HEMOGLOBIN STRUCTURE AND FUNCTION

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Normal hemoglobin consists of 4 heme groups, which contain a protoporphyrin ring plus iron, so haem is an iron containing porphyrin-iron protoporphyrin and globin, which is a tetramer of 2 pairs of polypeptide chains.

- The iron must be in the Fe(II) form or reduced form
- Molecular weight: 68000

Composition of hemoglobin:
1. A protein called globin made up of two alpha and two beta chains
2. heme molecule
   Each heme group bears an atom of iron, which can bind to one oxygen molecule
   Each hemoglobin molecule thus can transport four molecules of oxygen.

- The porphyrin nucleus is tetapyrrole & pyrrole rings joined together by 4 methine (=CH-) bridges.
  Eight side chains are attached to the pyrrole ring: 1, 3, 5, & 8 position are methyl(-CH₃)
  2 & 4 are vinyl (-CH=CH₂); 6, 7 are propionic acid.
NORMAL HEMOGLOBIN PRODUCTION DEPENDS ON 3 PROCESSES: ADEQUATE IRON DELIVERY AND SUPPLY, ADEQUATE SYNTHESIS OF PROTOPORPHYRINS AND ADEQUATE GLOBIN SYNTHESIS.

Iron content of haemoglobin is 0.33%, therefore 100 mL of blood containing 15 gm of Hb contains approx. 50 mg of iron.

**Synthesis of protoporphyrin:**
- Begins in the mitochondria where glycine + succinyl CoA → delta aminolevulenic acid (δ ALA). This is the rate limiting step.

**Iron delivery and supply:**
- Iron is delivered to the RBC precursor by transferrin. It goes to the mitochondria where it is inserted into protoporphyrin to form heme.
- In the cytoplasm 2 δ ALA
  - Prophobilinogen (PBG)
  - Protoporphyrin

**Factors:**
- Role of proteins:
- Role of iron:
- Role of other metals: copper: iron, cobalt: erythropoietin, calcium: iron
- Role of vitamins: nucleic acid
**Derivatives of haemoglobin**

- **Oxyhemoglobin** – hemoglobin bound to oxygen
  - Oxygen loading takes place in the lungs
  - Forms HbO₂
- **Deoxyhemoglobin** – hemoglobin after oxygen diffuses into tissues (reduced Hb)

- **Carboxyhemoglobin** - CO replaces O₂ and binds 200X tighter than O₂
  - This may be seen with heavy smokers
- **Carbaminohemoglobin** – hemoglobin bound to carbon dioxide \((\text{HbNHCOOH})\)
- Carbon dioxide loading takes place in the tissues
- **Methaemoglobin**- (HbOH) occurs when iron is oxidized to the +3 (ferric) state.

- **Glycosylated hemoglobin** : The most abundant form of glycosylated hemoglobin is HBA1c which has a glucose residues attached to β globin chains in hemoglobin RBCs.
  - Increased amounts of HBA1c are found in RBCs of patients with diabetes mellitus (DM).

- **HBA**: the major hemoglobin in humans
- **HBA2**: first appears 12 weeks after birth- a minor component of normal adult HB
- **HBF**: normally synthesized only during fetal development
- **HBA1C**: has glucose residues attached to β-globin chains – increased amounts in DM.
HbS

- Glutamic acid is replaced by a valine at the 6 position.
- Sickle Cell Anemia is a genetic disorder that is characterized by the formation of hard, sticky, sickle-shaped red blood cells, in contrast to the biconcave-shaped red blood cells (RBCs) found in “normal” individuals.
- This disease is caused by a mutation in hemoglobin.

Normal values

- Adult males- 14 - 18 g/ dL (15.5)
- Adult females- 12 – 15.5 g/ dL(14)
- At Birth-23 g/dL
- Clinically 14.8g/dL is considered as 100% Hemoglobin

1gm/dL Hb when fully saturated combines with 1.34 mL of oxygen. So Hb concentration is an index of oxygen carrying capacity of blood. Normal values of oxygen carrying capacity in males is about 21mL% & in females -18.5mL%

Destruction of Erythrocytes

- The life span of an erythrocyte is 120 days
- Old erythrocytes become rigid and fragile due to decreased NADPH activity, and their hemoglobin begins to degenerate

Dying erythrocytes are engulfed by macrophages
- Heme and globin are separated
  - Iron is removed from the heme and reuse
  - Stored as hemosiderin or ferritin in tissues
  - Transported in plasma by beta-globulins as transferrin

