MMed and DCH Lectures

Weekly by Zoom

Prof Trevor Duke

MMed and DCH Lectures

Anaemia in children

June 10, 2020

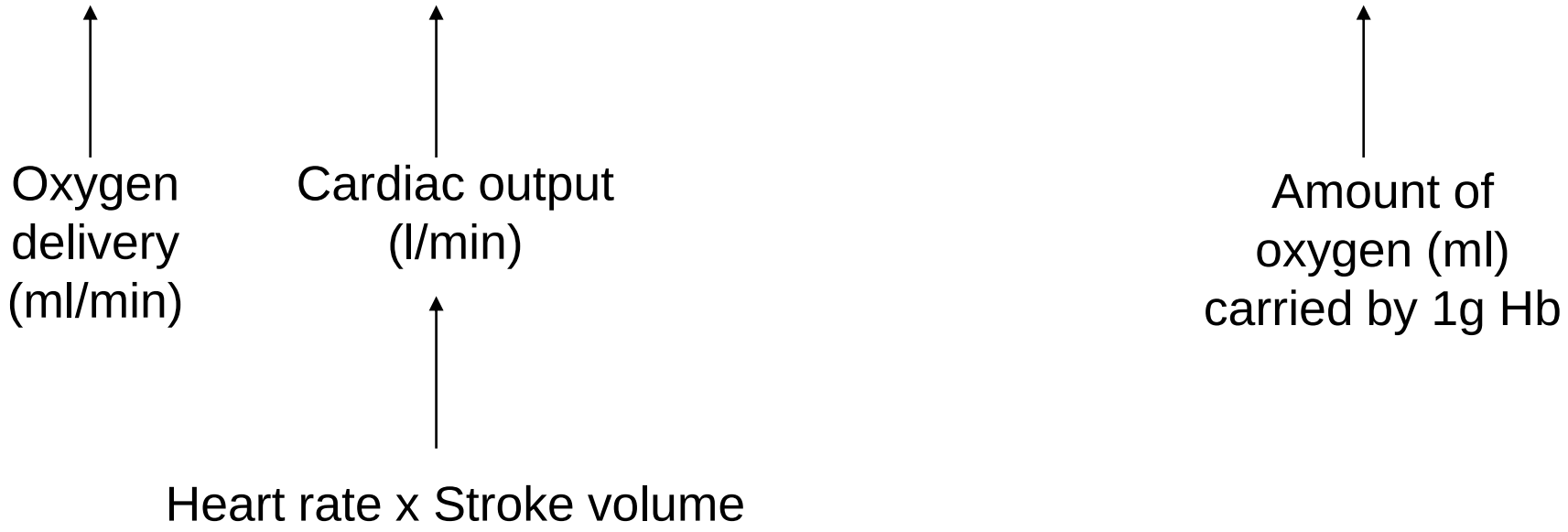
Prof Trevor Duke

Anaemia in children

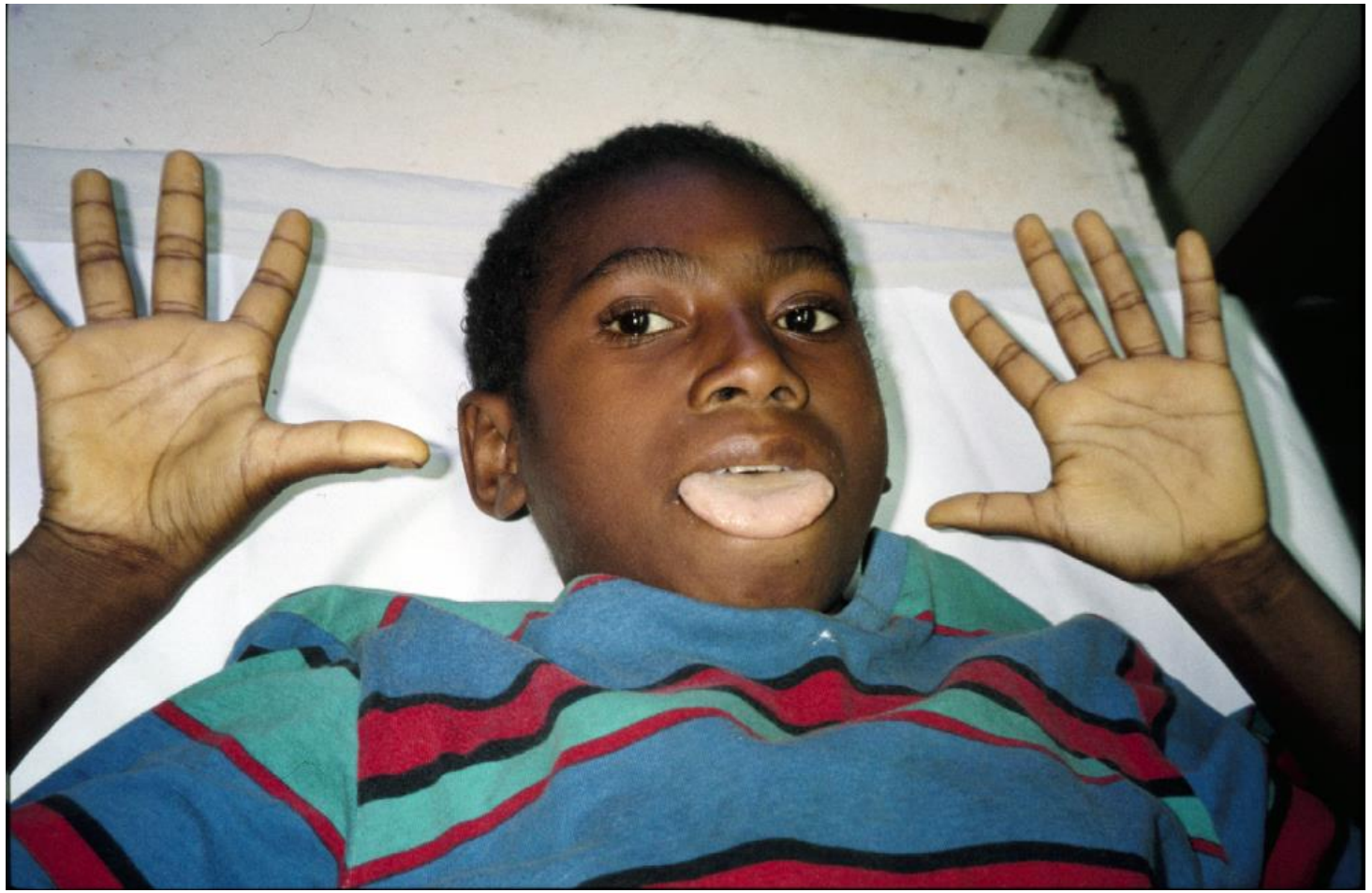
1. Physiology of blood, iron and oxygen delivery
2. Assessment of the child with anaemia
3. Iron deficiency
4. Thalassemia
5. Sickle cell disease

