Session 4
Lymphatic and Haematological Disorders 2
Bioscience Department
Session Learning Outcomes

At the end of the session, you should be able to

- Classify various types of anaemia in terms of their aetiology and morphology.
- Identify the causes, pathophysiology and clinical manifestations of various types of anaemia.
- Suggest appropriate investigations and management for the conditions.
- Define and describe the haemoglobinopathies in terms of their cause, pathophysiology, role of hereditary trait, treatment and management.
Session Plan

- The Anaemias:
  - Classification of anaemia
  - Iron deficiency anaemia
  - Megaloblastic anaemia
  - Anaemia of chronic disease
  - Haemolytic anaemia
  - Haemoglobinopathies
    - Sickle cell anaemia
    - Thalassemia
Anaemia

Definition: A state in which there is decrease in the level of haemoglobin in the blood below the reference level for the age and sex of the individual.

- Normal reference range: (varies with age, gender and ethnic origin of a person)
  - Adult male 130-195 g/L
  - Adult female 115-165 g/L

Red cell characteristics seen in different types of anaemia: (A) microcytic and hypochromic red cells, characteristic of iron deficiency anaemia; (B) macrocytic and misshaped red blood cells, characteristic of megaloblastic anaemia; (C) abnormally shaped red blood cells seen in sickle cell disease; (D) normocytic and normochromic red blood cells,

Images from: Grossman, S, Porth, CM 2013, Porth’s pathophysiology, Concepts of Altered Health States, 9th edn, Lippincott Williams & Wilkins
Classification of Anaemia

- Aetiological classification of anaemia:
  - Inadequate nutrients to synthesize RBC
    - Iron deficiency anaemia, Megaloblastic anaemia
  - Excessive loss of RBC
    - Haemolytic anaemia: destruction of RBCs
  - Genetic defect in Haemoglobin synthesis
    - Thalassemia, Sickle cell anaemia
Classification of Anaemia

- Morphological classification of Anaemia
  - Based on size of RBC
    - Macrocytic
    - Normocytic
    - Microcytic
  - Based on Content of Haemoglobin in the RBC
    - Hypochromic
    - Normochromic
Classification of Anaemia

Fig. 24.19 Factors which influence the size of red cells in anaemia. In microcytosis, the MCV is < 76 fl. In macrocytosis, the MCV is > 100 fl.
(MCV = mean cell volume; RBC = red blood cell)
General Signs and Symptoms, Anaemia

- Symptoms:
  - Fatigue
  - Headache
  - Tinnitus
  - Fainting
  - Breathlessness
  - Angina
  - Palpitation
  - Intermittent claudication

- Signs:
  - Pallor
  - Tachycardia
  - Systolic flow murmur
  - Cardiac failure
  - Papilloedema
Iron deficiency anaemia

○ Aetiology:
  • Blood loss
  • Malabsorption or dietary deficiency of Iron
  • Increased physiological demands

○ Pathophysiology:
  Lack of Iron $\rightarrow$ Decreased synthesis of Haemoglobin $\rightarrow$
  Decreased RBC size with decreased haemoglobin concentration $\rightarrow$
  Microcytic hypochromic anaemia $\rightarrow$
  Impaired oxygen transport
Iron deficiency anaemia

Iron digestion, absorption, enterocyte use, transport and distribution

Iron deficiency anaemia

Clinical features:

- Common symptoms of Anaemia
  - Pallor, Palpitation, Headache, lack of concentration, Shortness of breath
- Koilonychia
- Sore ulcers at the corner of the mouth (Glossitis and angular stomatitis)
- Severe cases may present with murmurs
Iron deficiency anaemia

- **Diagnosis:**
  - FBC: Haemoglobin, MCV, MCHC, haematocrit
  - Iron studies: Plasma Iron, Ferritin, Transferrin levels, Total Iron binding capacity
  - Peripheral smear of blood
  - Investigation of the cause

**Normal peripheral blood smear**

**Iron deficiency anemia peripheral blood smear**

http://library.med.utah.edu/WebPath/TUTORIAL/IRON/IRON.html#1
Iron deficiency anaemia

