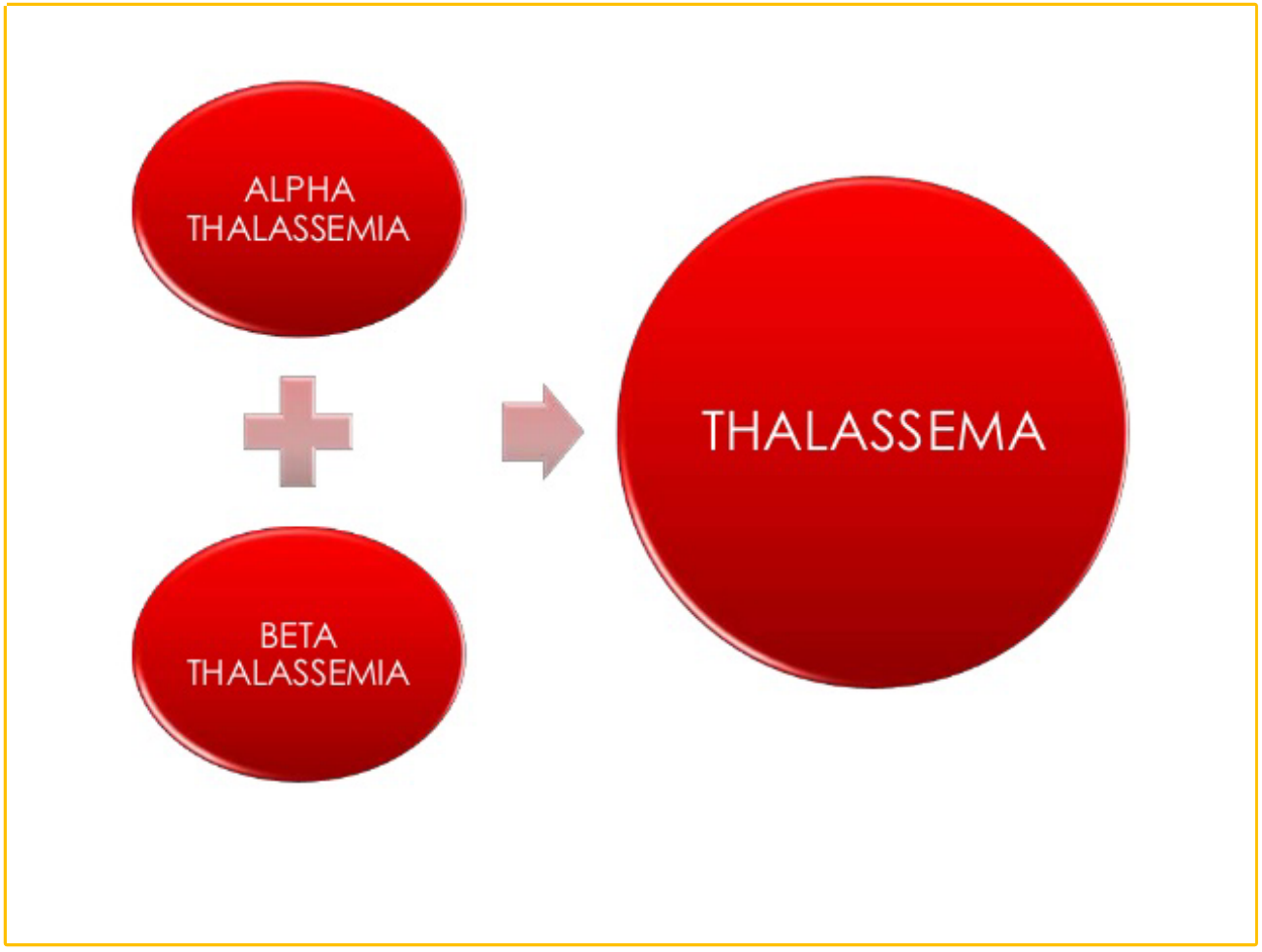