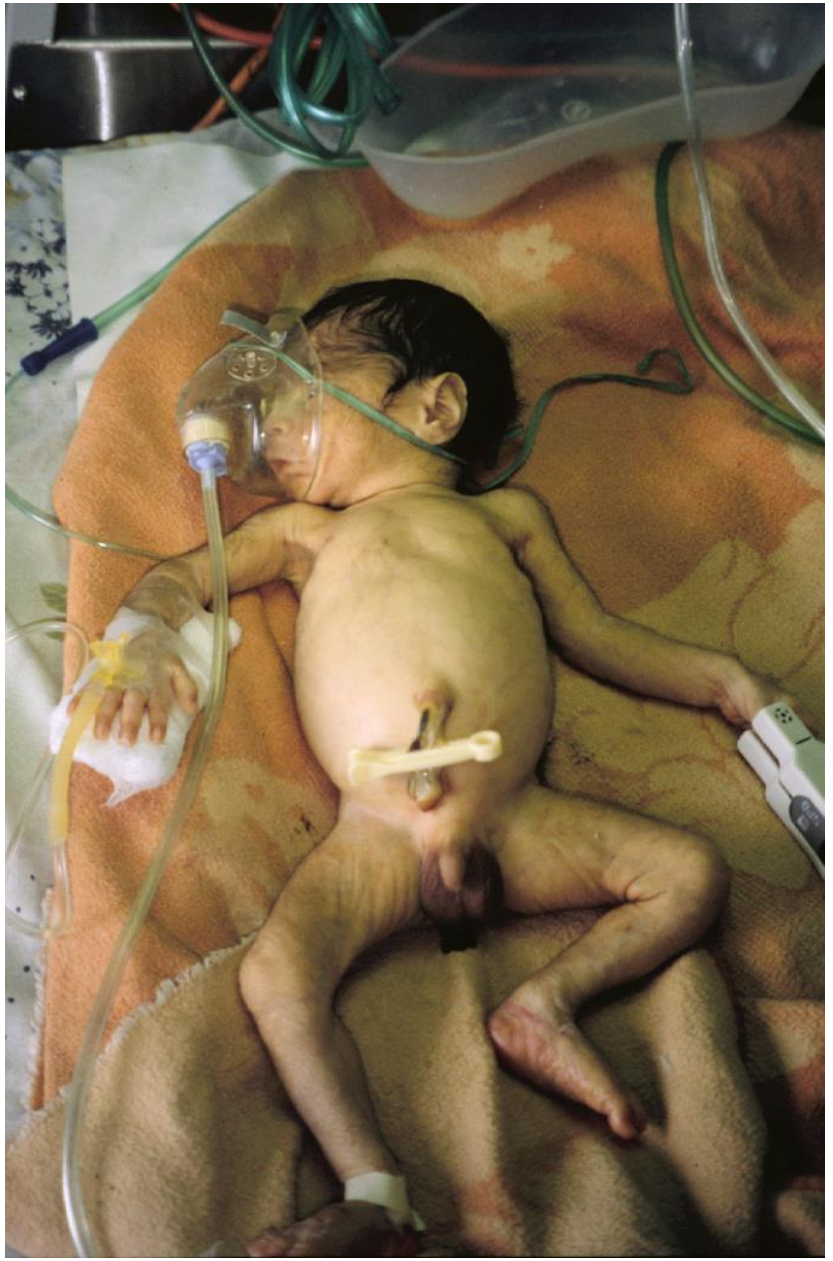
Oxygen delivery

$$DO_2 = CO \times Hb \times SpO_2 \times 1.31$$



The pale child





Assessment of the anaemic child

History

- Acute or chronic
- Perinatal
- Dietary
- Gastrointestinal history
- Drugs / Chemicals
- Bruising / bleeding
- Infections
- Family history

Examination

- Sick or well
- Skin for pallor, petechiae, bruising
- Conjunctivae for pallor and jaundice
- Liver, spleen, lymph nodes
- Growth failure
- Congenital abnormalities
- Cardiac decompensation

Anaemia

1. Reduced red cell production
2. Increased red cell destruction (haemolysis)
3. Red cell loss (bleeding)

Reduced red cell production

- Haematinic deficiency
  - **Iron**
  - Folate, B_{12}
- Bone marrow failure
  - Aplastic anaemia (drugs, congenital, idiopathic)
  - Replacement: leukaemia, malignancy, storage
- Isolated RBC defect
  - Congenital pure red cell aplasia (Blackfan Diamond)
  - Chronic renal disease, pyridoxine deficiency

