chain production decreased
  - β thalassemia: β globin chain production decreased
- The globin chains that are produced are normal
- Quantitative deficiency:
  - α0 thalassemia: No α-globin chain is made
  - β+ thalassemia: decreased β-globin chain is made
- With 4 α genes and 2 β genes there is wide phenotypic variation

Incidence of Thalassemia
- ~100,000 patients with homozygous β thalassemia world-wide
- Found in Mediterranean countries, South Asia and Far East

ANAEMIA: β Thalassemia
- One defective gene: thalassemia minor
- Two genes: thalassemia major (Cooley's anaemia or Mediterranean fever)
  - Detected during 1st year of life, usually after fetal hemoglobin synthesis ceases
  - Extremely fragile RBCs
  - Extramedullary haematopoiesis - Hepatomegaly, splenomegaly

ANAEMIA: β Thalassemia
- Painless enlargement of mandible and maxilla
  - “Chipmunk” facies
  - “Hair-on-end” appearance of calvaria

ANAEMIA: α Thalassemia
- 1 gene affected → no disease
- 2 genes affected → trait
- 3 genes affected → Hb H disease – Haemolytic anemia, splenomegaly
- 4 genes affected → hydrops foetalis – Fatal within hours of birth

ANEMIA: Aplastic
- All types of blood cells affected
- Cause: environmental toxins, drugs, viruses, genetic disorders (Fanconi’s anemia, dyskeratosis congenita)
- Laboratory values
  - < 500 granulocytes/µl
  - < 20,000 platelets/ µl
  - <10,000 reticulocytes/ µl
ANAEMIA: Aplastic

- Mild to severe
- Clinical findings
  - Symptoms of anaemia
  - Thrombocytopenia
  - Retinal & cerebral hemorrhage
  - Neutropenia, leukopenia, granulocytopenia
- Treatment
  - Antibiotics, transfusions, androgenic steroids, immunomodulatory therapy, BMT

Polycythemia (Rubra) Vera

- Rare idiopathic haematologic disorder
- ↑ RBC, also uncontrolled production of platelets and granulocytes
- Abnormal proliferation uncontrolled due to regulatory hormones such as erythropoietin
- Older patients

Polycythemia Vera

- Initially, nonspecific clinical symptoms, 40% of patients report pruritus
- CVA, MI
- Erythromelalgia: burning sensation & erythema
- Haemorrhage
- Gingival haemorrhage
- Increased risk for leukemia due to chemotherapy