Management:
- Control chronic blood loss
- Increase dietary intake of iron
- Administering supplemental iron
- Iron transfusion in severe cases
Iron deficiency anaemia: Low level of haemoglobin in blood due to lack of iron

**Blood loss, Malabsorption or dietary deficiency of Iron, Increased physiological demands**

- **Lack of Iron**
  - Decreased synthesis of Haemoglobin
  - Decreased RBC size with decreased haemoglobin concentration
  - Microcytic hypochromic RBCs
  - Impaired oxygen transport to body tissues
  - Epithelial atrophy

- **Pallor**
  - Palpitation
  - Headache
  - Lack of concentration
  - Shortness of breath
  - Systolic murmurs

Diagnosis:
- FBC
- Iron studies
- Peripheral smear of blood
- Investigation of the cause

Management:
- Control chronic blood loss
- Increase dietary intake of iron
- Administering supplemental iron
- Iron transfusion in severe cases

- Pallor, brittle hair and nails
- Koilonychias
- Smooth tongue
- Glossitis and angular stomatitis
- Dysphagia and decreased acid secretion

- Impaired oxygen transport to body tissues
- Waxy pallor
- Palpitation
- Headache
- Lack of concentration
- Shortness of breath
- Systolic murmurs
- Epithelial atrophy

**Colour Key:**
- Clinical features
- Definition
- Aetiology
- Pathophysiology

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Megaloblastic Anaemia

○ Aetiology:
  • Vitamin B12 deficiency:
    – Dietary deficiency
    – Gastric factors
    – Pernicious anaemia
    – Small bowel factors
  • Folic acid deficiency:
    – Dietary deficiency
    – Malabsorption
    – Increased demand
    – Drugs

Absorption of vitamin B12

Megaloblastic Anaemia

- Pathophysiology:
  - Lack of B12 and Folate $\rightarrow$ Poor methionine metabolism $\rightarrow$ High plasma levels of homocysteine and impaired DNA synthesis $\rightarrow$ Cell with arrested nuclear maturation but normal cytoplasmic development (megaloblast) $\rightarrow$ All proliferating cells (bone marrow cells, buccal mucosa, tongue, small intestine, cervix, vagina and uterus) exhibit megaloblastosis.
  - Lack of B12 $\rightarrow$ Focal demyelination affecting the spinal cord, peripheral nerves, optic nerves and cerebrum $\rightarrow$ Neurological symptoms
Megaloblastic Anaemia

Megaloblastic Anaemia

Clinical features:

Symptoms:
- Malaise
- Breathlessness
- Paraesthesiae
- Sore mouth
- Weight loss
- Altered skin pigmentation

- Impotence
- Poor memory
- Depression
- Personality change
- Hallucinations
- Visual disturbance
Megaloblastic Anaemia

• Signs
  - Smooth tongue
  - Angular cheilosis
  - Vitiligo
  - Skin pigmentation
  - Heart failure
  - Pyrexia

• Neurological findings in B12 deficiency
  - Glove and stocking paraesthesiae
  - Loss of ankle reflexes
  - diminished vibration sensation and proprioception
  - upper motor neuron signs
  - Dementia
  - Optic atrophy
  - Autonomic neuropathy
Megaloblastic Anaemia

- **Diagnosis:**
  - FBC: Haemoglobin, MCV, Blood cell counts
  - Serum Ferritin
  - Plasma lactate dehydrogenase (LDH)
  - Peripheral smear of blood
  - Bone marrow
  - Investigation of the cause
Megaloblastic Anaemia

- Management:
  - Management of Vit. B12 deficiency
  - Management of Folic acid deficiency

http://library.med.utah.edu/WebPath/HEMEHTML/HEME009.html
Megaloblastic anaemia: Low level of haemoglobin in blood due to lack of vitamin B12 or Folic acid.

