Thalassemia Syndromes

Are genetic(Autosomal Recessive) disorders in globin chain production.

In individuals with β-thalassemia, there is either:

(β^0-thalassemia) complete absence of β-globin gene production

or

(β^+-thalassemia) partial reduction of β-globin gene production

β-thalassemias can be classified clinically as

thalassemia trait
thalassemia minima
thalassemia minor
thalassemia intermedia
thalassemia major

HOMOZYGOUS β-THALASSEMIA

(THALASSEMIA MAJOR)

(COOLEY'S ANEMIA)

pathogenesis of β-thalassemia:

1. Reduction of β-chain synthesis.

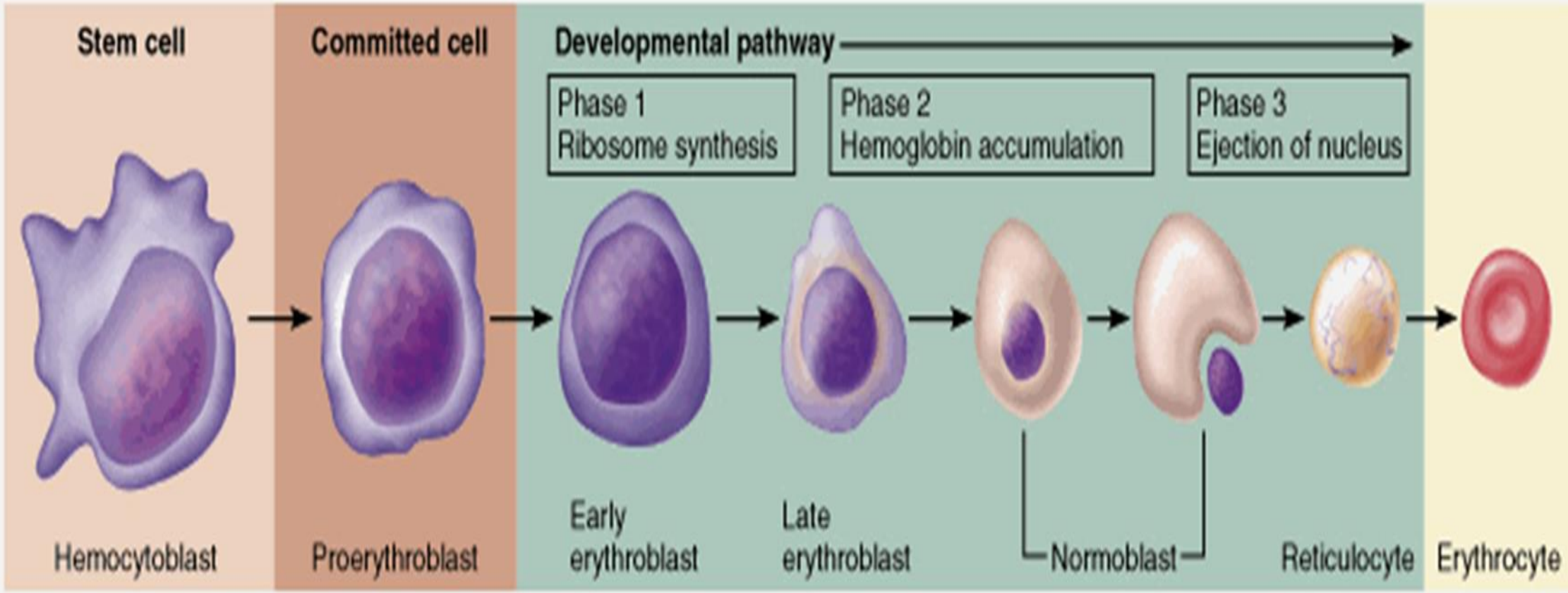
2. Relative α-globin chain excess resulting in intracellular precipitation of insoluble α-chains.

