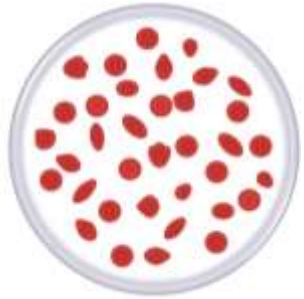
Alpha & Beta Thalassaemia



What is Thalassaemia?

- Thalassaemia is an **inherited blood disorder** in which the body produces an **abnormal form of hemoglobin** which results in excessive **destruction of red blood cells**.
- 2 types of Thalassaemia:

Alpha Thalassaemia

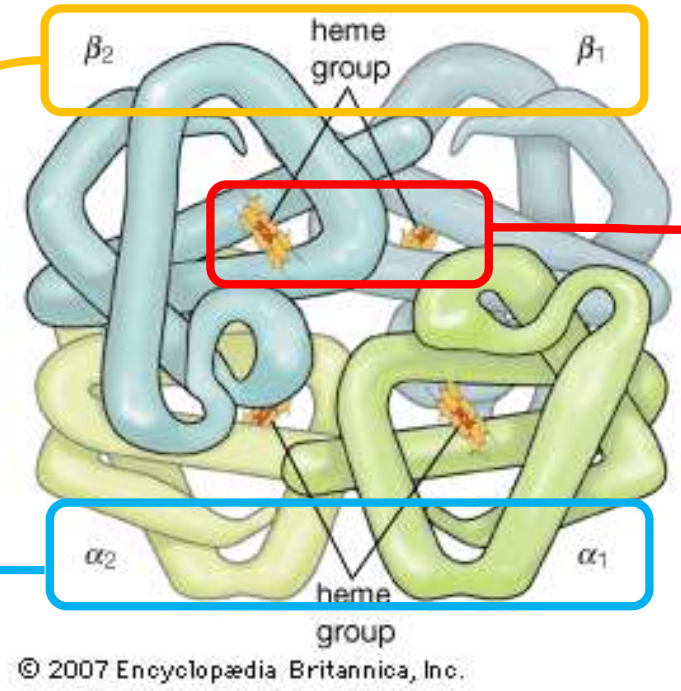
Beta Thalassaemia

Normal Hemoglobin

Structure: 2 parts : heme + globin

Globin: 4 globin chains

2 alpha 2 beta



Heme: porphyrin ring with central iron.

