HAEMATOLOGICAL DISEASES : ANAEMIA

Anaemia - is defined as reduced Haemoglobin (Hb) conc. in blood below the lower limit of normal range (Male - 13 g/dL, Female - 11.5 g/dL, Infant - 15 g/dL)

Pathophysiological Classification –

1. Anaemia due to increased blood loss –
   a) Acute post-haemorrhagic anaemia
   b) Chronic blood loss
2. Anaemias due to impaired red cell production
   a) Cytoplasmic maturation Defects
      (i) Deficiency Haem Synthesis → Iron Deficiency
      (ii) Deficiency Globin Synthesis - Thalassemia
   b) Nuclear maturation Defects -
      (1) Vit B_{12} / Folic acid Deficiency - Megaloblastic A
   c) Defect in stem cell proliferatn & differentiation
      (1) Aplastic A. (2) Pure red cell Anaemia
   d) Anaemia due to chronic disorder (Cancer, Kidney & Liver)
   e) Bone Marrow infiltration - (Leukamias, Lymphomas, Myelosclerosis, myeloma)
   f) Congenital Anaemia
3. Haemolytic Anaemia
   A) Extrinsic (Extracapsular) Red Cell Abnormilities
   B) Intrinsic (Intracapsular) Red Cell Abnormilities

Morphological Classification →

1. Microcytic, Hypochromic - MCV, MCH, MCHC are all reduced. e.g.,- Iron deficiency, Thalassaemia)
2. Normocytic, Normochromic - MCV, MCH, MCHC are all normal. e.g., - Acute blood loss, Haemolytic A. Bone merrow failure, chronic diseases.
3. Macrocytic - MCV is raised (Megaloblastic An.)

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① Mean Corpuscular Volume (MCV)

$$MCV = \frac{PCV \text{ in L/L}}{RBC \text{ count/L}}$$

* PCV = Packed Cell Volume
  Hametocrit

* PCV = IS the volume of Erythrocytes / L of blood (M = 0.47 ± 0.07 L/L, F = 0.42 ± 0.05 L/L)
* RBC Count (M = 5.5 ± 1 x 10^{12}/L, F = 4.8 ± 1 x 10^{12}/L)
* Hb - (M = 15 ± 2.5 g·l⁻, F = 14.0 ± 2.5 g·l⁻)
* MCV = 85 ± 8 fL

② Mean Corpuscular Haemoglobin (MCH)

$$MCH = \frac{Hb \text{ /dL}}{RBC \text{ count/L}} = 29.5 \pm 2.5 \text{ g/dl}$$

3) Mean Corpuscular Haemoglobin conc. (MCHC)

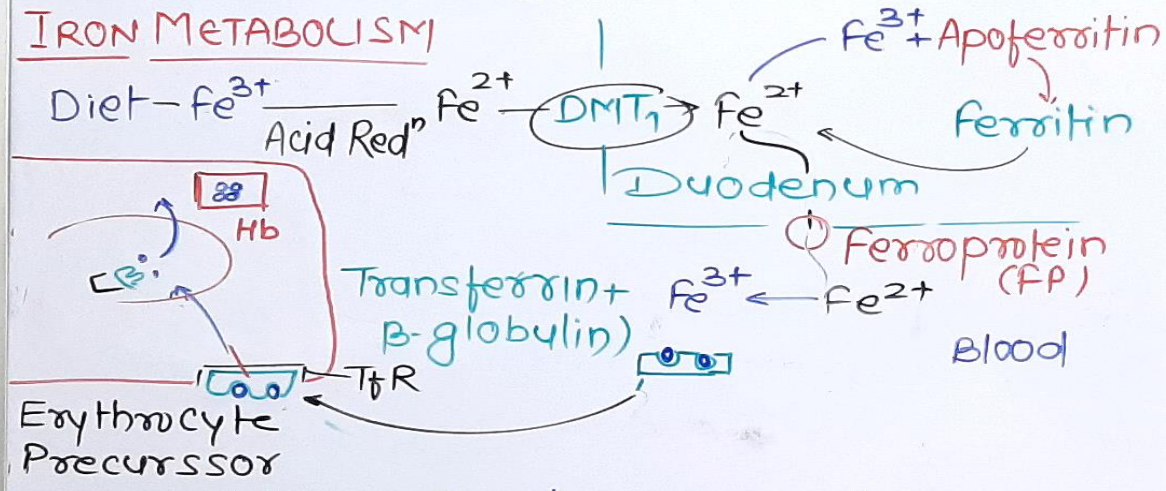
$$MCHC = \frac{Hb/dL}{PCV \text{ L/L}} = 32.5 + 2.5 \text{ g/dL}$$

d (deci) = 10^{-1}
m (emili) = 10^{-3}
μ (micro) = 10^{-6}
n (nano) = 10^{-9}
p (pico) = 10^{-12}
f (femto) = 10^{-15}