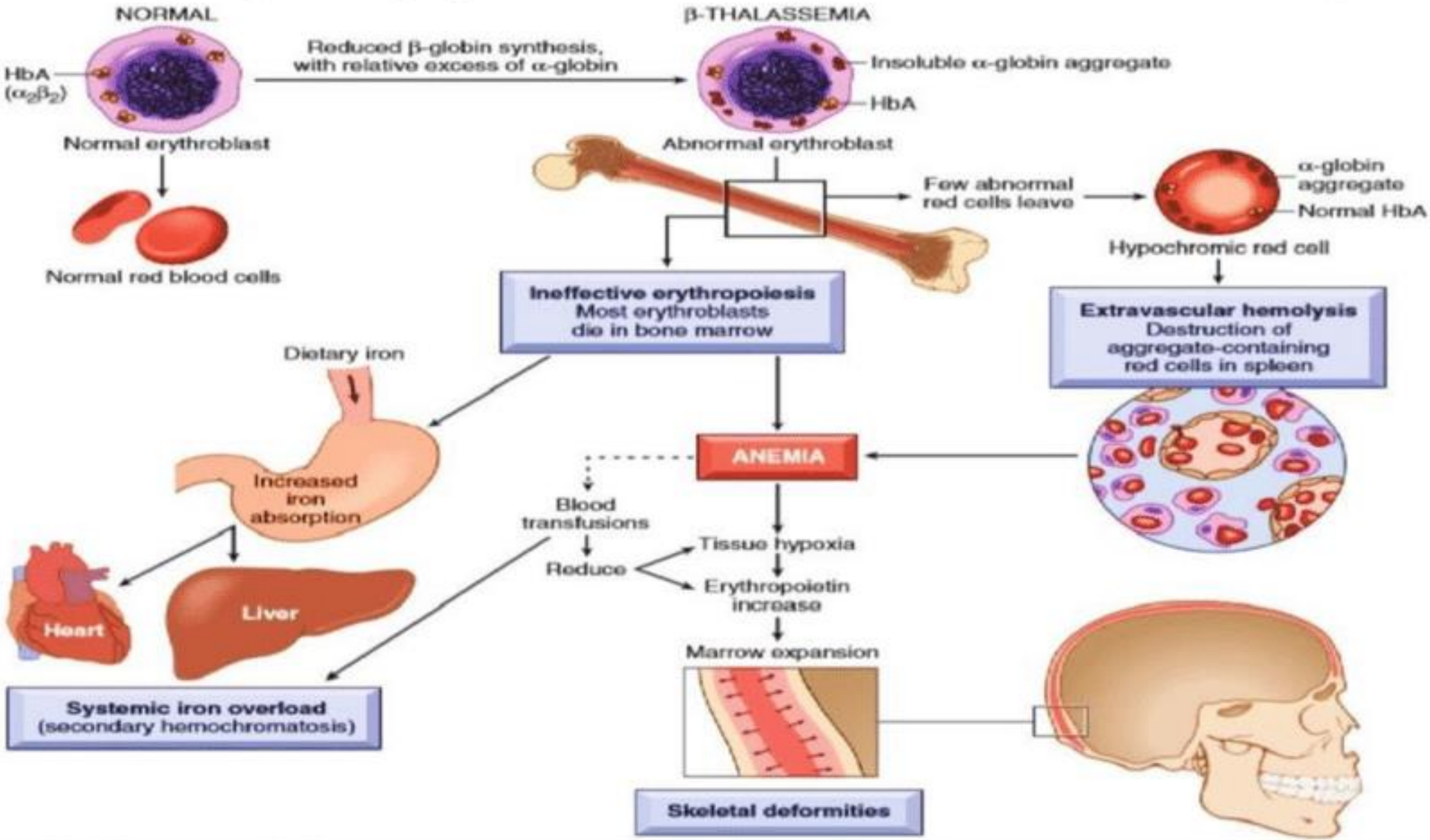
3. Increased but ineffective erythropoiesis with many red cell precursors prematurely destroyed; related to α-chain excess.

The γ-globin chains are produced in increased amounts, leading to an elevated Hb F ($\alpha_2\gamma_2$).

The δ-globin chains are also produced in increased amounts, leading to an elevated $HbA_2(\alpha_2\delta_2)$ in β-thalassemia.