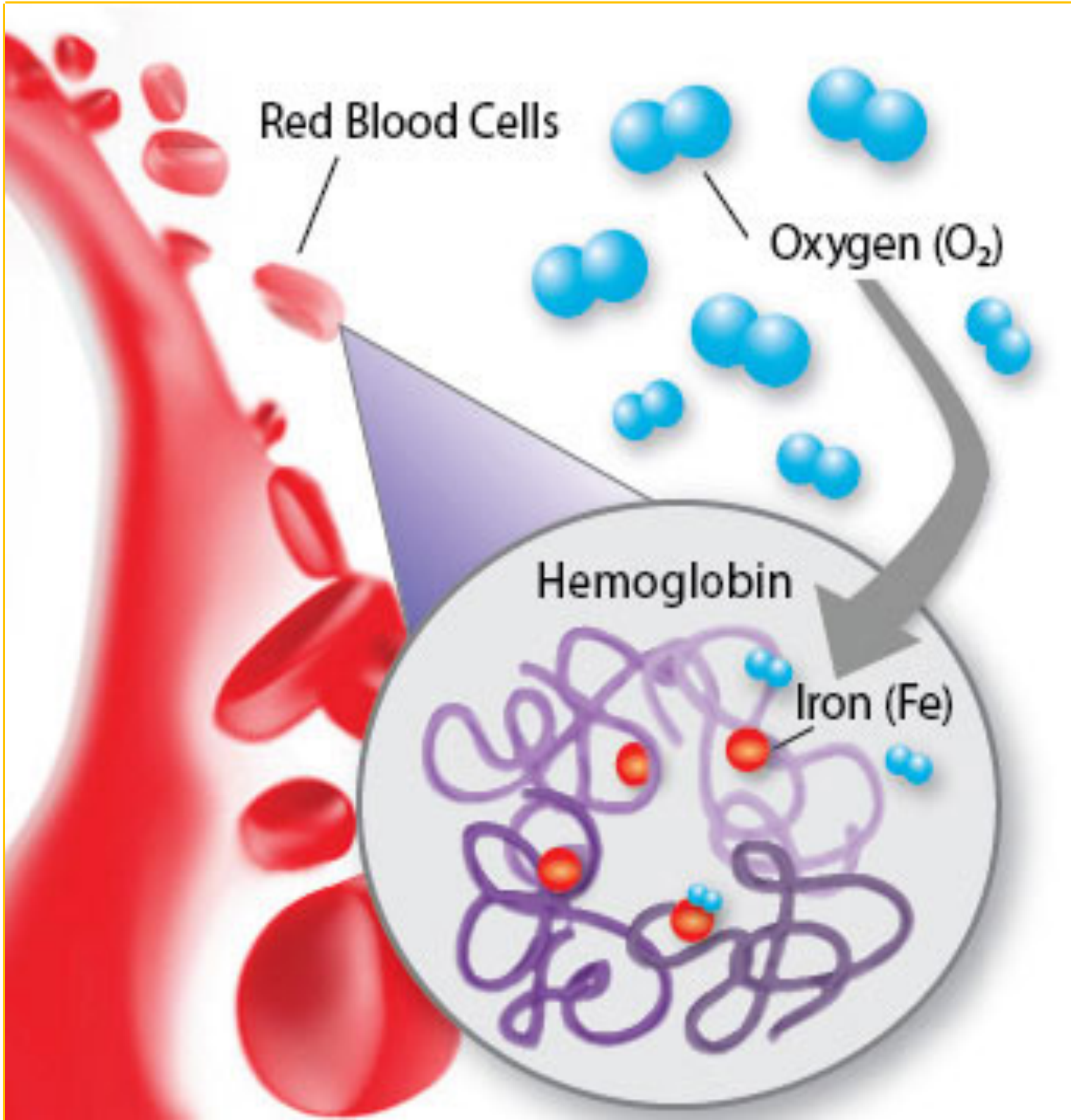
THALASSEMIA