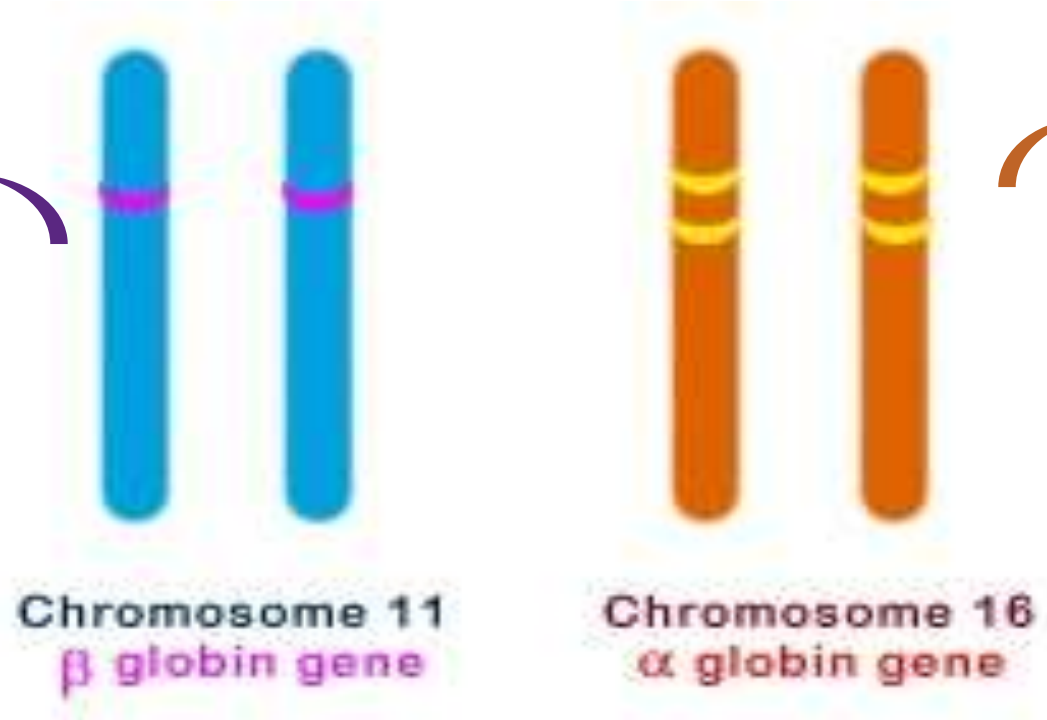
Types of hemoglobin

Type of Hemoglobin	Polypeptide chain	Percentage
Hemoglobin A (**HbA**)	2 alpha and 2 beta globins (A^2B^2)	97% of normal adult hemoglobin
Hemoglobin A2 (**HbA2**)	2 alpha and 2 delta globins ($\alpha^2\ \delta^2$)	2.5% of normal adult hemoglobin
Hemoglobin F (**HbF**)	2 alpha and 2 gamma globins ($\alpha^2\ \gamma^2$)	<2% in adult *Normal fetal hemoglobin

* After birth, the production of adult hemoglobin rapidly increases and fetal hemoglobin production drops off.
* By approximately six months of age, healthy infants will have transitioned to mostly HbA, a small amount of HbA2, and negligible HbF

Genetics

The hemoglobin beta genes (***HBB***) encodes the β-chain and is located on chromosome 11.