4. Shortened red cell life span; variable splenic trapping.




NORMAL
β-THALASSEMIA
HbA
($\alpha_2\beta_2$)
Reduced β-globin synthesis, with relative excess of α-globin
Insoluble α-globin aggregate
HbA
Normal erythroblast
Abnormal erythroblast
Normal red blood cells
Few abnormal red cells leave
α-globin aggregate
Normal HbA
Hypochromic red cell
Ineffective erythropoiesis
Most erythroblasts die in bone marrow
Extravascular hemolysis
Destruction of aggregate-containing red cells in spleen
Dietary iron
ANEMIA
Increased iron absorption
Blood transfusions
Reduce
Tissue hypoxia
Erythropoietin increase
Marrow expansion
Heart
Liver
Systemic iron overload
(secondary hemochromatosis)
Skeletal deformities

Sequelae

1. Hyperplastic marrow (bone marrow expansion with cortical thinning and bony abnormalities).

2. Increased iron absorption and iron overload (especially with repeated blood transfusion), resulting in:

- Fibrosis/cirrhosis of the liver
- Endocrine disturbances (e.g., diabetes mellitus,hypothyroidism, hypogonadism, hypoparathyroidism, hypopituitrism)
- Skin hyperpigmentation
- Cardiac hemochromatosis causing arrhythmias and cardiac failure.

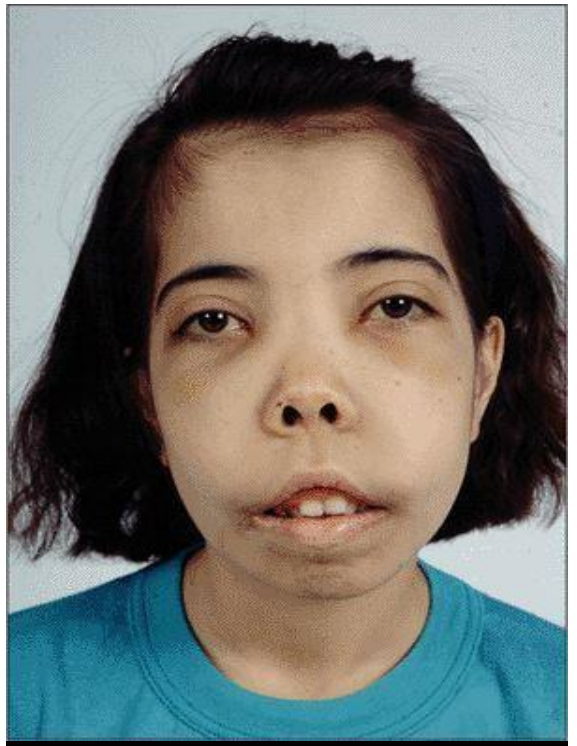
3. Hypersplenism:

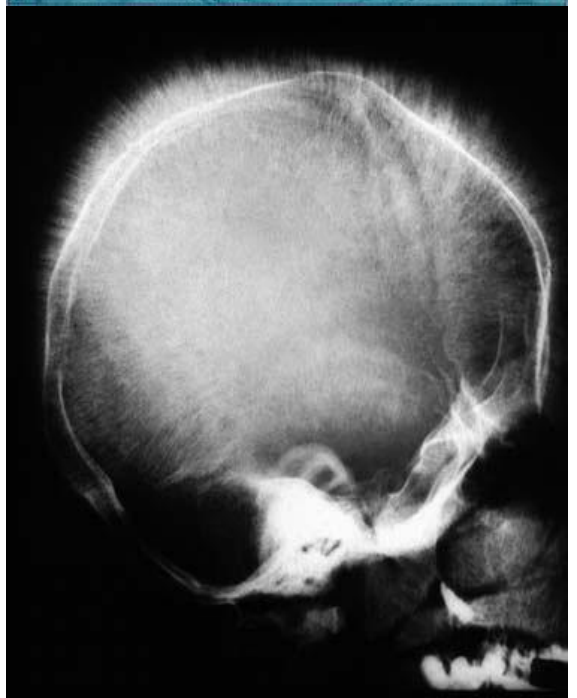
- Plasma volume expansion
- Shortened red cell life.
- Leukopenia
- Thrombocytopenia.