Dr. M. A. SOFI
MD; FRCP (London); FRCPEdin; FRCSEdin

Hemoglobin molecule: is the iron-containing oxygen-transport metalloprotein in the red blood cells of all vertebrates.

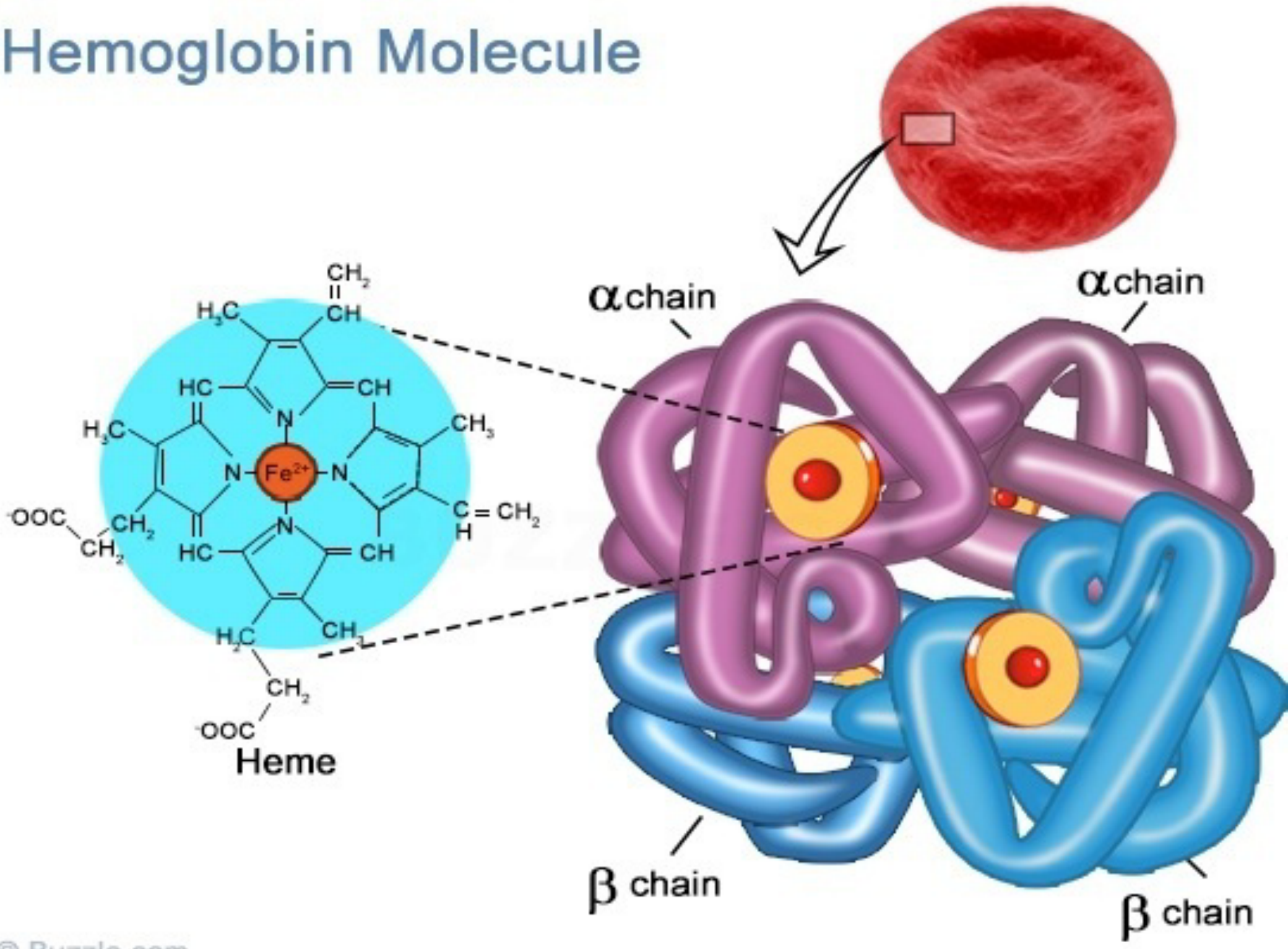


THALASSEMIA

The normal haemoglobin molecule has a haem base surrounded by two pairs of globin chains.

- The types of globin are called alpha (α), beta (β), gamma (γ) and delta (δ).
- HbA, the most common form of adult haemoglobin, has two α and two β chains.
- Fetal hemoglobin (HbF) has two α and two γ components (this is the predominant type of Hb before birth).
- HbA2 is present in smaller amounts, with two α and two δ chains.

Hemoglobin Molecule



THALASSEMIA

- The thalassaemias are a group of recessively autosomal inherited conditions characterized by decreased or absence of synthesis of one of the two polypeptide chains (α or β) that form the normal adult human hemoglobin molecule (HbA, α_2/β_2).
- β-globin gene defects may give rise to **β-thalassemia** mutations of the α globin gene cause **α-thalassemia**.
- Over 300 mutations giving rise to thalassemia have been identified and its clinical severity varies enormously.
- Thalassemia major, intermediate and minor refer largely to disease severity.

THALASSEMIA: EPIDEIOLOGY

- Approximately 5% of the worldwide population has a variation in the alpha or beta part of the hemoglobin molecule, although not all of these are symptomatic and some are known as **silent carriers.**
- **β thalassaemia** is prevalent in areas around the Mediterranean, in the Middle East, in Central, South, and Southeast Asia.
- **α thalassaemia** is prevalent in Southeast Asia, Africa, and India.
- Increasing migration has resulted in increasing prevalence of thalassemia gene mutations in all parts of the world

THALASSEMIA

α thalassaemia minor

(genotype α,α/,--): slightly anemic, low MCV and MCH;

Clinically asymptomatic.

HbH disease (genotype α,-/-,-): HbH. Anemic, very low MCV and MCH; splenomegaly, variable bone changes.

α thalassaemia major

(genotype -,-/-,-):

Hb Bart's.

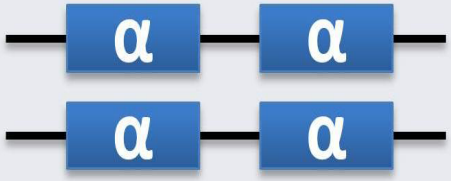
- Severe non-immune intrauterine hemolytic anemia.
- Hb Bart's hydrops fetalis, usually fatal.