Vitamin B12 deficiency:
- High plasma levels of homocysteine and impaired DNA synthesis
- All proliferating cells with arrested nuclear maturation but normal cytoplasmic development (megaloblastosis)
- Megaloblastosis in cells of bone marrow, buccal mucosa, tongue, small intestine, and genital tract
- Malaise, Breathlessness, weight loss, Smooth tongue, pyrexia, Angular cheliosis, Sore mouth, altered skin pigmentation, Impotence

Folic acid deficiency:
- Poor methionine metabolism
- Diagnosis: FBC, Serum Ferritin, Plasma lactate dehydrogenase (LDH), Peripheral smear of blood, Bone marrow, Investigation of the cause

Dietary deficiency:
- Malabsorption, Increased demand

Gastric factors:
- Pernicious anaemia
- Small bowel factors

Dietary deficiency:
- Dietary deficiency

Dental factors:
- Poor methionine metabolism

Upper motor neuron signs:
- Dementia,
- Optic atrophy
- Autonomic neuropathy

Clinical features:
- Malaise, Breathlessness, weight loss, Smooth tongue, pyrexia, Angular cheliosis, Sore mouth, altered skin pigmentation, Impotence

Definition:
- Clinical features
- Diagnosis
- Management
- Complications

Aetiology:
- Dietary deficiency
- Gastric factors
- Pernicious anaemia
- Small bowel factors

Pathophysiology:
- Focal demyelination affecting the spinal cord, peripheral optic nerves and cerebrum
- Paraesthesiae
- Loss of ankle reflexes
- Diminished vibration sensation and proprioception
- Upper motor neuron signs
- Dementia
- Optic atrophy
- Autonomic neuropathy

Management:
- Management of Vit. B12 deficiency
- Management of Folic acid deficiency
Anaemia of chronic disease

- **Aetiology:**
  - Chronic infection
  - Chronic inflammation
  - Neoplasia

- **Pathophysiology:**
  Pro-inflammatory cytokines in chronic disease →
  Induce hepcidin production by liver cells →
  Hepcidin binds to ferroportin and internalise ferroportin into iron storing cells →
  reduced release of iron →
  Low circulatory Iron →
  Reduced Erythropoiesis →
  Normocytic normochromic anaemia
Anaemia of chronic disease

Anaemia of chronic disease

- **Diagnosis:**
  - FBC: Haemoglobin, MCV
  - Iron studies: Serum Iron, Ferritin, Transferrin levels, Total Iron binding capacity
  - Serum soluble transferrin receptor
  - Bone marrow

- **Management:**
  - Measures to reduce the severity of the underlying disorder
Anaemia of chronic disease

- Differential diagnosis
  - Iron deficiency anaemia

Haemolytic anaemia

- **Definition:** Anaemia resulting from increased rate of RBC destruction

- **Types:**
  - **Extravascular haemolysis:**
    - Rapid red cell destruction in the reticuloendothelial cells in the liver or spleen.
    - No free haemoglobin in the plasma.
  - **Intravascular haemolysis:**
    - Red cell lysis within the blood stream
    - Free haemoglobin is released into the plasma
Haemolytic anaemia

Aetiology:
- Inherited causes of haemolysis
  - Red cell membrane defect: hereditary spherocytosis/elliptocytosis
  - Haemoglobin abnormalities: Thalassemia, sickle cell disease
  - Red cell enzyme deficiencies: G6PD deficiency, Pyruvate kinase deficiency, pyrimidine 5’nucleotidase deficiency
Haemolytic anaemia

- Aetiology:
  - Acquired causes of haemolysis
    - Immune: autoimmune diseases, haemolytic diseases of newborn, transfusion reactions, drug induced
    - Non immune – acquired membrane defects, mechanical causes, secondary to systemic diseases related to liver and kidneys, Infections, Drugs and chemicals, Burns
Haemolytic anaemia

- Clinical features:
  - Severe pallor, shortness of breath and heart failure
  - Episodic jaundice in some patients
  - Young children may show failure to thrive
  - Gall bladder stones due to excessive bilirubin formation in chronic cases
  - Increased pulmonary hypertension due to hypoxic conditions and right ventricular failure
Haemolytic anaemia

- **Diagnosis:**
  - Full blood count
  - Peripheral blood smear
  - Red blood cell enzymes
  - Serum bilirubin, lactate dehydrogenase
  - Urine and stool examination
  - Bone marrow
  - Coomb’s test for antibodies against red cells

- **Management:**
  - Treatment of underlying cause
  - Corticosteroids
  - Blood transfusion
Haemoglobinopathies

- Definition: The diseases caused by mutations of the genes encoding the globin chains of the haemoglobin molecule.