Clinical Features

Clinical manifestations of beta thalassemia major include:

- Failure to thrive in early childhood
- Anemia
- Jaundice, usually slight; gallstones
- Hepatosplenomegaly, which may be massive; hypersplenism
- Bone abnormalities:
  - Abnormal facies, prominence of malar eminences, frontal bossing, depression of bridge of the nose and exposure of upper central teeth
  - Skull radiographs showing hair-on-end appearance due to widening of diploic spaces
  - Fractures due to marrow expansion and abnormal bone structure
  - Generalized skeletal osteoporosis.
- Growth retardation, delayed puberty, primary amenorrhea in females and other endocrine disturbances secondary to chronic anemia and iron overload
- Leg ulcers
- Skin bronzing.





Complications

Complications develop as a result of:

1. Chronic anemia (in patients who are undertransfused)
2. Iron overload – Due to repeated red cell transfusions in β-thalassemia major.

Even in carefully managed patients, the following complications may develop:

a. Endocrine disturbances (e.g., growth retardation, pituitary failure with impaired gonadotropins, hypogonadism, insulin-dependent diabetes mellitus, adrenal insufficiency, hypothyroidism, hypoparathyroidism)
b. Cirrhosis of the liver and liver failure (exacerbated if concomitant hepatitis B or C infection is present)
c. Cardiac failure due to myocardial iron overload (often associated with arrhythmias and pericarditis may occur)
d. Osteopenia and osteoporosis