IRON DEFICIENCY ANAEMIA

Anaemia due to Iron deficiency → ↓Hb Syn
Hypochromic & Microcytic anaemia
↓ Red Cell indices (MCV, MCH, MCHC)
Daily Req.- 0.5-1 mg/day (M) & 1-2 mg/day (F)

IRON METABOLISM



Iron - Hb (65%), Ferretin & Haemosiderin (30%), Myoglobin (3.5%), Parenchymal iron (2.5%)

SYMPTOMS - Fatigue, Weakness, Pale skin, headach. Cold hand & feet, Brittle nail, poor appetite.

ETIOLOGY -

1 Increased Blood Loss

A) Uterine losses - Excessive menstruation, Miscarriage, Post menopausal Bleeding

B.) Renal Losses - Haematourea, Haemoglobinurea

c) GI losses - Peptic ulcer, Stomach cancer, Haemorr-hoid hookworm infection, hiatus hernia, ulcerative colitis, chronic Aspirin ingestion

d) Nose - Repeated Epistaxis (bleeding)

e) Lungs - haemoptysis (Coughing of blood)

2. Increased Requirements

↳ Spurts of growth in infancy, childhood, adolescence
↳ Pregnancy & Lactation
↳ Prematurity

3 Inadaquate Dietary Intake

1. Poor Economical State - Starvation
2. Anorexia during pregnancy
3. Elderly individual

4. Decreased Absorption

↳ Partial/total Gastrectomy
↳ Achlorhydria
↳ Coeliac disease- ↓Intestinal Absorpt"

PATHOGENSIS :- Imbalance of Demand, Supply, Absorption, Transport defect, and Loss →

* Anaemia → Hypoxia → Hypoxic cell/organ injury → Disease

Treatments - ① Iron Supplements

2) Dietary Intake - Liver, Red Meat, Eggs, Dry beans, Dry Fruits, Banana, Apple, Spinach, Vegitable

3) Treating underlying causes

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MEGALOBLASTIC ANAEMIA

Vitamin B12 & Falic acid Deficiency Anaemia
Associated with Macrocytic blood picture & Megaloblastic marrow erythopoiesis.
Proerythroblast → Mature Erythrocyte
Diet → Vit B_{12} & Folate ↑ ↓ Size & loss of Nucleus
↳ Megaloblast - "Ehrlich" 1880
MCV (77-93 fl) > 94 fl

Vit B12 (Cobalamin) - Coblat containg Vitamin

Metabolically Active Form - methyl-Clb, Adenosyl-Clb
Therapeutic preparatn of Vit B_{12} - Cyanocobalamin

Diet — Vit B_{12} (B) → B-Gastric R binder (glycoprotein)
(Animal proteins) ((Saliva, milk, plasma, phagocytes)
↓ Duodenum
Ileum mucosal
B — B-IF — B-IF (IF - Intrinsic factor) secreted by parital cell of stomach
Blood — B — (TC)II Transcobalamin
B → Taken up by "Liver", Bone merrow

Storage - 2mg-Liver, 2mg-kidney, heart, brain

Folic Acid - Diet (Vegitables & meats)

Polyglutamate
F. Conjugase
Monos & Diglutamate
Duodenum
Jejunum
THF ← M/DG ← Mono & Diglutamate
Methyl THF ← THF (MG)
m-THF → Polyglutamate (MG)

Thymidylate Synthatase Reactn

dump — dTMP → DNA
Methylene-THF
DHF
DHF Reductase
THF
Methionine
methyl Vit B_{12}
Homocysteine
Methyl-THF

- Folate Deficiency
- Drug (MTX)
- Vit B_{12} Deficiency

Homocystein-methionine Reactn

ETIOLOGY:- I. Vitamin Vit B12 Deficiency

a) Inadequate Diet Intake - Vegetarians
b) Malabsorption - # GI Causes (pernicious anaemia, gastrectomy, Congenital lack of IF
Intestinal Causes (Crohn's disease, Fish-tapworm infection, Intestinal blind loop syndrome

II Folate Deficiency -

a) Inadequate Dietary intake - Alcoholic, teenagers, infant, oldage, poverty
b) Malabsorption - Coeliac dis., gastractomy, Crohns dis
c) Excessive Demand -
1) Physiological - Pregnancy, lactatn, infancy
2) Pathological - Cancer, TB, rheumatoid Arthritis
D) Excessive urinary loss - Liver Disease, Congenital Heart failure

SICKLE CELL ANAEMIA

Sickle cell anaemia is an inherited red blood cell disorder in which there aren't enough healthy RBCs to carry oxygen throughout the body.