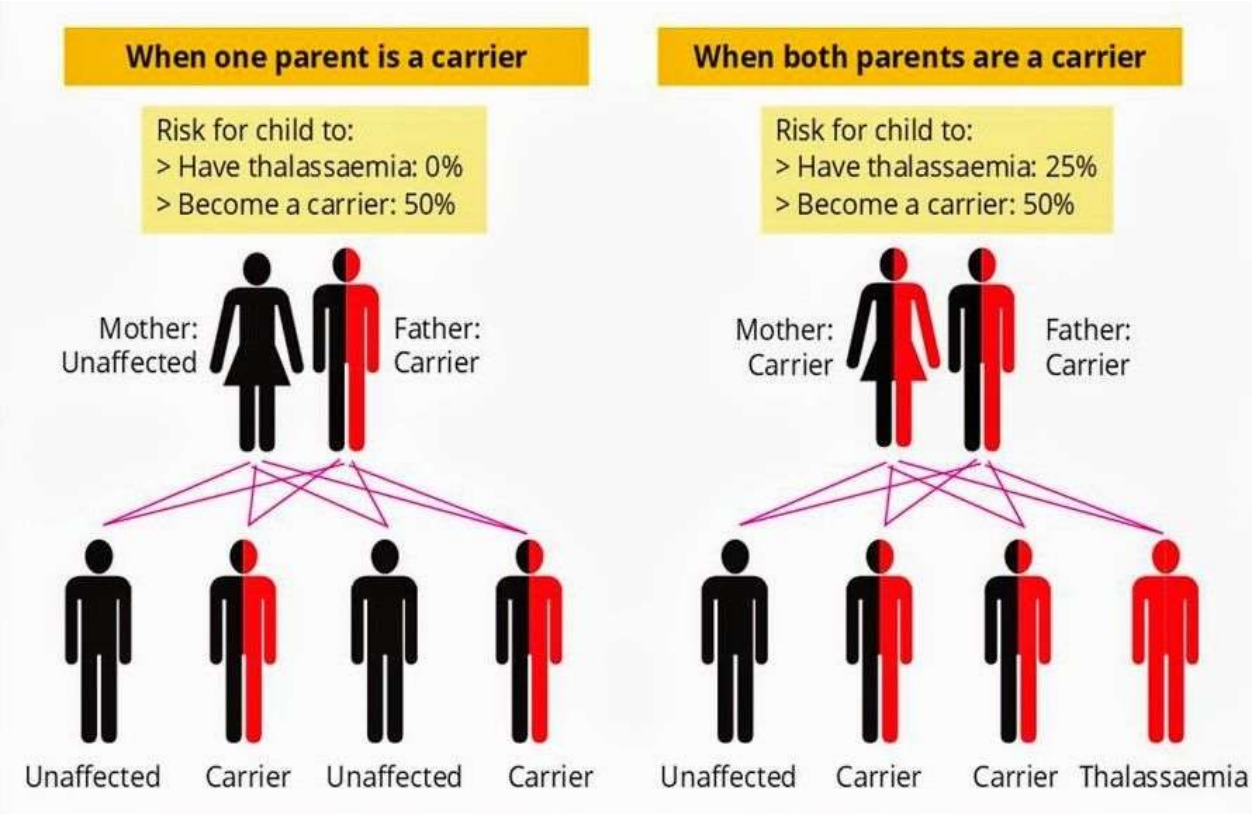


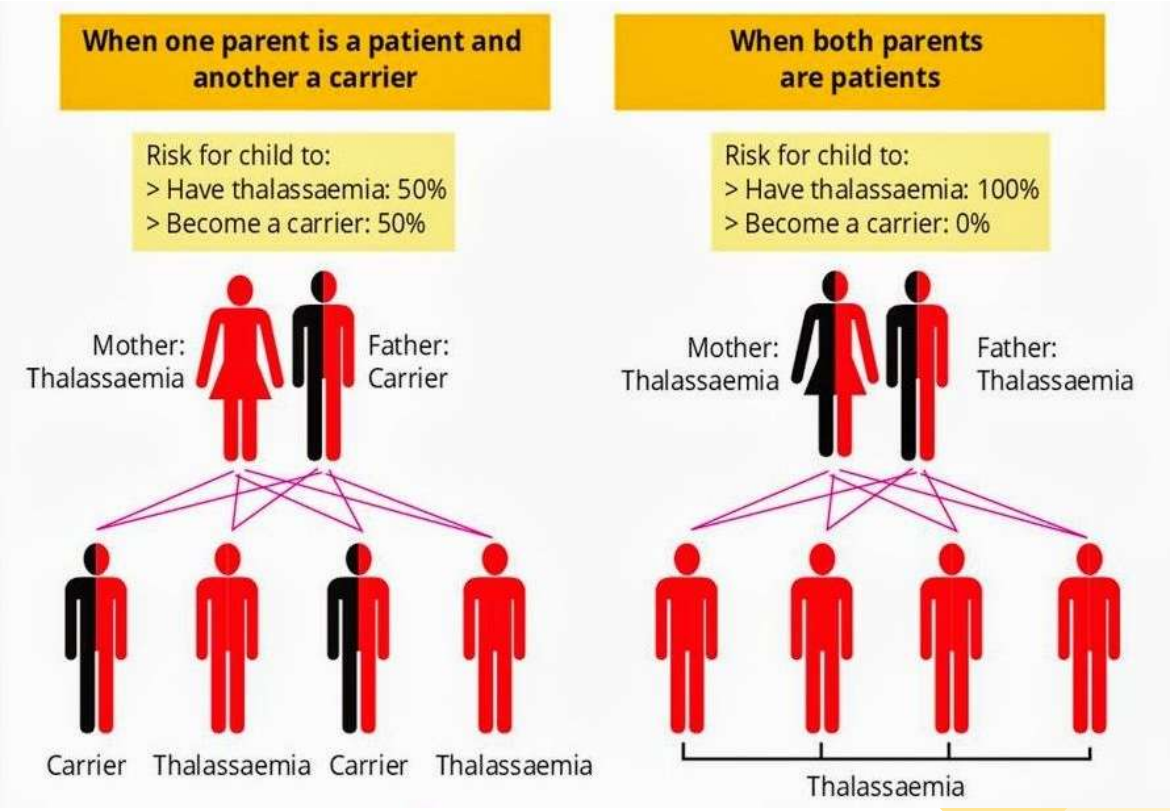
There are two copies of the hemoglobin alpha gene **(*HBA1* and *HBA2*)**, which each encode an α-chain, and both genes are located on chromosome 16.

- The genes controlling globin production are on **chromosome 16** (**alpha** globin genes), and **chromosome 11** (**beta** globin genes)

Inheritance

- Thalassemia is inherited in an **autosomal recessive** manner.
- However, the inheritance can be quite complex as multiple genes can influence the production of hemoglobin.





Alpha Thalassaemia

Genetics

- Alpha thalassemia is caused by a **decrease** in production of **alpha globin chains** due to a deletion or mutation of one or more of the four alpha globin genes located on **chromosome 16**.
- Alpha globin gene has **4 alleles** and disease severity ranges from mild to severe depending on the number of deletions of the alleles.