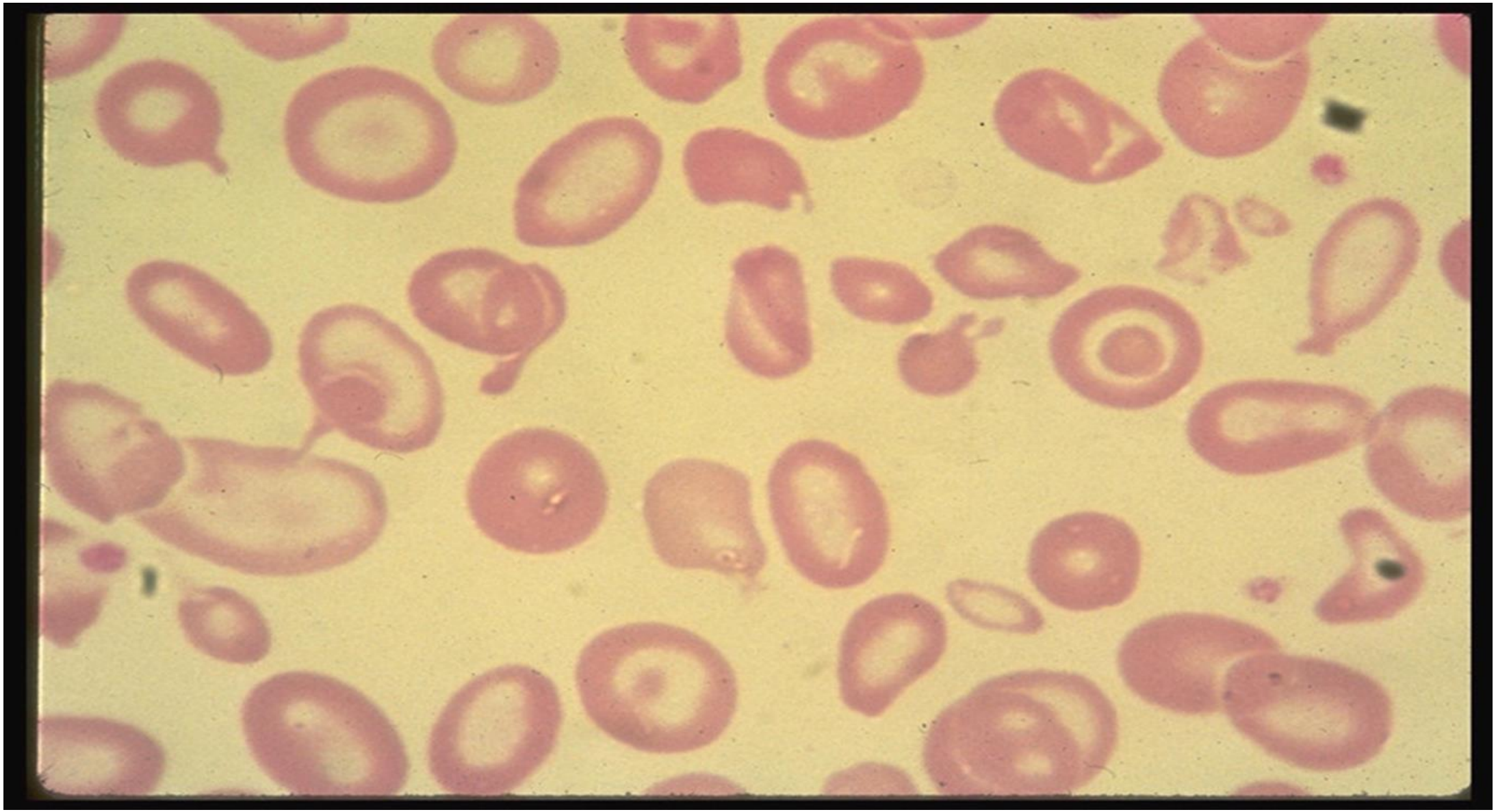
Causes of Death

1. Congestive heart failure.
2. Arrhythmia.
3. Sepsis secondary to increased susceptibility to infection post-splenectomy.
4. Multiple organ failure due to hemochromatosis.

LABORATORY FINDINGS

Hematology

1. Anemia – hypochromic, microcytic.
2. Reticulocytosis.
3. Leukopenia and thrombocytopenia (may develop with hypersplenism).
4. Blood smear – target cells and nucleated red cells, extreme anisocytosis, contracted red cells, polychromasia, punctate basophilia, circulating normoblasts.
5. Bone marrow – may be megaloblastic (due to folate depletion); erythroid hyperplasia.
6. Serum ferritin – raised.



7.Haemoglobin Electrophoresis

- In homozygous β^0 thalassaemia:
  Hb F accounts for up to 98 % of the total
- In double heterozygous β^+ thalassaemia:
  Hb F accounts for 40-60 %
- Hb A2 is increased in both defects.

Biochemistry

1. Raised bilirubin (chiefly indirect).
2. Evidence of liver dysfunction (late, as cirrhosis develops).
3. Evidence of endocrine abnormalities (e.g., diabetes , hypogonadism [low estrogen and testosterone], hypothyroidism [elevated thyroid stimulating hormone]).

Management

lines of treatments includs

Transfusion Therapy

Splenectomy

Bone marrow transplantation

Gene Therapy

Transfusion therapy

1. **Indications** for the initiation of regular red cell transfusions include hemoglobin level less than 7 g/dL (on at least two measurements; OR:

a. poor growth
b. facial bone changes
c. Fractures
d. the development of other complications (pulmonary hypertension, extramedullary hematopoiesis, etc.).

2. **Transfusion regimen:**

a. Goal is to maintain the **pretransfusion** hemoglobin more than 9.5 g/dL. Higher trough levels may be indicated in the setting of heart failure or clinical symptoms.

b. Typical programs involve transfusion of 10-15 cm3/kg of packed leukodepleted red cells every 3-5 weeks.

c. Blood should be matched for ABO, Cc, Ee, and Kell antigens to reduce the risk of alloimmunization (some centers perform extended red cell antigen matching).

3. Goals of successful transfusion regimen:

a. maximizing growth and development,
b. minimizing extramedullary hematopoiesis and decreasing facial and skeletal abnormalities,
c. reducing excessive GI iron absorption
d. retarding the development of splenomegaly and hypersplenism by reducing the number of red cells
containing α-chain precipitates that reach the spleen, and
e. reducing and/or delaying the onset of complications (e.g., cardiac).