α thalassaemias: genetic, clinical, laboratory

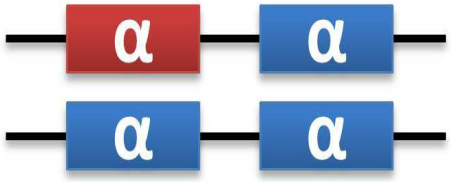
Disorder	Genotype	MCV	Anemia	Signs and symptoms
Silent carrier	**α α / α -**	NL	None	Asymptomatic
Minor	**α α / - - or α - / α -**	Low	Mild	Asymptomatic
Hb H disease	**α - / - -**	Low	Moderate	Moderate to severe hemolytic anemia, ineffective erythropoiesis, splenomegaly, variable bone changes
Major (fetal	**- - / - -**	Low	Fatal	Causes non-immune hydrops fetalis,

Alpha-thalassemia Genetics and Clinical Consequences

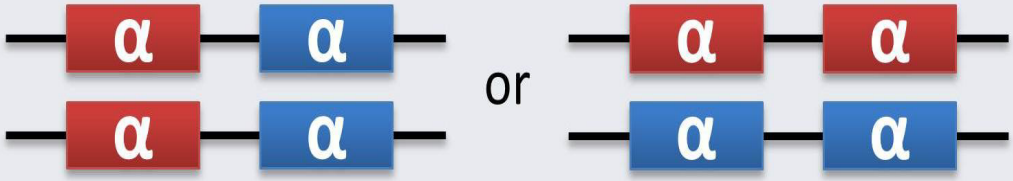
Normal



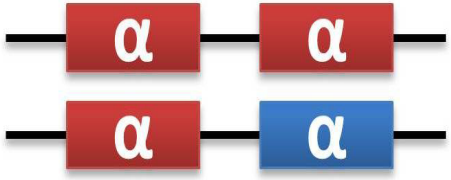
Carrier: Asymptomatic
No abnormalities



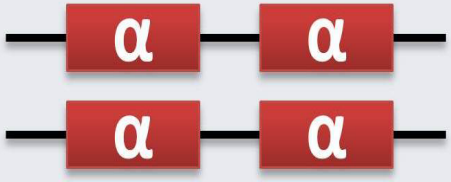
α-thal minor: Asymptomatic
Mild microcytic anemia



Hb H Disease: Symptomatic
Hemolytic and Microcytic anemia
Splenomegaly



Incompatible with Life
Hydrops Fetalis



β thalassaemias

- **Normal**: genotype β_2/β_2.
- **β-thalassaemia trait** (genotype -/β_2): HbA_2 >4%. Slightly anemic, low MCV and MCH
- Clinically asymptomatic.
- **β thalassaemia intermedia** (genotype -/βo or β+/β+): high HbF, variable.
- Anemic (symptoms usually develop when the hemoglobin level remains below 7.0 g/dL)
- Very low MCV and MCH;
- Splenomegaly
- Variable bone changes
- Variable transfusion dependency.
- **β thalassaemia major** (genotype -o/-o): HbF >90% (un-transfused).
- Severe haemolytic anaemia,
- Very low MCV and MCH
- Hepatosplenomegaly,
- Chronic transfusion dependency.

Prototypical Forms of Beta Thalassemia

VARIANT	*CHROMOSOME 11*	*SIGNS AND SYMPTOMS*
Beta thalassemia trait	One gene defect	Asymptomatic
Beta thalassemia intermedia	Two genes defective (mild to moderate decrease in beta globin synthesis)	Variable degrees of severity of symptoms of thalassemia major
Beta thalassemia major	Two genes defective (severe decrease in beta globin synthesis)	Abdominal swelling, growth retardation, irritability, jaundice, pallor, skeletal abnormalities, splenomegaly; requires lifelong blood

β thalassemia Signs:

- Presentation varies with severity. Thalassemia minor rarely has any physical abnormalities with hemoglobin ≥9 g/dL.
- In patients with the severe forms, the findings vary widely depending on how well the disease is controlled.
- In severe, untreated cases there may be:
- **Hepatosplenomegaly** .
- **Bony deformities** (frontal bossing, prominent facial bones).
- **Marked pallor**
- **Slight to moderate jaundice**.

β thalassemia Signs:

- **Exercise intolerance**, **cardiac flow murmur** or **heart failure** secondary to severe anemia.

These features are absent in well-treated patients

- **Growth restriction** is common even with well -controlled chelation therapy.
- **Iron overload** can cause endocrinopathy with diabetes, thyroid, adrenal and pituitary disorders.