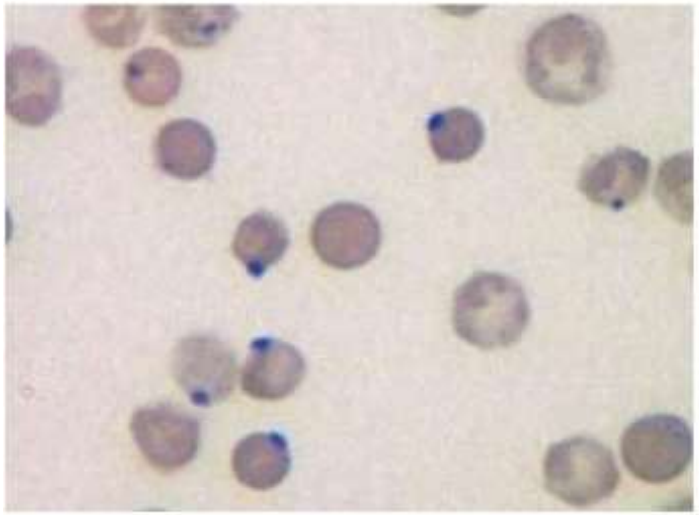
Epidemiology

- Alpha thalassaemia occurs most often in persons of African and Southeast Asian descent.

Alpha Thalassaemia

Pathophysiology

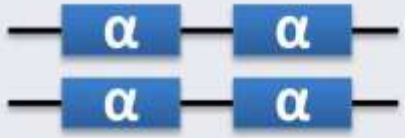
- Absence of alpha globin chain results in **excess** production of **gamma** globin chains (in fetus and newborn) or **beta** globin chains (in children and adults).
- The beta globin chains are capale of forming soluble tetramers (beta-4, or **HbH**).
- This form of hemoglobin is unstable and precipitates wihtin cell, forming insoluble inclusions called **Heinz bodies**, that damages the red cells.
- This further damage the erythrocyte precursors and ineffective eryhtropoiesis in bone marrow, **hypochromia and microcytosis.**



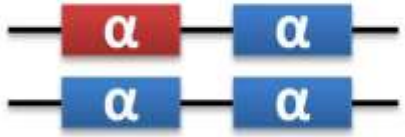
Heinz bodies

Forms of Alpha Thalassaemia

Normal

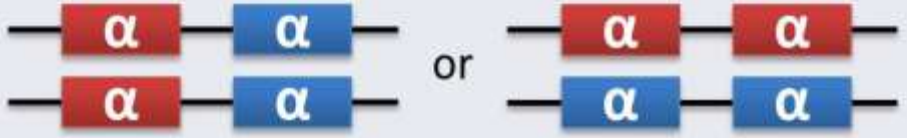


Carrier: Asymptomatic
No abnormalities



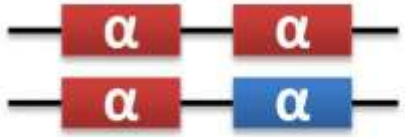
One deletion

α-thal minor: Asymptomatic
Mild microcytic anemia



Two deletions

Hb H Disease: Symptomatic
Hemolytic and Microcytic anemia
Splenomegaly



Three deletions

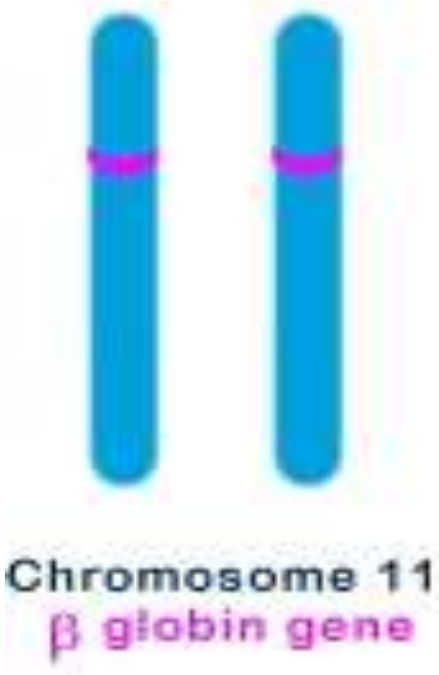
Incompatible with Life
Hydrops Fetalis

Four deletions

Beta Thalassaemia

Genetics

- Beta thalassemia is the result of **deficient or absent** synthesis of **beta** globin chains, leading to **excess alpha** chains.
- Beta globin synthesis is controlled by one gene on each **chromosome 11**. Thus, patient may have only one or both alleles of the beta globin chain affected.
- Beta thalassemia occurs from any of more than 200 point mutations and (rarely) deletions of the two genes.