Iron overload results from:

- Ongoing transfusion therapy
- Increased gut absorption of iron

Chelation Therapy

Indications for chelation therapy in patients receiving chronic transfusions include:

- **Received more than 10-20 transfusions**
- **Serum ferritin level more than 1,000 ng/ml**

Deferoxamine (Desferal): it chelates iron allowing its excretion in urine and stool.

Deferoxamine is given subcutaneously over 10–12 hr, 5–6 days a week. The number of hours deferoxamine is used daily is more important than the daily dose. High-dose, short-term infusions increase toxicity with little efficacy.
Nightly subcutaneous administration of deferoxamine is time-consuming and painful and interferes in many ways with the lifestyle of the patient.

Side effects include ototoxicity with high-frequency hearing loss, retinal changes, and bone dysplasia with truncal shortening.

Two oral chelators:

Deferasirox (Exjade) is supplied as orally tablets, which are dissolved in a glass of water or juice and administered 1/2 hour before meals .

Deferiprone for children >2 yr of age. Deferiprone may not be as effective as deferoxamine in total body iron chelation, but may be more effective in removing cardiac iron. Side effects include neutropenia, so weekly blood counts are needed.

Splenectomy

1. Splenectomy reduces the transfusion requirements in patients with **hypersplenism**. It is used in patients with severe leukopenia and/or thrombocytopenia due to hypersplenism and for patients with very high **annual packed RBC requirements (>250 mL/kg per year)** and uncontrolled iron overload.

2. More recently, splenectomy is utilized **less frequently** due to the increased risk of pulmonary hypertension,thromboembolism, and infection after splenectomy.

3. At least 2 weeks prior to splenectomy, a **polyvalent pneumococcal and meningococcal vaccine** should be given. If the patient has not received a H. influenzae vaccine, this should also be given. Following splenectomy, **prophylactic penicillin 250 mg bid** is given to reduce the risk of overwhelming postsplenectomy infection.

Supportive Care

1. Folic acid, 1 mg daily orally, is given to patients who are not receiving regular red cell transfusions.
2. Hepatitis A and B vaccination should be given to all patients.
3. Cardiology consultation and administration of appropriate inotropic, antihypertensive, and antiarrhythmic drugs when indicated for cardiac dysfunction.
4. Endocrine intervention (i.e., thyroxine, growth hormone, estrogen, and testosterone) should be implemented
when indicated.
5. Cholecystectomy should be performed if symptomatic gallstones are present.
6. Referral to gastroenterology for the **management of chronic hepatitis B or C infection.**
7. HIV-positive patients should be treated with the appropriate antiviral medications.
8. Genetic counseling and prenatal diagnosis (when indicated) should be carried out using chorionic villus sampling or amniocentesis.
9. Management of **osteoporosis**

Bone marrow transplantation

All children who have an HLA-matched sibling should be offered the option of bone marrow transplantation.

Gene Therapy

Non-transfusion-dependent β-thalassemia (β-thalassemia intermedia)

Although patients are homozygous or compound heterozygous, the resultant anemia is milder than in thalassemia major.

Clinical features

1. Patients generally **do not require** transfusions and maintain a hemoglobin level between 7 and 10 g/dL.
2. Medullary expansion may result in nerve compression, extramedullary hematopoiesis, hepatosplenomegaly,growth retardation, and facial anomalies.
3. Pulmonary hypertension and increased risk of thrombosis, particularly in splenectomized patients.
4. Patients are most healthy if management is as vigorous as that for TDT.

Management

1. Folic acid 1 mg/day PO should be administered.

2. Iron-fortified foods should be avoided. A **cup of tea with every meal** will reduce the absorption of nonheme iron.

3. Chelation therapy **is required at an older age** than in thalassemia major because patients have received fewer transfusions.

Indications for chelation include **elevated transferrin saturation of 70%, ferritin of 800 ng/mL or higher**

4. Transfusions generally are not required except during periods of erythroblastopenia (erythroid aplastia due to parvovirus B19) or during acute infection.

If hemoglobin falls below 7 g/dL, growth is poor, or other complications develop, **chronic transfusion** therapy should be initiated. Children should be monitored for facial bone changes, which can be prevented, but not reversed, by chronic transfusions.