Increased red cell destruction (haemolysis)

Immune

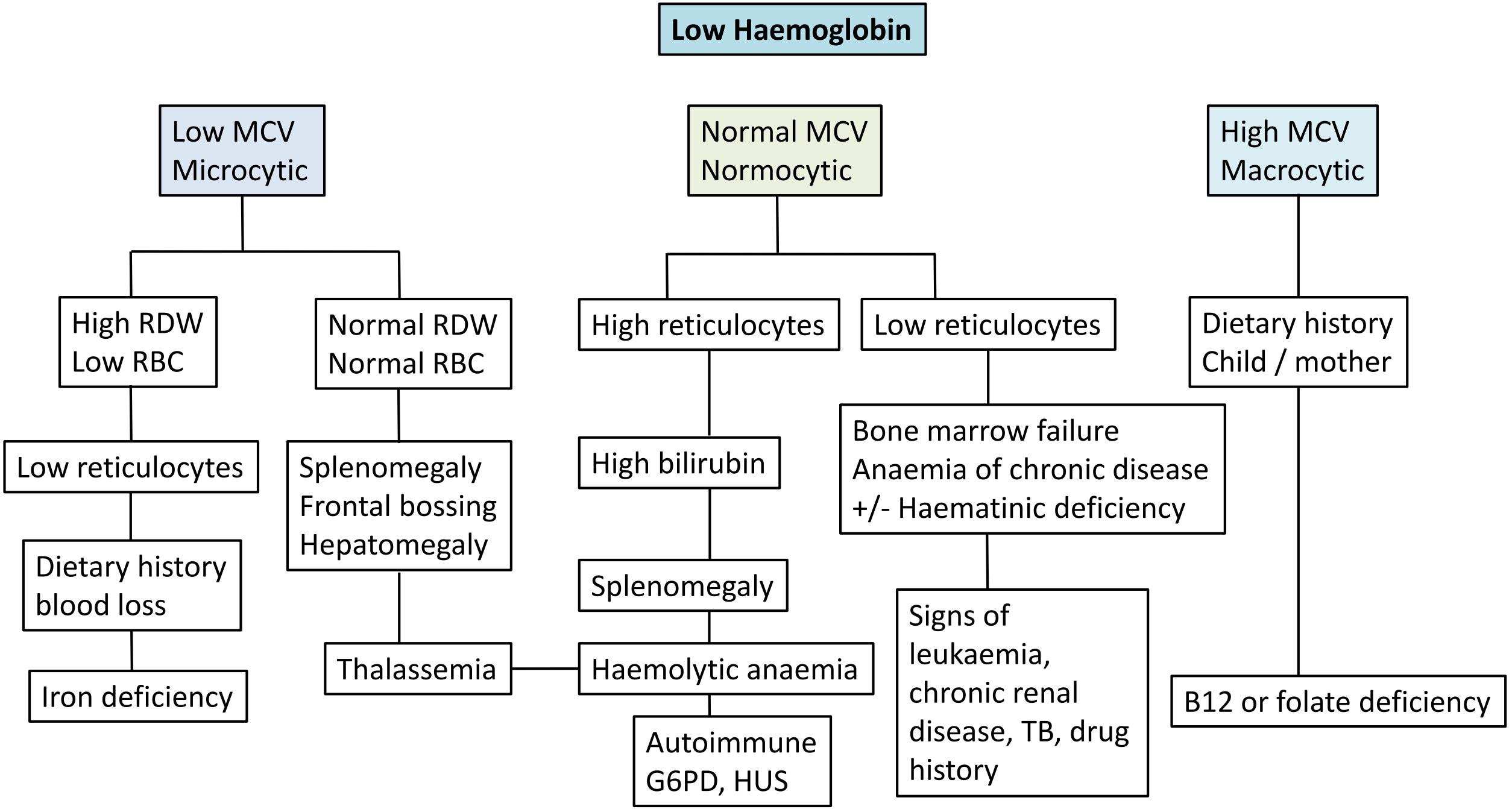
- Autoimmune haemolytic anaemia

Non-immune

- Red cell enzyme defects (G6PD)
- Red cell membrane defects (spherocytosis, eliptocytosis)
- Haemoglobinopathies
  - Thalassemia, Sickle Cell
- Physical forces, malaria

Malaria anaemia

- Destruction of red cells containing parasites rupture
- 90% haemolysis of *non-infected* RBCs
- Bone marrow failure in acute infection (pro-inflammatory cytokines, nitric oxide, lipoperoxides)
- Increased clearance of RBCs by enlarged spleen