Epidemiology

- Beta thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent.

Beta Thalassaemia

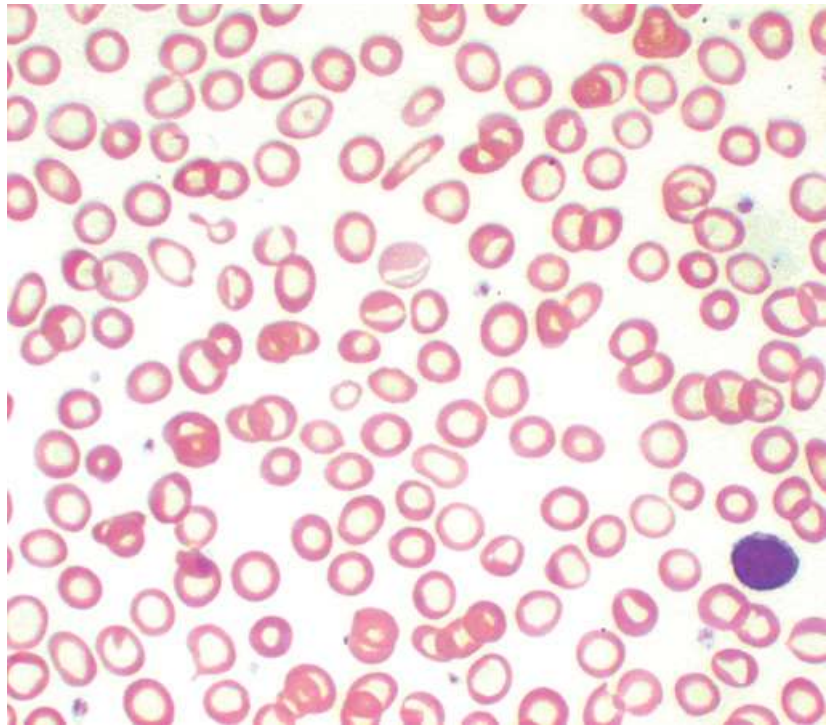
Pathophysiology

- Mildly reduced synthesis of beta globin (seen in heterozygous mutation) can cause reduced production of normal Hb

  → observed as mild hypochromic microcytic anaemia.

- Severe reduction of beta globin (seen in homozygous mutation) can cause accumulation of highly insoluble alpha-globin particles

  → damage erythrocyte membrane and render it less flexible yielding ineffective eryhtropoiesis and extrvascular hemolysis.



Forms of Beta Thalassaemia

Variant	Chromosome 11	Sign & Symptoms
Beta thalassaemia trait	One gene defect	Asymptomatic
Beta thalassamia intermedia	2 genes defect (mild to moderate decrease in beta globin synthesis)	Variable degrees of severity of symptoms of thalassemia major
Beta thalassaemia major	2 genes defect (severe decrease in beta globin synthesis)	Abdominal swelling, growth retardation, dark urine, jaundice, pallor, skeletal abnormalities, splenomegaly, lifelong blood transfusions.

Olivieri NF. The beta-thalassemias [published correction appears in *N Engl J Med*. 1999;341(18):1407]. *N Engl J Med*. 1999;341(2):99–109.

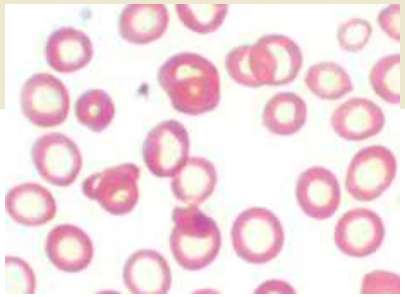
Lab evaluation of Thalassaemia

1) Complete blood count (CBC)

