Hemoglobinopathies

- Altered structure, function, or production.
- Usually inherited.

- Range in severity from asymptomatic laboratory abnormalities to death in utero.
- Different hemoglobins are produced during embryonic, fetal, and adult life.

Properties of the Human Hemoglobins

- Hemoglobin critical- oxygen delivery.
- Can alter red cell shape, deformability, and viscosity.
- tetramer –bind upto 4 O_2
- 2**α** chains(141 amino acids)& 2**β** chains(146 amino acids).

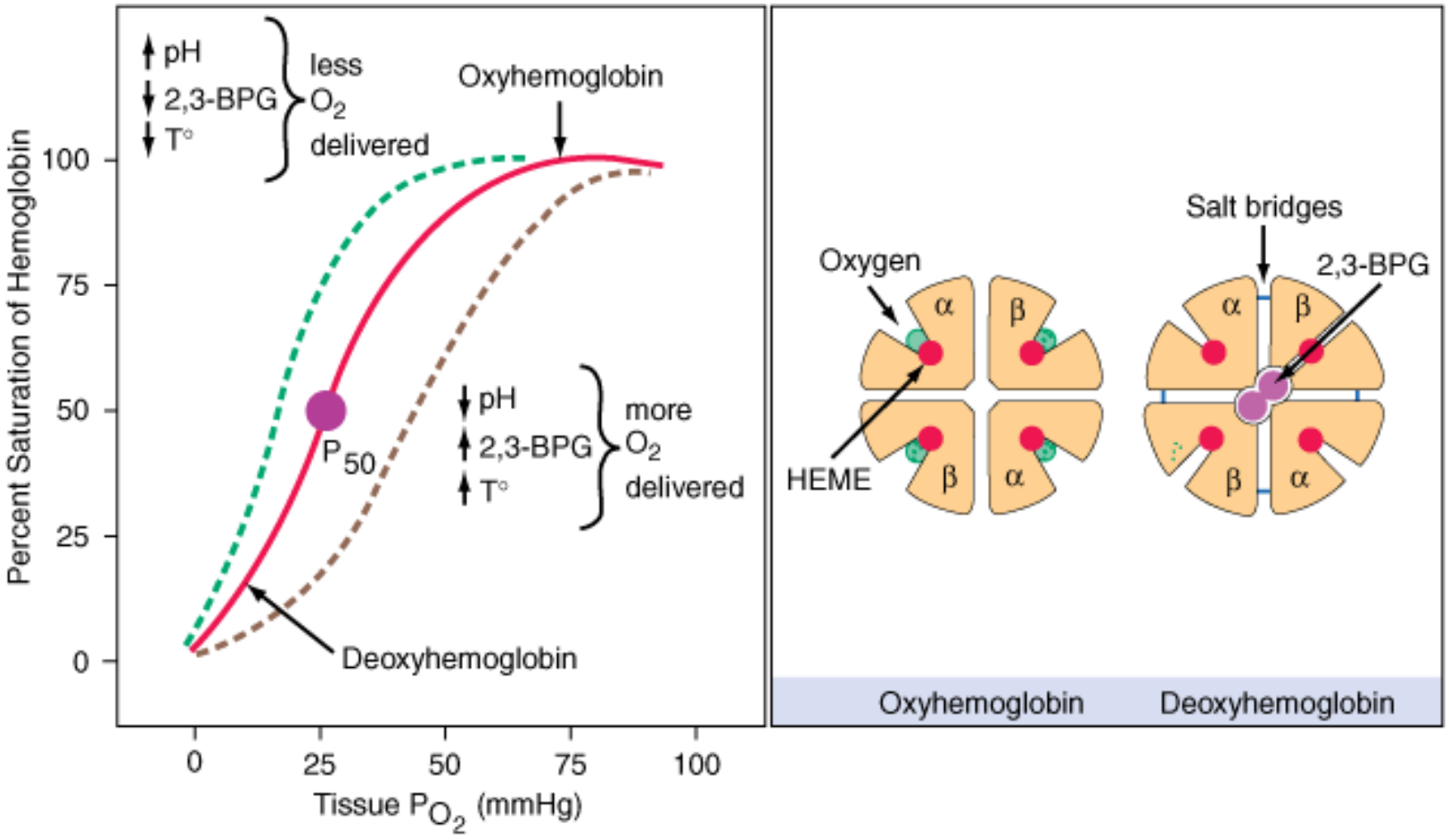
Properties of the Human Hemoglobins

- HbA1(**α2 β2)-** major adult
- HbA2(**α2δ2)-**minor
- HbF(**α2γ2)**
- hemoglobin tetramer-highly soluble but individual globin chains are insoluble.
- Unpaired globin precipitates, forming inclusions that damage the cell.