Low Haemoglobin
Low MCV
Microcytic
Normal MCV
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Macrocytic
High RDW
Low RBC
Normal RDW
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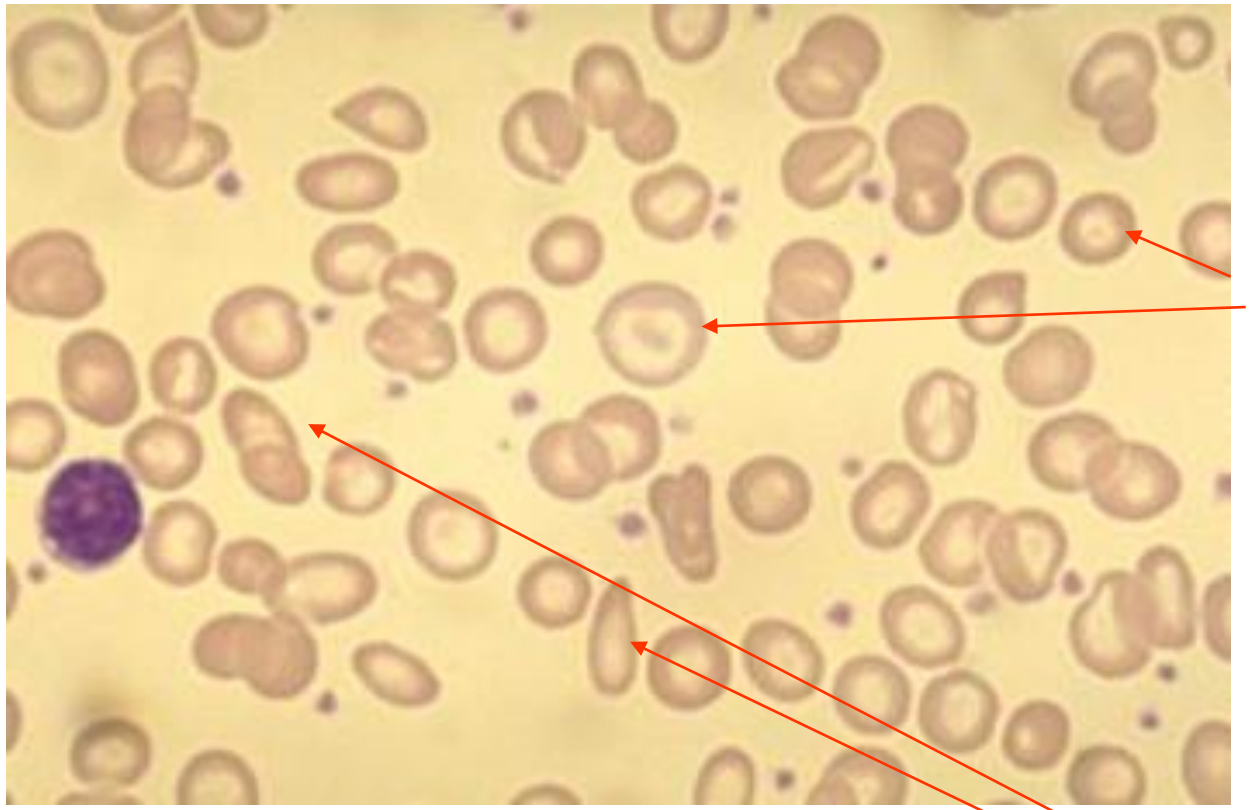
High reticulocytes
Low reticulocytes
Dietary history
Child / mother
Low reticulocytes
Splenomegaly
Frontal bossing
Hepatomegaly
High bilirubin
Bone marrow failure
Anaemia of chronic disease
+/- Haematinic deficiency
Dietary history
blood loss
Splenomegaly
Signs of
leukaemia,
chronic renal
disease, TB, drug
history
Iron deficiency
Thalassemia
Haemolytic anaemia
B12 or folate deficiency
Autoimmune
G6PD, HUS

Diagnosis of anaemia based on FBC

	MCV	RDW	RBC	Reticulocyte
Iron deficiency	<65 ↓↓	High	Low	Low
Thalassemia	<65↓	Normal	Normal	Normal-high↑
Haemolysis	Normal	High	Low	High ↑↑
Folate / B12 deficiency	>90↑	High	Low	Low
Chronic disease	Normal	Normal	Low-normal	Low



MCV < 65 fl (n=80-96 fl)
Microcytic
Hypochromic
Poikilocytosis (marked variation in shape and size → ↑↑ RDW)

Iron physiology

- Dietary iron absorbed by gut mucosal cells
- If body stores high, gut mucosal cells retain iron and it is lost when mucosal cell shed 2-3 days later
- Used for Hb, myoglobin, iron-containing enzymes
- Forms:
  - 25% in storage form: ferritin and haemosiderin in bone marrow, liver and spleen
  - Bound to plasma proteins
  - Small amounts in plasma

Iron physiology

- Birth: 250 mg (75 mg/kg)
- Adults: 2-3.5 g
- Requirement in first year 150-200 mg iron 1.5 mg per day (more if LBW)
- Human breast milk (50% absorbed) and cows milk (10% absorbed) both low in iron: 0.5-1 mg / L.
- Amount of iron in breast milk declines postnatally

Iron deficiency: causes

- Increased requirements
  - LBW
  - Rapid growth (first year, adolescents)
  - Feto-maternal, feto-fetal, placental, umbilical bleed
- Inadequate intake
  - Diets rich in milk, but poor in meat and vegetables
- Malabsorption
  - Chronic diarrhoea, Coeliac disease
- Blood loss
  - Hookworm, cows milk allergy, adolescent girls

Iron deficiency: treatment

- Identify cause
- Ferrous gluconate (10-12% elemental iron) 6 mg/kg/day
- Dietary advice
  - red meat, white meat, legumes, green vegetables, egg yolk

- Prevention
  - 1mg/kg/day elemental iron
  - Diet of iron fortified cereals, meats and green vegetables. Limit cow's milk
  - LBW infants 2 mg/kg/day

Iron deficiency: treatment

- Take with orange juice to aid adsorption
- Warn of black stools, constipation
- Brush teeth to avoid staining
- Keep out of reach of children

Haemoglobin physiology

- 4 peptide chains each bound to a haem group
- HbA: $\alpha_2\beta_2$
- HbF: $\alpha_2\gamma_2$
- If defect / absent β-globin gene, HbF is normally functioning (e.g. in β-Thal and Sickle Cell Disease)
- If defect in both α-globin genes for each α-globin subunit (e.g. 4 defective / absent α-globin genes in α-Thal) then *neither* HbA or HbF will be functional – hydrops foetalis

Genetics and types of Thalassaemia

- 4 α-globin genes: defects or absent
  - 4 = Hydrops foetalis
  - 3 = “Haemoglobin H disease” (β_4) – haemolytic anaemia and jaundice at birth
  - 2 = Thal minor, mild anaemia, generally no symptoms
  - 1 = No symptoms – protection from malaria
- 2 β-globin genes
  - 2 absent = Thalassemia major (Cooley's anaemia)
  - 2 abnormal = Thalassemia intermedia
  - 1 = Thalassemia minor – healthy, normal heterozygous.