Heme is degraded to a yellow pigment called bilirubin
- Liver secretes bilirubin into the intestine as bile
- Intestine metabolize bilirubin into urobilinogen
- Urobilinogen leaves the body in stool, in a pigment called stercobilinogen
- Globin is metabolized into amino acids which are then released into the circulation
The tissue macrophage system (reticulo endothelial system) includes the following phagocytic cells:
- 1. in the liver
- 2. in the spleen
- 3. in the lymph nodes

Clinical Manifestations:
- 1. Palloriness of skin & mucous membrane
- 2. Fatigue, weakness.
- 3. Dyspnea: **difficulty in breathing**, or **air hunger**.
- 4. Palpitations, tachycardia

- 5. Headache, dizziness, and restlessness.
- 6. Slowing of thought.
- 7. Nausea, is a sensation of unease and discomfort in the upper stomach. Nausea, is a sensation of unease and discomfort in the upper stomach with an involuntary urge to **vomit**.
- Constipation

ANAEMIA

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An anaemic individual will have the following two key compensatory mechanisms:

1. The cardiovascular system

Cardiac compensation is the major adaptation. Both stroke volume and heart rate increase mobilizing greater volumes of oxygenated blood to the tissues. This can present with palpitations, tachycardia and heart murmurs. Dyspnoea which occurs in severely anaemic patients may be a sign of cardio-respiratory failure.

2. The skin

A common sign is generalised pallor due primarily to vasoconstriction with redistribution of blood to key areas (brain, myocardium).

classification of anaemia

Essentially there are two ways to classify anaemia, by red cell size (morphological classification) or by cause (etiological classification).

1. Morphological classification
2. Etiological classification

Nursing Management:
1. Direct general management toward addressing the cause of anemia and replacing blood loss as needed to sustain adequate oxygenation.
2. Promote optimal activity and protect from injury.
3. Reduce activities and stimuli that cause tachycardia and increase cardiac output.
4. Provide nutritional needs.
5. Administer any prescribed nutritional supplements.
6. Patient and family education

ETIOLOGICAL CLASSIFICATION

- Hemorrhagic anemia
- Megaloblastic Anemias
- Hemolytic Anaemia
- Aplastic Anaemia
- Iron deficiency Anemia
Hemorrhagic anemia: – due to acute or chronic loss of blood:

- **Acute**: Due to hemorrhage, plasma is replaced in 1-3 days. Normocytic normochromic
- **CHRONIC**: Microcytic Hypochromic Anemia: Low levels of hemoglobin in RBCs due to chronic blood loss resulting in low iron levels in newly produced RBCs.

Megaloblastic Anemias

- Characterized by large RBCs which are fragile and easily destroyed
- Common forms of megaloblastic anemia
  1. Cobalamin deficiency
  2. Folic acid deficiency

Megaloblastic anemia due to Deficiency of vitamin B\textsubscript{12}

Causes of vitamin B12 deficiency:
1) Lack of intrinsic factor: Pernicious anemia is due to absorption failure (atrophic gastric mucosa).
2) Severe pancreatic deficiency leading to non freeing of vitB\textsubscript{12} from R binder protein.
3) Severe disorders of small intestinal epithelium e.g. malabsorption syndrome
4) Gastrectomy

Pernicious Anemia: impaired absorption of Vitamin B-12 because of a lack of intrinsic factor (IF) in gastric secretions. **It is an autoimmune disease.** Vitamin B12, in turn, is necessary for the formation of red blood cells.

- Schilling Test: a medical investigation used for patients with vitamin B12 deficiency. The purpose of the test is to determine if the patient has pernicious anemia, corrected by addition of I.F

Important points:
- Although macrocytic anemia due to vit B12 deficiency may respond to folate therapy, neurologic findings will not improve
  - Neurologic defects may be permanent if not treated early.
  - Clinical features: level will be very low

Clinical manifestations
- General symptoms of anemia
- Macrocyte
- MCV, MCH increase
- Hb decrease
- Anisocytosis, poikilocytosis
Lifespan of RBCs decreases
- Reticulocyte count increases
- Serum bilirubin increases
- Serum iron & ferritin increases
- Weakness
- Altered thought processes
- Confusion → dementia

2. Folic Acid Deficiency: also causes megablastic anemia (RBCs that are large and fewer in number)
- Folic Acid required for RBC formation and maturation
- Causes
  - Poor dietary intake
  - Malabsorption syndromes
  - Drugs that inhibit absorption
  - Alcohol abuse