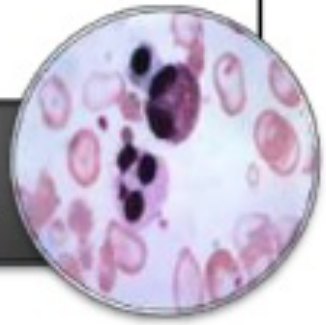
Investigations:

- FBC shows a **microcytic, hypochromic anaemia**
- In the severe forms hemoglobin level ranges from 2-8 g/dL.
- WBC is elevated due to hemolytic process.
- Platelet count may be depressed in splenomegaly.
- **Serum iron level is elevated** with saturation as high as 80%.
- **Ferritin** is also raised.
- **Hemoglobin electrophoresis** usually reveals the diagnosis.
- Normal HbA_2 is between 1.5 and 3.0% whilst **HbA2 >3.5 % is diagnostic of β-thalassaemia trait .**
- DNA analysis should be offered to confirm couples at risk, in prenatal testing
- **α-thalassemia trait** requires measuring either the α-β chain synthesis ratio or using polymerase chain reaction (PCR) assay tests.

Laboratory Diagnosis

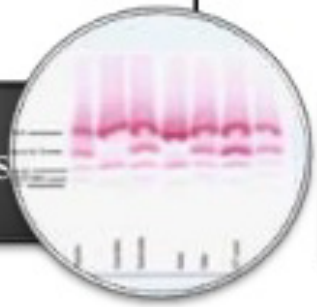
Blood examination

- Mircocytic hypochromic
- Anisocytosis
- Poikilocytosis
- Normoblasts
- Fragmented RBC's
- Target cells
- Reticulocytosis
- :indirect BR raised
- MCH MCHC ↓
- TIBC ↓



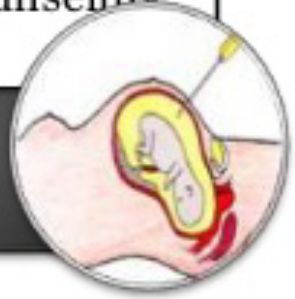
Electrophoresis

- **Thal major:**
  Hb F 30-98%
  Hb A2-2%, no Hb A
- **Thal minor:**
  Hb A2-3.5-7%
  Hb F raised < 5%



Antenatal Diagnosis

- Should be done in the first trimester by chorionic villi sampling performed b/w 9-12 weeks of gestation or
- Amniocentesis at 14-16 weeks
- DNA analysis is performed
- Genetic counseling of parents



Electrophoretic patterns in common hemoglobinopathies

Condition	HbA	HbS	HbC	HbF	HbA2
Normal	95 to 98*	0	0	<1	2.5 ± 0.2
Beta thalassemia minor	90 to 95	0	0	1 to 3	>3.5¶
Sickle cell trait	50 to 60	35 to 45 Δ	0	<2	<3.5
Sickle-beta(+) thalassemia	5 to 30	65 to 90	0	2 to 10	>3.5
Sickle-beta(0) thalassemia	0	80 to 92	0	2 to 15	>3.5
Sickle-HbC disease	0	45 to 50	45 to 50	1 to 8	<3.5
Homozygous sickle cell					

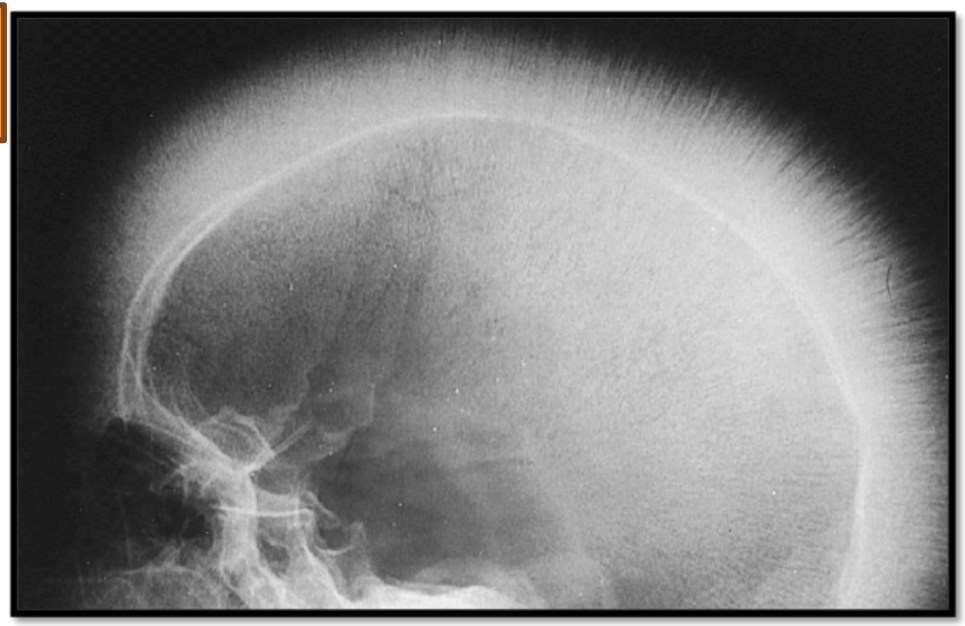
Hb: hemoglobin.* Numbers indicate the percent of total hg for an untransfused adult patient. ¶ Beta thalassemia minor, due to Hbδβ thalassemia, have normal or low HbA2 levels with markedly increased HbF levels.