α-Thalassaemia in PNG

- Haemoglobin Barts detected in cord blood samples from 81% of 217 infants born in Madang
- Heterozygous α^+ thalassemia common in Madang
- No Hb Barts in infants born in Goroka
- α-Thalassemia 2 common in regions where malaria has been hyperendemic but in low frequencies in non-malarious highland regions.
- Similar distribution to ovalocytosis and G6PD

Oppenheimer S. α Alpha-thalassemia in Papua New Guinea. Lancet 1984: 323: 424-426
Yenchitasomanus P. Alpha-thalassemia in Papua New Guinea. Human Genetics 1986: 74:432–437

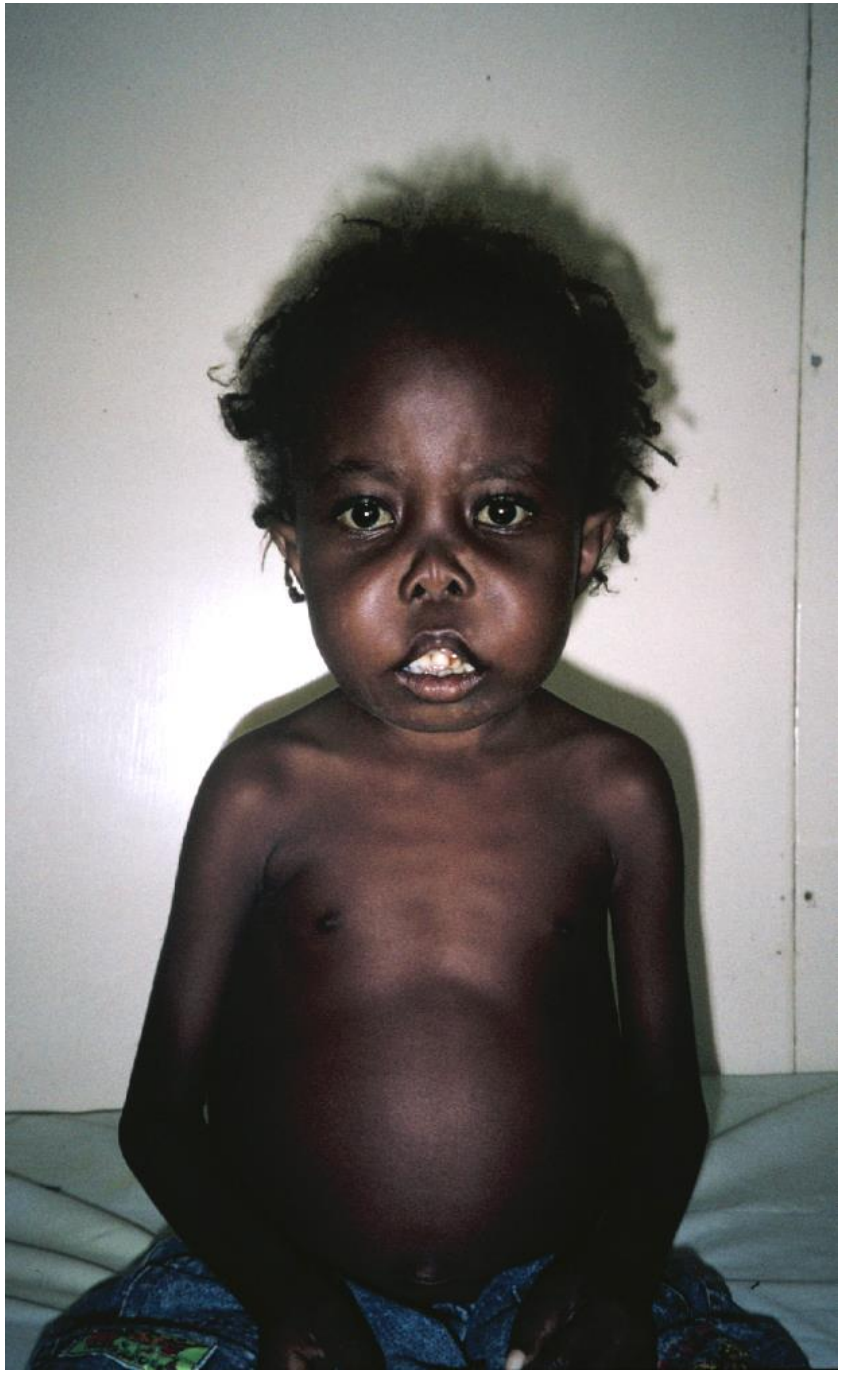
β-Thalassaemia

- Thalassemia major – both β-globin genes absent
- Thalassemia intermedia – alterations in both β-globin genes
- Thalassemia minor – one β-globin gene absent

- 200 different genetic mutations in Thalassemias

Thalassemia major

- Progressively pale, feeding problems and irritability from 3 months.
- Massive hepatosplenomegaly (haemolysis and extramedullary haematopoiesis)
- Poor growth and muscular development
- Pathological fractures
- Frontal bossing and maxillary prominence
- Increased gastrointestinal iron absorption, haemosiderosis of liver and heart