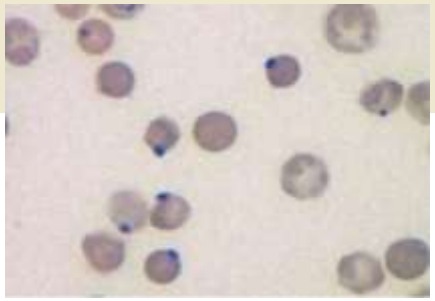
- **Low hemoglobin and low MCV** is the first indication of thalassemia (after ruling out iron deficiency anemia)
- **Mentzer** index : (mean corpuscular volume divided by red cell count)
  - **< 13** suggests that the patient has **thalassemia**
  - **> 13** suggests that the patient has anemia due to **iron deficiency**

2) Peripheral blood smear

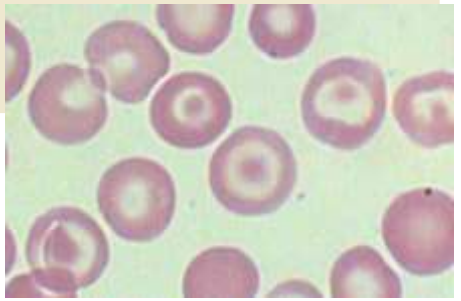
- Microcytic (low MCV), hypochromic cells
- Variation in size and shape (anisocytosis & poikilocytosis)
- Increased percentage of reticulocytes
- Target cells
- Heinz bodies



Microcytic, hypochromic



Heinz bodies



Target cells

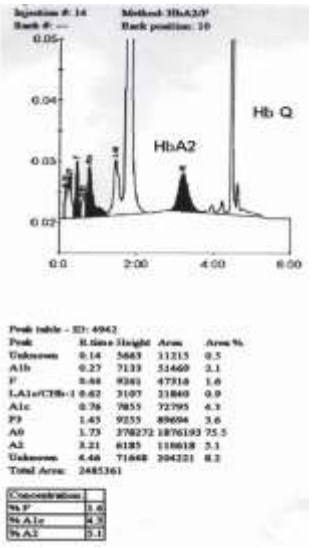
Lab evaluation of Thalassaemia

3) Haemoglobin electrophoresis

- Assess **type** and relative **amount** of haemoglobin presents in red cells.
- Beta thalassaemia major: high % of HbF and HbA2, absent or very low HbA.
- Beta thalassaemia minor: Mild elevation of HbA2, mild decrease of HbA.
- HbH seen in some cases of Alpha thalassaemia.
- HbS seen in people with sickle cell disease.

4) Iron studies

- Serum iron, ferritin, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and percent saturation of transferrin are done to rule out iron deficiency anemia as the underlying cause.