Δ Percent HbS can be as low as 21 percent in patients with sickle

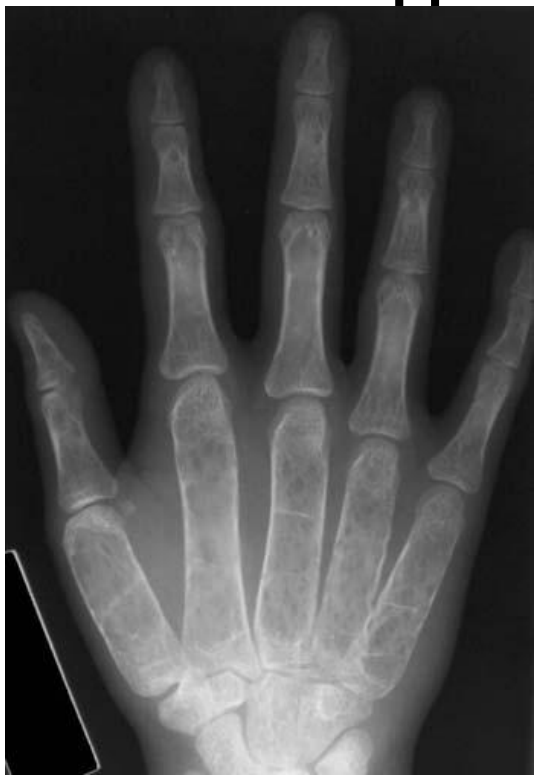
Investigations:

Imaging

- Skeletal surveys show classical changes to the bones
- Plain skull X-ray may show the classical ”**hair-on-end' appearance**”.
- A generalized loss of bone density is observed. The cortex is thinned, and the trabeculae are coarsened and outline localized lucency. Widening of the medullary cavity has resulted in squaring of the metacarpals.