Normal RBC (Biconcave, disk) → Sickle RBC
HbA → Sickle haemoglobin (Hbs) (Crescent shaped)

Sickle Syndrome occurs in 3 different form –
1. As heterozygous state for Hbs → Sickle Cell Trait (AS)
2. As homozygous state for Hbs → Sickle Cell Anaemia (SS)
3. As double heterozygous for Hbs → Sickle β-thala-ssaemia, Sickle-C dis. (SC), Sickle-D dis. (SD)

Autosomal recessive Disease → Abnormal gene present on the Autosomes

Hb^A (normal) — 1. $Hb^A Hb^S$ → AS (Carrier/Trait)
Hb^S (Sickle) — 2. $Hb^S Hb^S$ → SS (Diseased)

PATHOGENESIS – Single point mutat^n, ^{m}HBB gene, Ch-11,

HbA RBC ← 6th / 146 of β-chain (Hb)

DNA ... G A G ...
... C T C ...

mRNA GAG
(Glutamic ā)
– Pro – "Glu" – Gly –
Hydrophilic

Sickle Cell
– G T G
C A C

Hbs

$Hb\alpha_2\beta_2^S$

GUG
(Valine)
– Pro – "Val" – Gly –
Hydrophobic

"Sickling"

O_2 + Hb → deoxygenation → O_2 – Tissue

Tactoid → Crystalizat^n of Hbs → Sticky End → Clumping → Sickling

Rod-like polymer

* Reversible Sickling – Oxygenation
* Irreversible Sickling – Deoxygenation

CONSEQUENCES

Sickling → Weakned Cell mem. → Destruction

Sickling → (+) Acidosis, Low Flow Vessels → ##

Hb → Intravascular Haemolysis

Hb Recycled by Haptoglobin → Unconjugate Bilirubin → # Jaundice, # Gall Stones

Low Haptoglobin = # Detectable parameter

Anaemia → ↓RBCs, ↓Hb →

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SICKLE CELL ANAEMIA

Intravascular Haemolysis (low Haptoglobin) # → Sickle Cell Anaemia

Sickle Cell Anaemia → Extra medullary Haemopoiesis → Liver → # Hepatomegaly

Sickle Cell Anaemia → Bone Marrow → New Bone Formation → Expension of medullary cavities in skull ← # Enlarged cheeks

Bone Marrow → ↑ Reticulocyte (Immature RBC)

Sickle Cell — Vaso-Occlusion

Vaso-Occlusion → Infancy → Bones of Hands & Feet → # Dactylitis (Digit) (Inflammatn)

Vaso-Occlusion → Other Bones → # Pain # Avascular Nacrosis

Vaso-Occlusion → Spleen → Infarction

Spleen → Splenic Sequestration (backup of blood)

Spleen → Autosplenectomy (non functional spleen) → # Suscceptible for encapsulated Bac. infectn

Vaso-Occlusion → Cerebral vasculature → # Brain Stroke # Moya-Moya

Vaso-Occlusion → Lungs → # Acute chest syndrome

Hypoxic Vasoconstrictn → deoxy RBC → Block other RBC

Vaso-Occlusion → Renal → Nacrosis → # Hematuria # Proteinuria

Symptoms → Anaemia, Episodes of pain, Infection, painfull swelling, delayed Growth, Retinopathy.

Diagnosis -

Newborn blood spot Screen
Blood Smear
Hbs - Protein Electrophoresis

Treatments :-

1. Improved with O_2/Fluids - ↓ Hypoxia, Acidosis, dehydration
2. opoids — ↓ pain
3. Antibiotic - ↓ Infection
4. Hydroxy urea — ↑ γ-globin → ↑ HbF ($Hb\alpha_2\gamma_2$)
5. Blood Transfusion
6. Vaccination for infectn like pneumonia
7. Bone merrow Transplantation
8. Nitric Oxide
9. Gene therapy

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THALASSAEMIAS

TH. are the genetic inherited blood disorder in which there is reduced synthesis of one/more of the globin polypeptide chain, that lead to abnormal Hb formation. Hb → 4 globin chain (α, β, γ, δ)

Types - 1. α-Thalassaemia 2. β-Thalassaemia

1. α-THALASSAEMIA

Defective (↓) Synthesis of α-globin chain → ↓ Hb
α-globin containing Hb → HbA, HbA_2, HbF
Occurs due to deletion of one/more α-chain gene
Four gene involved - Chromosome 16 (short Arm)
Autosomal Recessive Disease (HBA1 gene)

A) One Gene deletion - α-Thalassaemia trait (carrier)
B) Two Gene deletion - α-Thalassaemia train (minor)
C) Three gene deletion - HbH disease
D) Four gene deletion - Hb Bart's hydrops Foetalis

HbF ($\alpha_2\gamma_2$), HbA ($\alpha_2\beta_2$) HbA_2 ($\alpha_2\delta_2$)

① α-Carrier
↳ No Symptom
↳ pass gene to child.