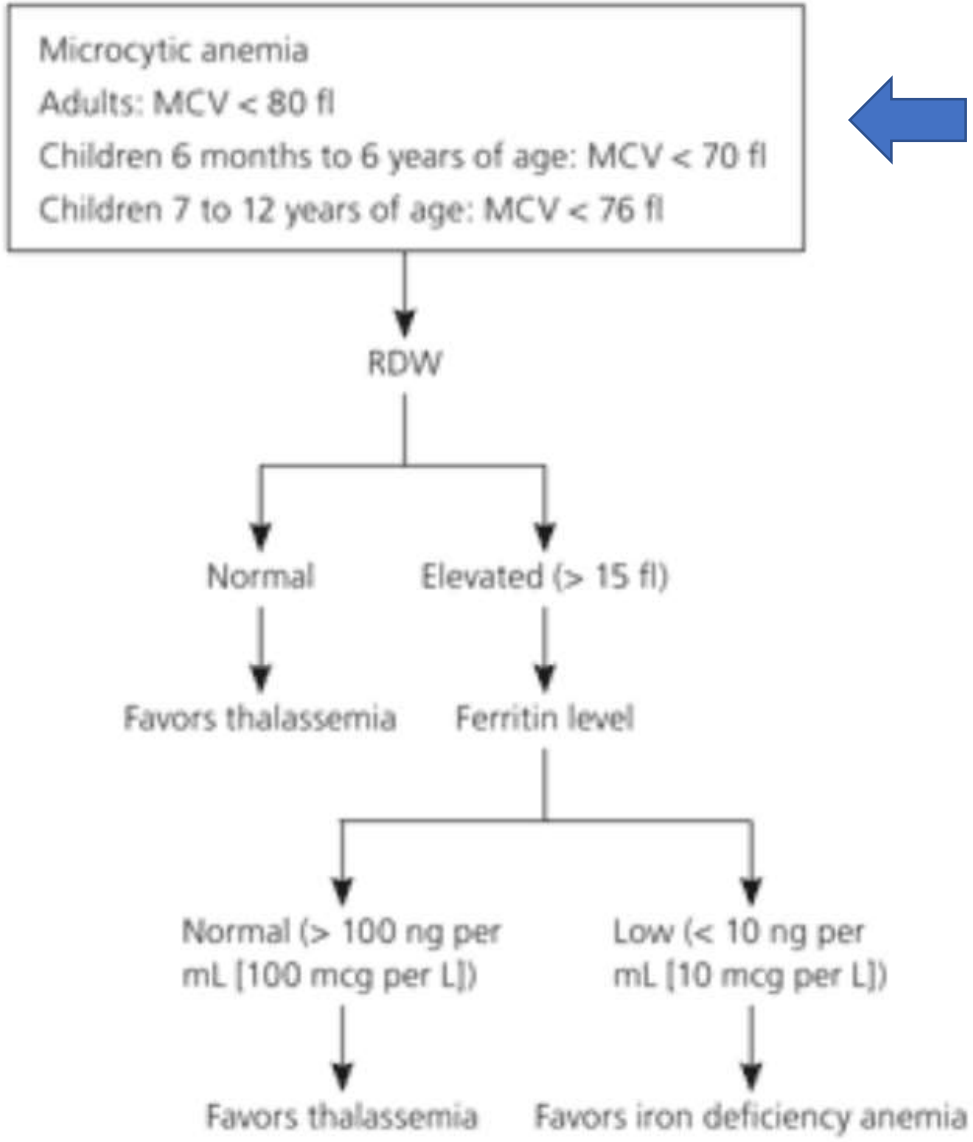
Lab evaluation of Thalassaemia

Table 3.
Hematologic Indices of Iron Deficiency and Alpha and Beta Thalassemia

TEST	*IRON DEFICIENCY*	*BETA THALASSEMIA*	*ALPHA THALASSEMIA*
MCV (abnormal if < 80 fl in adults; < 70 fl in children six months to six years of age; and < 76 fl in children seven to 12 years of age)	Low	Low	Low
Red blood cell distribution width	High	Normal; occasionally high	Normal
Ferritin	Low	Normal	Normal
Mentzer index for children (MCV/red blood cell count)	> 13	< 13	< 13
Hb electrophoresis	Normal (may have reduced HbA2)	Increased HbA2, reduced HbA, and probably increased HbF	Adults: normal Newborns: may have HbH or Hb Bart's

Hb = hemoglobin; HbF = fetal hemoglobin; MCV = mean corpuscular volume.

Lab evaluation of Thalassaemia



Use of **RDW** values in the Diagnosis of Thalassaemia

Marsh WL Jr, Bishop JW, Darcy TP. Evaluation of red cell volume distribution width (RDW). *Hematol Pathol*. 1987;1(2):117–123.

Treatment / Management

Blood transfusion

Persons with beta thalassemia major require lifelong blood transfusions to maintain hemoglobin level. Alpha thalassemia intermedia (HbH disease) causes mild to moderate hemolysis. Transfusions will occasionally be necessary depending on the severity of the clinical condition.

Iron chelation

Due to chronic transfusions, iron starts to get deposited in various organs of the body. Iron chelators (deferasirox, deferoxamine, deferiprone) are given concomitantly to remove extra iron from the body.

Stem cell transplant

Bone marrow transplantation in childhood is the only curative therapy for beta thalassemia major. Hematopoietic stem cell transplantation generally results in an excellent outcome in low-risk persons.

Complications & Prognosis

COMPLICATIONS

- **Iron overload** from regular blood transfusions. Iron is deposited in visceral organs (mainly the heart, liver, and endocrine glands).
- **Hepatosplenomegaly** due to extramedullary hematopoiesis and excess iron deposition due to repeated blood transfusions.
- **Cardiac failure** due to severe anemia, cardiomyopathies, and arrhythmias - cardiac involvement is the major cause of mortality in thalassemia patients.
- Jaundice and gall stones due to hyperbilirubinemia.

PROGNOSIS

- Thalassemia minor is usually asymptomatic and has a good prognosis. It normally does not increase morbidity or mortality.
- Thalassemia major is a severe disease, and the long-term prognosis depends on the treatment adherence to transfusion and iron chelation therapies.