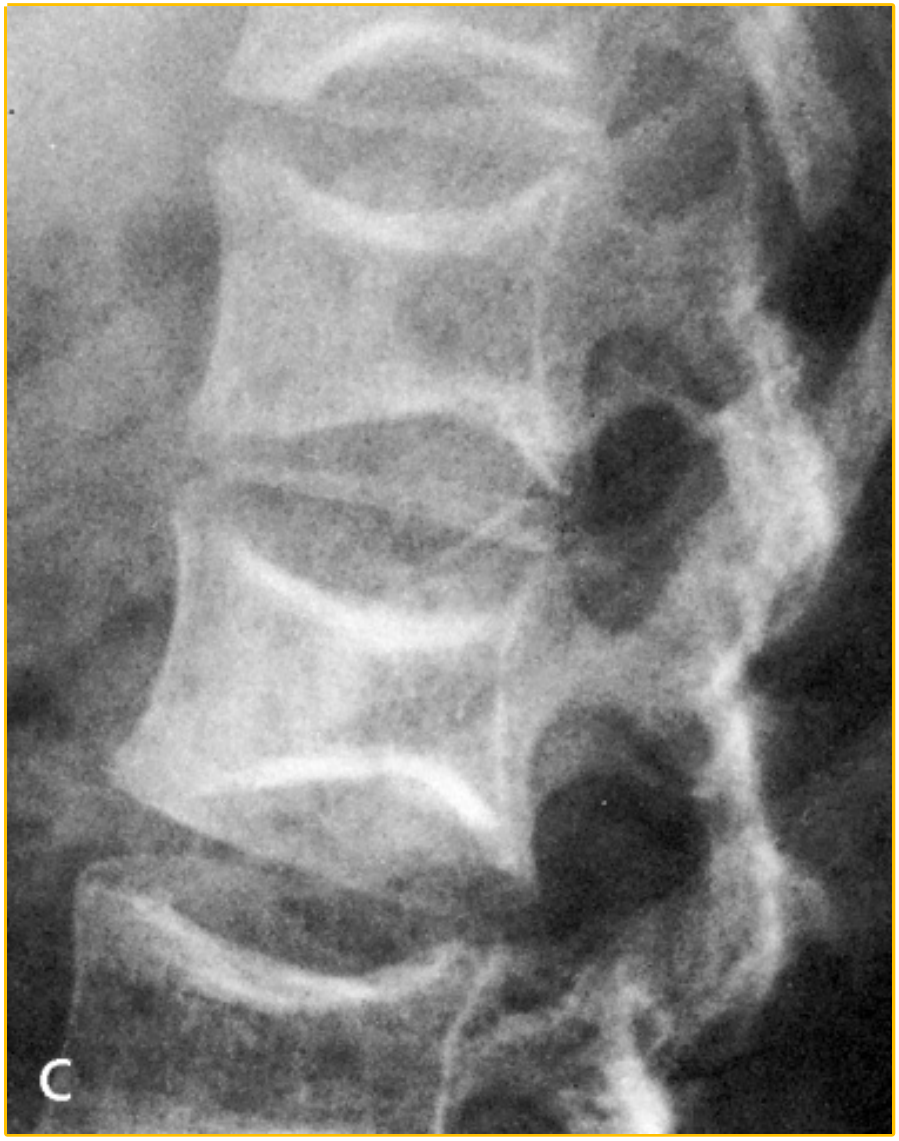


Classic Hair on end appearance

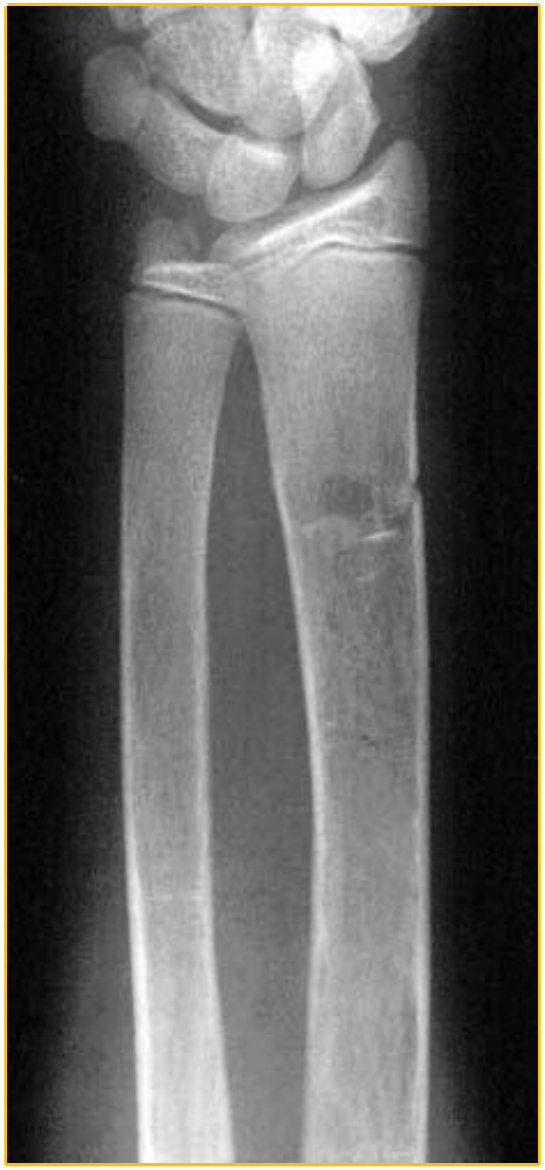


Osteoporosis

INVESTIGATIONS



Biconcave "fish vertebrae" secondary to marrow hyperplasia, osteopenia, and softening of the vertebral end-plates.



A fracture is noted in the distal radius. Evidence of medullary expansion and cortical thinning is observed

MANAGEMENT

The principles of management include:

- Asymptomatic carriers: require no specific treatment but should be protected from detrimental iron supplementation

Thalassemia intermedia or HbH disease:

- Need to be closely monitored for progression of complications induced by **chronic hemolytic anemia**.

Occasional blood transfusion

- Infection-associated aplastic or hyper-hemolytic crises
- Growth impairment
- Skeletal deformities.

Hypersplenism develops, splenectomy may be considered, although this carries severe risks of life-threatening infections, pulmonary hypertension, and

Management:

Thalassemia major:

- **Regular transfusion** to maintain a hemoglobin level higher than 9.5 g/dL.
- **Transfusion improves both quality and quantity of life in severe cases**. The target is not to let Hb fall below 9.5 g/dL.
- **Iron chelation** to prevent overload syndrome.
- **Care by multidisciplinary team** (hematologist, specialized nurse, social worker, psychologist, genetic counselor, cardiologist and liver specialist)
- **Splenectomy** may be indicated if hypersplenism causes a marked increase in transfusion requirements.