- Types:
  - Qualitative abnormalities
    - Alteration in the amino acids structure/sequence
    - Example: Sickle cell anaemia
  - Quantitative abnormalities
    - reduced rate of production of one or other of the globin chains
    - Example: Thalassemias
Sickle cell Anaemia

○ **Definition:** an inherited disorder in which an abnormal haemoglobin (HbS) leads to chronic haemolytic anaemia, pain, and organ failure.

○ **Aetiology:**
  - Inherited as an autosomal recessive trait
  - Substitution of one glutamic acid to valine in the amino acid chain of Beta Haemoglobin

○ **Pathophysiology:**
  Abnormal haemoglobin → Sickle shaped RBC → Early destruction of RBC
Mechanism of sickling and its consequences in sickle cell anaemia

Sickle cell Anaemia

- Clinical features:
  - Hypoxia
  - Acidosis
  - Dehydration
  - Infection
  - Acute syndromes:
    - Vaso-occlusive crisis
    - Sickle chest syndrome
    - Sequestration crisis
    - Aplastic crisis
  - Chronic organ damage
Sickle cell Anaemia

Sickle cell Anaemia

○ Diagnosis:
  • FBC: Hb
  • Blood film examination
  • HbS screening: Exposing red cells to a reducing agent such as sodium dithionite
  • Haemoglobin electrophoresis

○ Management:
  • Prophylaxis, vaccination
  • Aggressive rehydration, analgesics, O₂, antibiotics, transfusion
  • Allogeneic stem cell transplants
  • Hereditary trait counselling
Thalassaemia

- **Definition:** an inherited impairment of haemoglobin production, in which there is partial or complete failure to synthesise either the α- or β-globin chains of HbA.

- **Types:**
  - Beta thalassaemia
    - Thalassaemia minor
    - Thalassaemia major
  - Alpha thalassaemia
Thalassaemia

- **Aetiology:**
  - Beta thalassaemia: Multiple point mutations in the β-globin gene causing a defect in β-chain synthesis
  - Alpha thalassaemia: Deletion of alpha gene alleles on chromosome 16

- **Pathophysiology:**
  
  Genetic mutation → reduced rate of production of one or other of the globin chains → alpha to non-alpha chains ratio altered → the excess chains precipitate within RBC precursors → formation of abnormal haemoglobin with less affinity for oxygen → RBC membrane damage and haemolysis → Microcytic Hypochromic anaemia
Beta Thalassaemia

- **Clinical features:**
  - Severe, blood transfusion–dependent anemia
  - Bone marrow hyperplasia early in life.
  - Impaired bone growth and Bone deformities
  - Splenomegaly, Hepatomegaly

- **Complications:**
  - Iron overload leading to Cardiac, hepatic, and endocrine diseases and organ damage
Beta Thalassaemia

Management:
- Regular blood transfusions
- Iron chelation therapy
- Stem cell transplantation

Alpha Thalassaemia

- Clinical features: related to the number of gene deletions
  - One gene deletion: no clinical effect.
  - Two genes deletion: mild hypochromic anaemia.
  - Three gene deletion: Haemoglobin H disease.
  - Four gene deletion: stillborn baby (hydrops fetalis).

- Management:
  - Folic acid supplementation
  - Transfusion if required
  - Avoidance of iron therapy
Reading and Resources

- Crowley LV, 2012, *An Introduction to Human Diseases – Pathology and Pathophysiology Correlations*, 9th edn, Jones and Bartlett Learning
Reading and Resources

- Mosby’s dictionary of medicine, nursing and health professions 2013, 9th edn, Elsevier, St. Louis, MO.
- VanMeter, KC & Hubert, RJ 2014, *Gould’s pathophysiology for the health professions*, 5th edn, Elsevier, St Louis, MO.
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