Thalassemia major – blood transfusion

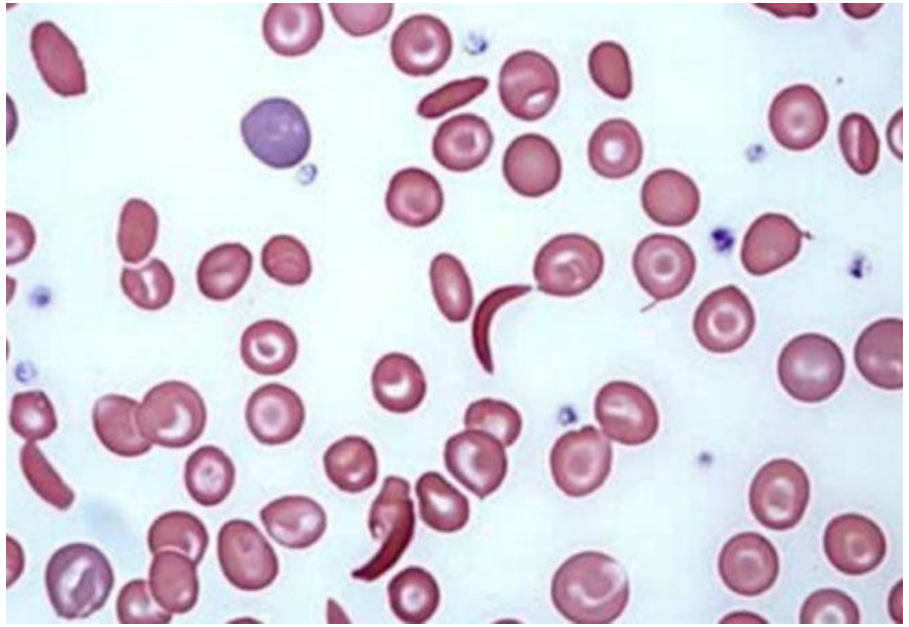
- Red blood cell transfusions to haemoglobin level >9.5 g/dL
- Each unit of blood each unit of contains 200 mg of iron
- Cardiomyopathy
- Liver cirrhosis
- Endocrine organs: hypothalamus, pituitary, gonads, pancreas, thyroid and parathyroid glands - growth impairment, delayed puberty, diabetes mellitus, infertility
- Transmission of viral infections (HIV, hepatitis B and C)

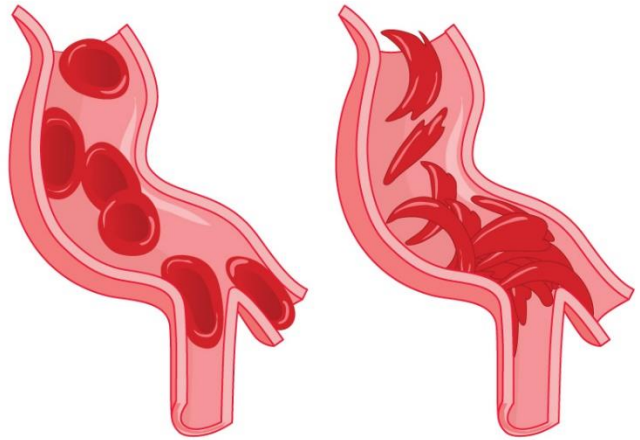
Thalassemia – other treatment

- Iron chelation
  - Deferoxamine – subcutaneous infusion
  - Deferiprone and Deferasirox – oral iron chelators
- Supportive
  - Growth, nutrition, endocrine function
- Splenectomy for hypersplenism
- Hydroxyurea
- Bone marrow transplant