Absence of neurologic problems
- Treated by folate replacement therapy
- Encourage patient to eat foods with large amounts of folic acid
  - Leafy green vegetables
  - Liver
  - Mushrooms
  - Oatmeal
  - Peanut butter
  - Red beans

3. Aplastic Anemia: Decreased RBC production in bone marrow due to chemical, drug, or radiation exposure, gold salts.
- Diagnosis can be confirmed by bone marrow examination.
- RBCs are normocytic normochromic

Iron deficiency anaemia
- Etiology:
  1. Inadequate dietary intake
  2. Increased Blood loss:
     - internal bleeding from the gastrointestinal tract
   - Peptic ulcer, increased menstrual blood loss
- 3. increased demand: infancy, childhood, pregnancy
- 4. decreased absorption: gastrectomy, achlorhydria (lack of gastric acid secretion) malabsorption diseases.
- Daily requirement: 5-10 mg/day
  females: 20 mg/day & 40 mg
Clinical Manifestations
- Second most common: angry red, inflammation of the tongue (glossitis)
- Mouth may show angular stomatitis
- Weakness and fatigue
- Headache, Irritability, loss of concentration
- Nails dry, soft, spoon shaped
- Dysphagia (difficulty in swallowing)
- Most common: pallor

Diagnostic Studies
- MCV, MCH, MCHC & CI decrease
- RBC: Microcytic hypochromic
  - Iron levels: Total iron-binding capacity (TIBC) increases, Serum iron decreases.
  - Peripheral smear shows anisocytosis & poikilocytosis

Hemolytic anemia
- Anemia of increased destruction of rbc
  - Normochromic, normochromic anemia
  - Shortened RBC survival

- INTRACORPUSCULAR HEMOLYSIS (cause of RBC destruction)
- Hereditary in nature
  - Metabolic Abnormalities
  - Hemoglobinopathies
- EXTRACORPUSCULAR HEMOLYSIS
  - Antigen-antibody mn
  - Infection: Malaria
  - Toxic effects of drugs & chemicals (Penicillin, lead)

- Sickle-cell Anemia: Genetic mutation causing abnormal beta chains. When this hemoglobin is exposed to low O2 concentrations, it precipitates into long crystals that cause the cells to become sickle-shaped.
  - Glutamic acid is replaced by a valine at the 6 position.
HbS

- Sickle Cell Anemia is a genetic disorder that is characterized by the formation of hard, sticky, sickle-shaped red blood cells, in contrast to the biconcave-shaped red blood cells (RBCs) found in "normal" individuals.

-β-thalassaemia major requires repeated blood transfusion

- G6PD deficiency anaemia:
  - G6PD is a key enzyme in the hexose monophosphate shunt. An important function of the shunt is maintain healthy haemoglobin by protection from oxidant stress. It is required in the formation of NADPH, which in turn maintains glutathione, in the reduced state. In G6PD deficiency, haemolytic anaemia occurs.

Avoid precipitants of oxidative stress; drugs (anti-malarials, analgesics),
- Blood transfusion if required.

Jaundice

- Jaundice refers to the yellow appearance of the skin, sclera and mucous membrane resulting from an increased bilirubin concentration. Clinically, jaundice is detectable when the plasma bilirubin exceeds 2-3mg/dL.
**Category**
- **Pre-hepatic/ hemolytic:** The pathology is occurring prior to the liver.
- **Hepatic/ hepatocellular:** The pathology is located within the liver.
- **Post-Hepatic/ cholestatic/obstructive:** The pathology is located after the conjugation of bilirubin in the liver.

**Pre-hepatic jaundice** is caused by anything which causes an increased rate of hemolysis caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells) caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells). In tropical countries, *malaria* caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells).

**Hepatocellular (hepatic) jaundice:** can be caused by acute or chronic hepatitis, cirrhosis, can be caused by acute or chronic hepatitis, cirrhosis, drug induced hepatitis and alcoholic liver disease can be caused by acute or chronic hepatitis, cirrhosis, drug induced hepatitis and alcoholic liver disease. Cell necrosis reduces the

**Post-hepatic jaundice,** also called obstructive jaundice, is caused by an interruption to the drainage of bile caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones caused by an interruption to the drainage of bile in the biliary system. The most common causes are gallstones in the common bile duct cause by an interruption to the