Non-drug

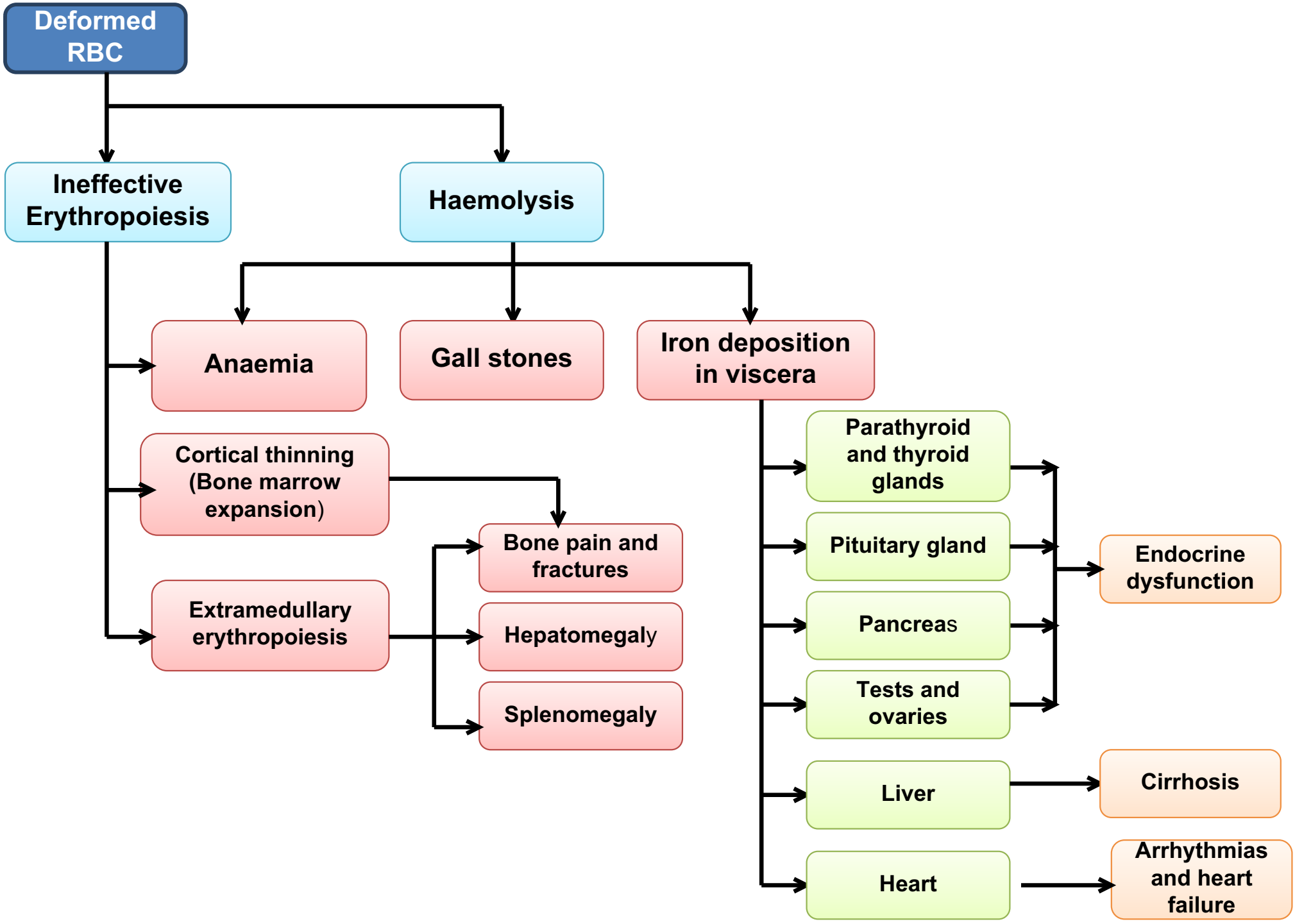
- Psychological support.
- Genetic counseling.
- Avoid food rich in iron.
- Extra vitamin E, folic acid and some vitamin C may be beneficial.

Management:

Do not treat anemia with iron unless iron deficiency had been substantiated.

- **Desferrioxamine** is given parenterally to aid iron excretion. The dose and means of delivery vary according to the needs of the patient.
- **Oral chelating agents** have been developed and are now in use, including deferasirox and deferiprone.
- There is hope for **new combination therapies** - e.g., oral deferiprone used in combination with desferrioxamine, producing a greater effect than either alone
- **Hydroxyurea** may increase the expression of γ chains (HbF) and remove the excess α chains, which could potentially correct ineffective erythropoiesis.

Thalassemia: Disease presentation and complications



THANK YOU