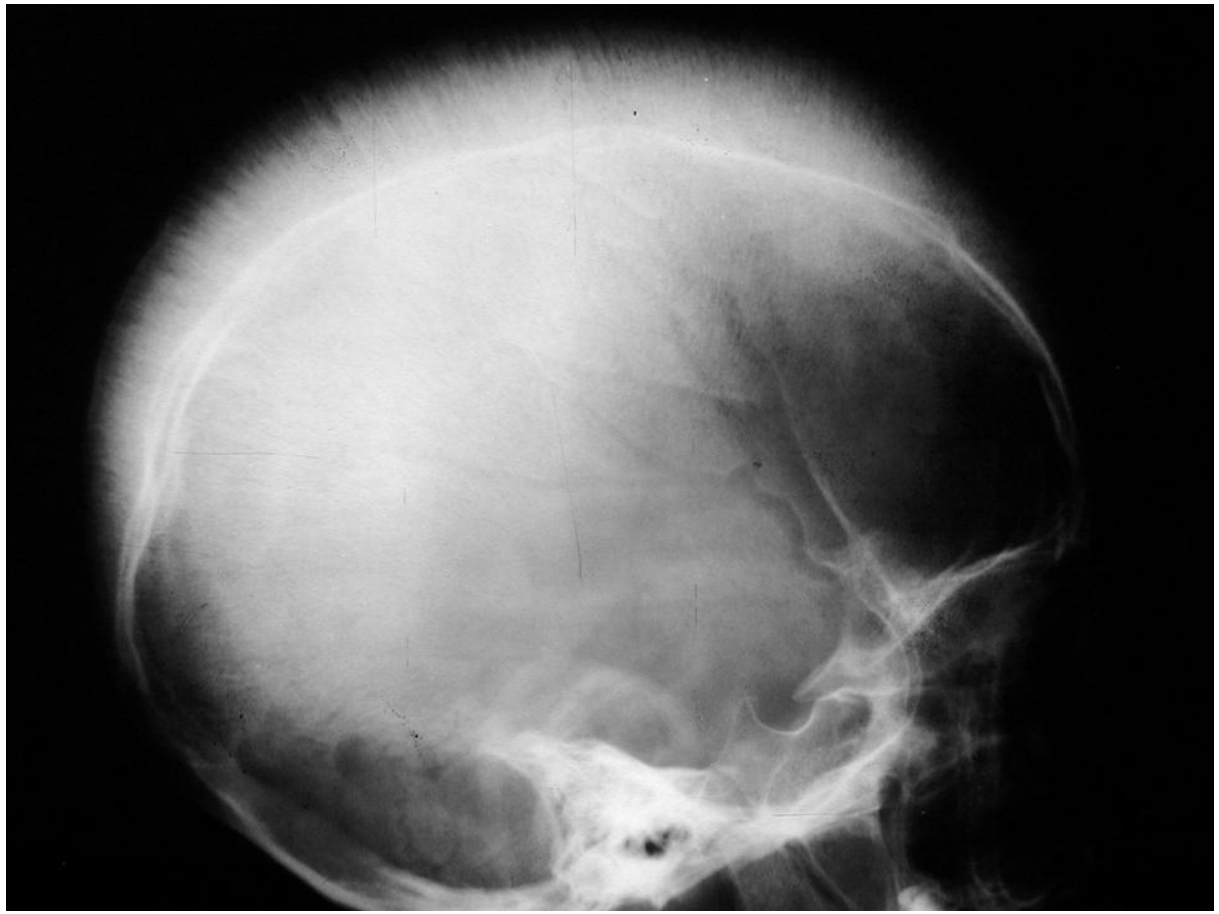
Sickle cell disease

- Abnormal HbA ($\alpha_2\beta_2$): in the β-globin subunit
- Single point mutation in *both* β-globin genes
- Sickle trait protects against severe malaria (heterozygote advantage)
- Sickle Hb carries O_2 well, but forms a sickle-shaped polymer when deoxygenated→ obstruction of blood flow.
- Types
  - HbSS: Sickle cell anaemia
  - Sickle β-thalassaemia (PNG) $HbS\beta^0$

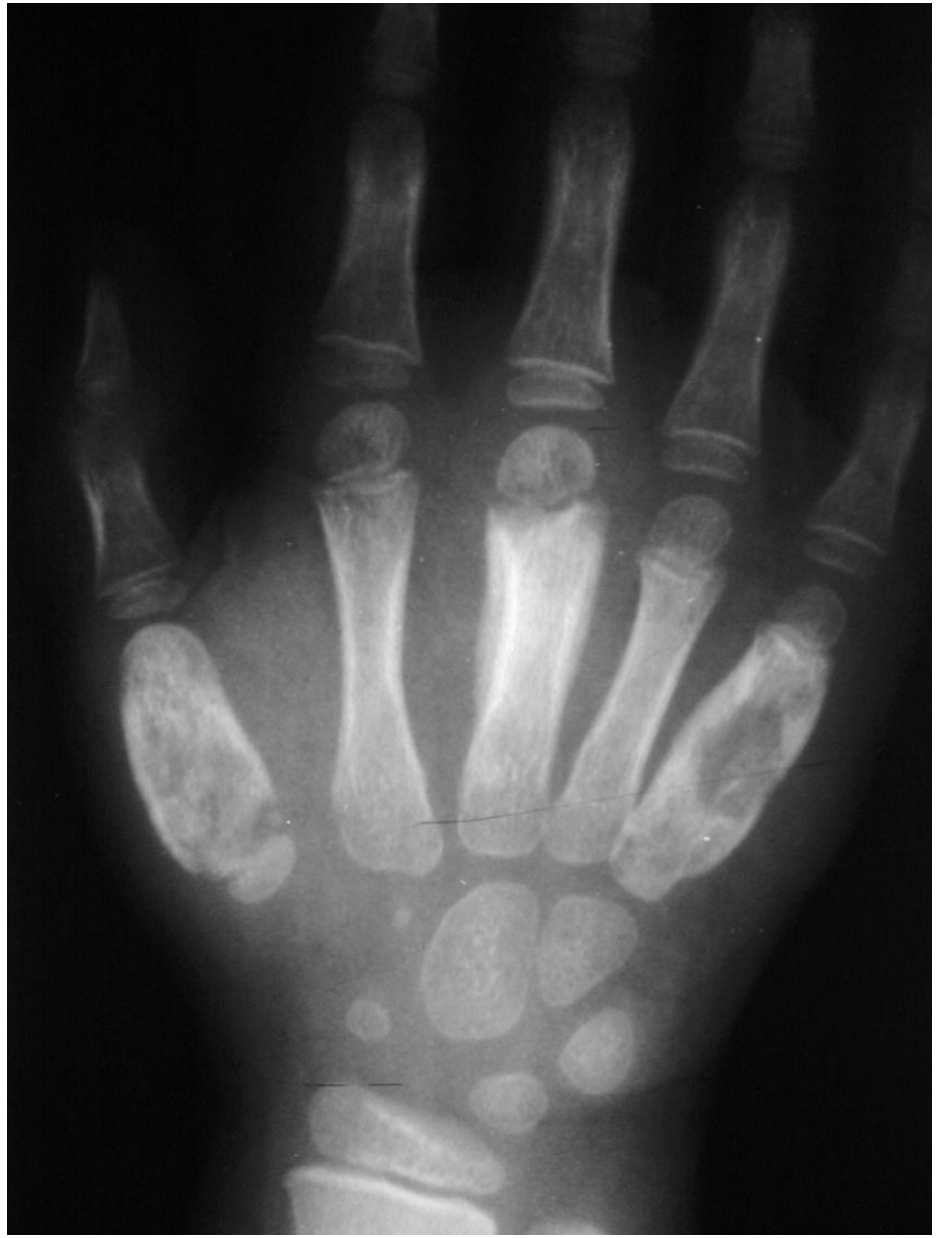




- Expansion of medullary cavity – diploic space expanded, trabeculae vertically orientated “hair on end”.
- Extramedullary haematopoiesis (red blood cell production *outside* the BM) → hepatomegaly
- Spleen