5. Splenectomy may improve hemoglobin level. However, the risk of infection with encapsulated organisms,pulmonary hypertension, and hypercoagulability are increased following splenectomy; therefore splenectomy is often avoided.

β-Thalassemia minor or trait
(heterozygous β0 or β1)

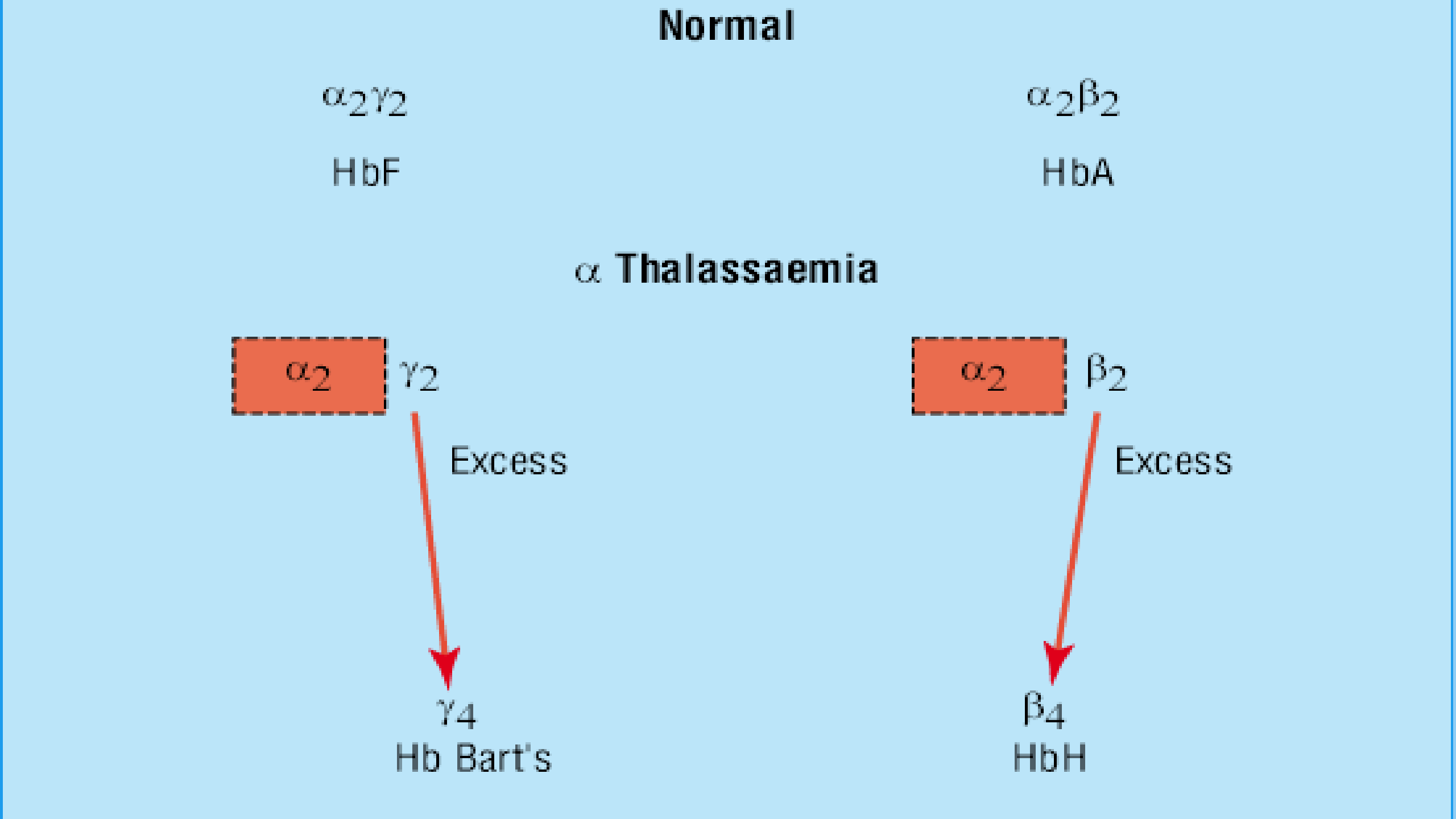
Asymptomatic (physical examination is normal).