② Asian Cis-deletn
African Trans-del.
α-Trait → Minor Symptom

③ HbH dis
↳ Excess β-Chain
↳ Hb (B_4)
↳ Hypoxia
↳ Heinz bodies on RBC

④ Hb Bart's Hydrops Foetalis
↳ Most sever
↳ Hb-Bart's (γ_4)
↳ Sever Hypoxia
↳ Fetal toxic

HbH → Hb has high affinity for O_2 & dosen't release

Hypoxia ← Haemolysis (Intramedullary/Extravascular)
Haemopoiesis (Intra/Extra medullary)
Digestn of blood cell on spleen
↳ Enlarge - Bone Merrow, Liver, Spleen

Hb-Bart's Hydrops Foetalis

Hb-Bart's (γ_4) → Super Affinity for O_2 (100 times)
Sever Hypoxia → Cardiac Failure, Enlargement of Liver & Spleen
Edema - Hydrops Foetalis - Life Incompatible

Symptoms - Pallor, Short breath, Fatigue, Skeletal deformities, Hepato/splenomegali

Diagnose # Blood Test (↓Hb, MCV, MCH)
Blood Smear - Microcytic & Hypochromic


Target Cell


Golf Ball-like RBC (HbH)

Hb-Electrophoresis
Genetic Testing

Treatment :- # Blood Transfusion
Iron chelating agent
Intra Uterine Transfusion
Bone Merrow Transplantation
] - HbH

THALASSAEMIAS

TH. are the genetic inherited blood disorder in which there is reduced synthesis of one/more of the globin polypeptide chain, that lead to abnormal Hb formation. Hb – 4 globin chain ($\alpha, \beta, \gamma, \delta$)

Normal Hb → HbF ($\alpha_2\gamma_2$), HbA ($\alpha_2\beta_2$), HbA_2 ($\alpha_2\delta_2$)

β-THALASSAEMIA

↓ Synthesis of β-globin chain → ↓ HbA ($\alpha_2\beta_2^*$)
Autosomal Recessive, - mutation on HBB gene (Ch. 11)
Different type of mutation on single base pair
Single point mutation → β^0 (Absent), β^+ (Partial)

1. Transcription defect - affect Transcriptional promoter sequence → ↓ synthesis, β^+-Thalassaemia
2. Translation defect - Mutation on coding sequence (Stop codon) → x-β-globin mRNA, β^0 Thalassaemia
3. mRNA Splicing defect - defective mRNA - β^+ or β^0 Th.

A. β^0 or β^+
→ β-Th. trait/minor (Heterozygous form)
→ mild symptoms & moderate ↓ of β chain Syn.
↳ δβ Th. minor – Absent of δ & β – ↑HbF
↳ Hb Lepore Syndrome – – nt of β – Hb-Lepore

B. $\beta^+\beta^+/\beta^0$
→ β-Th. intermedia (Heterozygous)
→ Intermidiate severity, No require blood transfusion

C. $\beta^0\beta^0$
→ β-Thalassaemia major (Homozygous)
→ Mediterranean or Cooley's Anaemia
→ Congenital Haemolytic anaemia
→ ↑ HbF & HbA_2

↓ β-chain → α-chain Accumulation → Intracellular inclusions → Haemolysis → Anaemia → Hypoxia → Haemopoiesis

Haemolysis → Extravascular → Splenomegali
Haemolysis → Intramedullary → Haem → Bilirubin + Fe
Bilirubin → Jaundice
Fe → 2° Haemochromatosis

Enlarge bone & Liver ← Haemopoiesis

Symptoms → Anaemic (Pallor, Short breath, Fatigue), Abdominal Swelling (Hepatosplenomegaly, Growth retardation, Haemochromatosis – (Arrhythmia, Pericarditis, Cirrhosis, Diabetes, Hypothyroidism), Chipmunk Faces,

Diagnosis # Blood (↓Hb & MCV, ↑RBC distribut^n width)
Blood Smear – Microcytic, Hypochromic, Targeted cell
Serum – ↑ Iron, Ferritin, Transferrin
Hb Electrophoresis – ↓ HbA, ↑HbF & HbA_2

Treatment :–
Blood transfusion + Fe chelating agent
Splenectomy