- Bone pain
- Chest crisis
- Dactylitis in children – pain and swelling in hands and feet



Hydroxyurea

- Reduces painful crises, acute chest crises and transfusion by 50%
- Ribonucleotide reductase inhibitor: Reduces bone marrow cellularity→ increased nucleated RBCs producing HbF (2Ɣ2α)
- Macrocytosis, more RBC hydration
- Also ↓ levels of circulating leukocytes and platelets, which decreases the adherence of neutrophils to the vascular endothelium
- Improved “rheology”
- Adverse effects: neutropenia, ALT / AST ↑, vomiting, infertility

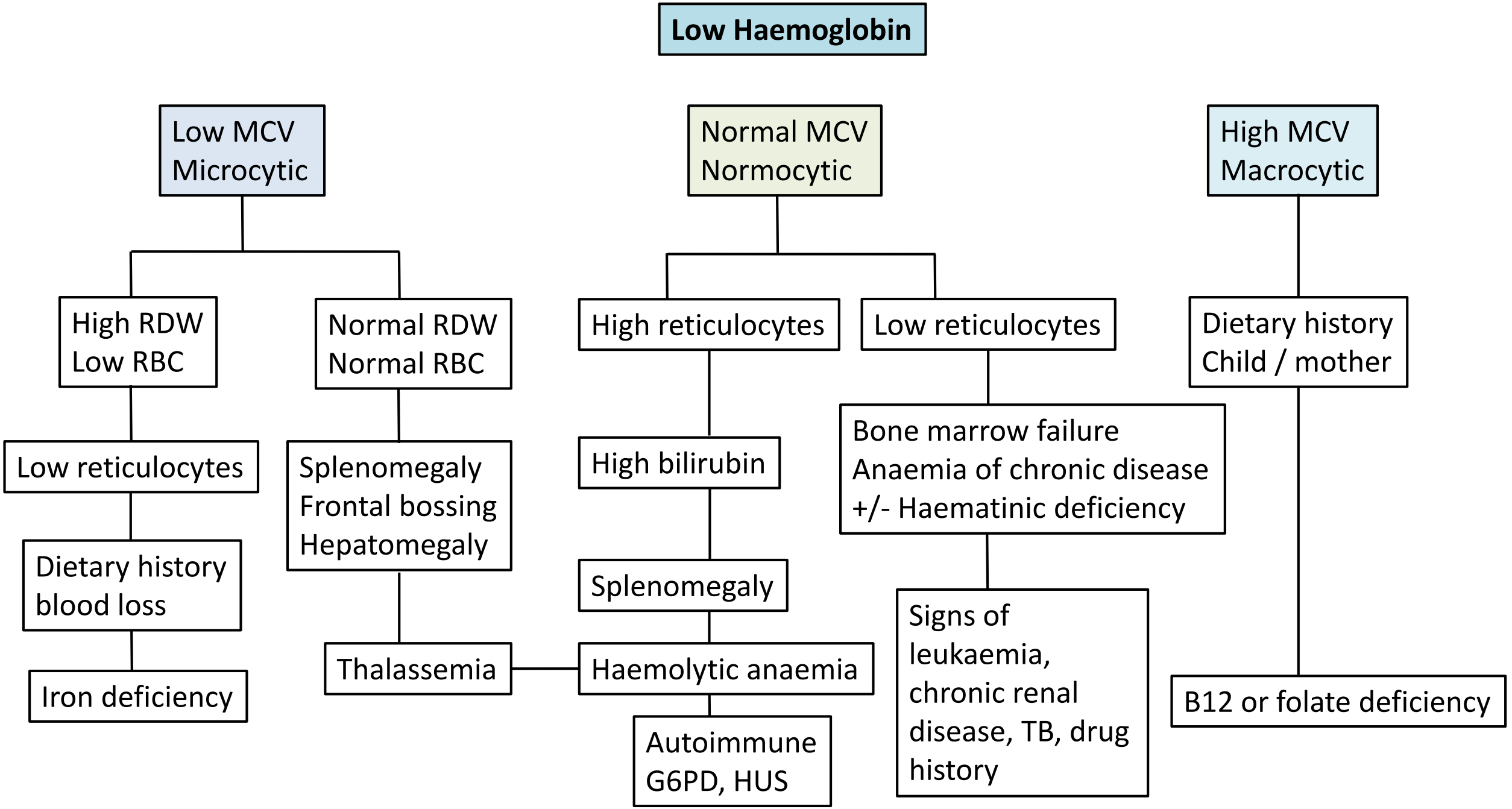
G6PD deficiency

- Haemolysis on exposure to drugs and foods
- Pallor, jaundice, dark urine (urobilinogen)
- Splenomegaly
- Gastrointestinal symptoms

- X-linked

- Sulphonamides
- Cotrimoxazole
- Chloramphenicol
- Nitrofurantoin
- Chloroquine / hydroxychloroqine
- Primaquine
- Quinine
- Aspirin

- Broad beans
- Food colouring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Signs of
leukaemia,
chronic renal
disease, TB, drug
history
Iron deficiency
Thalassemia
Haemolytic anaemia
B12 or folate deficiency
Autoimmune
G6PD, HUS