a. Discovered on routine blood test—slightly reduced hemoglobin, basophilic stippling, low MCV, normal red cell distribution width.

b. Discovered in family investigation or family history of heterozygous or homozygous β-thalassemia.

c. Confirmed with **hemoglobin electrophoresis, demonstrating slightly decreased HbA (90-95%), increased HbA2 (more than 3.5%); hemoglobin F mildly elevated in 50% of cases.**

α-THALASSEMIA


Normal
$\alpha_2\gamma_2$
HbF
$\alpha_2\beta_2$
HbA
α Thalassaemia
α_2
γ_2
Excess
γ_4
Hb Bart's
α_2
β_2
Excess
β_4
HbH

In In **α-thalassemia**, there are relatively fewer α-globin chains and an excess of β- and γ-globin chains. These excess chains form **Bart's hemoglobin (γ_4)** in fetal life and **Hb H (β_4)** after birth. These abnormal tetramers are not as lethal, but lead to extravascular hemolysis. Prenatally, a fetus with α-thalassemia may become symptomatic because Hb F requires sufficient α-globin gene production, whereas postnatally, infants with β-thalassemia become symptomatic because Hb A requires adequate production of β-globin genes.

Infants are identified in the newborn period by the increased production of **Bart's hemoglobin** (γ_4) during fetal life and its presence at birth.

There are four α-globin genes and four deletional α-thalassemia phenotypes:

Type	Genotype
Normal	α α / α α
α^+ heterozygote	α – / α α
α^+ homozygote	α – / α –
α^0 heterozygote	– – / α α
α^0 homozygote	– – / – – (Barts hydrops foetalis)
α^0 α^+ Double heterozygote	– – / α – (hemoglobin H disease)

The deletion of 1 α-globin gene (silent trait) is not identifiable hematologically. No alterations are noted in the mean corpuscular volume and mean corpuscular hemoglobin. During the newborn period, typically **<3% Bart's** hemoglobin is observed.

The deletion of 2 α-globin genes results in α-thalassemia trait.

The globin genes can be lost in *trans* (-α/-α), or in *cis* (α,α/--).

The α-thalassemia traits present as a microcytic anemia that can be mistaken for iron-deficiency anemia. The hemoglobin analysis is normal, except during the newborn period, when Bart's hemoglobin is commonly **<8%, but >3%.**

The simplest way to distinguish between iron deficiency and α-thalassemia trait is with a good dietary history. Children with iron-deficiency anemia often have a diet that is low in iron. Alternatively, a brief course of iron supplementation, along with monitoring of the red blood cell parameters, may make the diagnosis of iron deficiency.

The deletion of 3 α-globin genes leads to the diagnosis of Hb H disease.

The simplest manner of diagnosing Hb H disease is during the newborn period, when the Bart's hemoglobin level is commonly >25%. In addition, supporting evidence must be obtained from the parents (at least 1 parent must have α-thalassemia trait).

Later in childhood, there is an excess of β-globin chain tetramers that results in Hb H. A definitive diagnosis of Hb H disease requires DNA analysis.
Individuals with Hb H disease have marked microcytosis, anemia, mild splenomegaly, and occasionally, scleral icterus or cholelithiasis. Transfusion is not commonly used for therapy because the range of hemoglobin is 7.0–11.0 g/dL.

The deletion of all 4 α-globin genes

causes profound anemia during fetal life, resulting in **hydrops fetalis**.
There are no normal hemoglobins present at birth (primarily Bart's hemoglobin, with Gower-1, Gower-2, and Portland). If the fetus survives, immediate exchange transfusion is indicated.
These infants with α- thalassemia major are transfusion-dependent, and bone marrow transplant is the only cure.

Treatment

-folate supplementation,
-possible splenectomy (with the attendant risks),
-intermittent transfusion during severe anemia, and chronic transfusion therapy or bone marrow transplant for survivors of hydrops fetalis.
-These children also should not be exposed to oxidant medications.