Function of Hemoglobin

- oxygen transport
- Bind O_2 efficiently & retain at high O_2 tension (alveolus).
- Release at low O_2 tension(tissue).
- *cooperativity* or *heme-heme interaction*
- Bohr effect (ability of hemoglobin to deliver more oxygen to tissues at low pH)

Hemoglobin-oxygen dissociation curve



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Classification of Hemoglobinopathies

I. **Structural hemoglobinopathies**—hemoglobins with altered amino acid sequences eg HbS

II. **Thalassemias**—defective biosynthesis of globin chains

III. **Thalassemic hemoglobin variants**—structurally abnormal Hb associated with co-inherited thalassemic phenotype HbE, Hb Constant Spring,Hb Lepore

IV**. Hereditary persistence of fetal hemoglobin**

V. **Acquired hemoglobinopathies**

A. Methemoglobin

B. Sulfhemoglobin

C. Carboxyhemoglobin

D. HbH in erythroleukemia

Sickle cell syndrome

- Mutation in β globin gene that changes sixth amino acid from glutamic acid to valine
- HbS polymerises reversibly when deoxygenated, to form a gelatinous network of fibrous polymer that stiffens the erythrocyte membrane, ↑viscosity. These changes produce characteristic sickle shape- prone to hemolysis

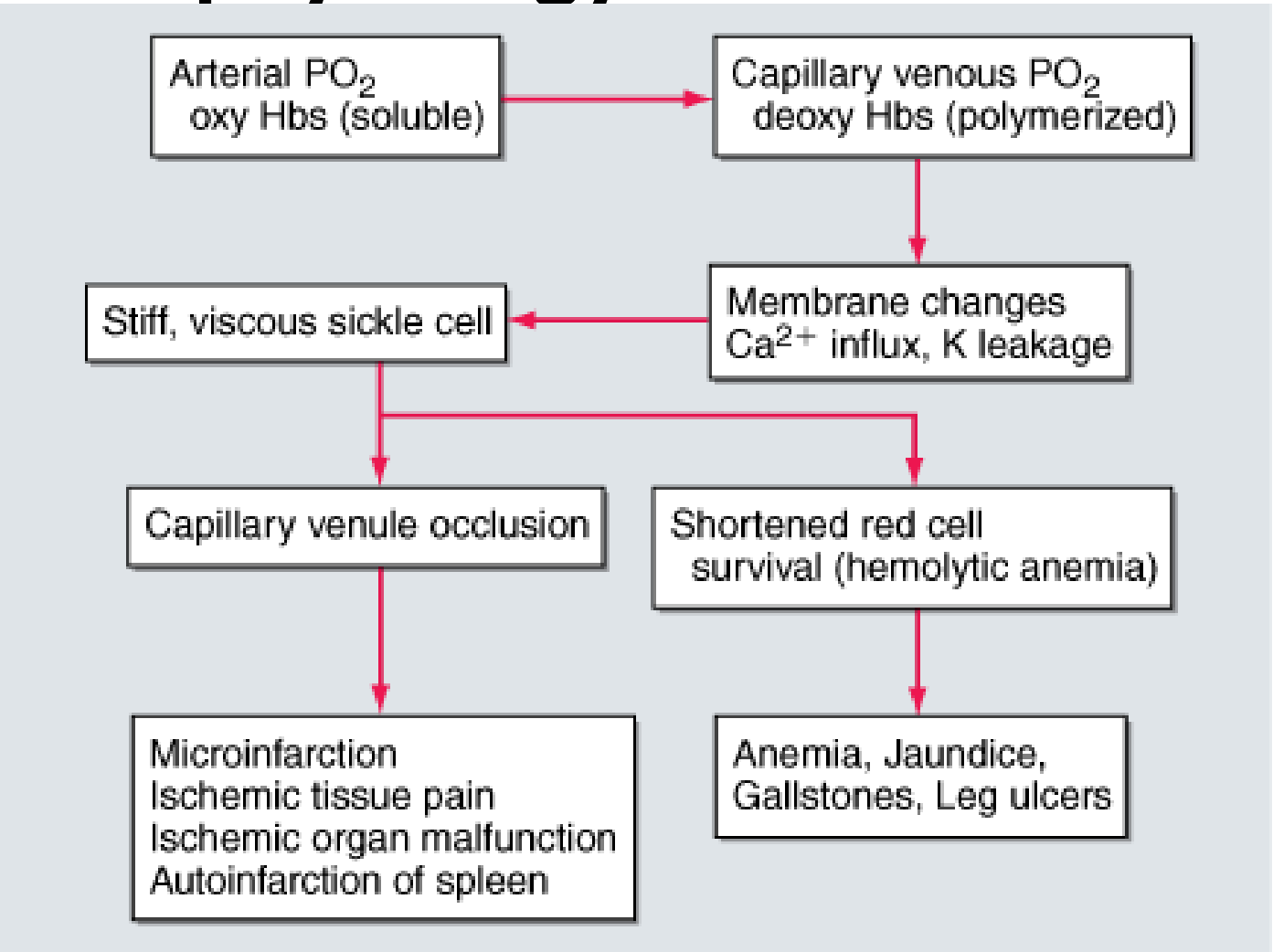
Classification

- Homozygous SS sickle cell anaemia
- Heterozygous AS sickle cell trait (generally asymtomatic – protects against falciparum malaria)

Factors increasing sickling

- Hypoxia
- Low pH
- Fever
- Infection
- Excess exercise
- Anxiety, dehydration
- Abrupt tem. changes

Pathophysiology of sickle cell crisis



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Clinical features

- Anaemia
- Jaundice
- Splenomegaly
- Painful swelling hands &feet
- Chronic lower leg ulcers probably arise from ischemia and super infection in the distal circulation.

- Constitutional symptoms - impaired growth
  ↑susceptibility to infection

Clinical features

- **Vasooclusive phenomenon**
- Microinfarct – abdomen, chest pain, back pain, joints (recurrent painful crises)
- These recurrent episodes, called *painful crises*, are the most common clinical manifestation.
- Macroinfarct –splenic sequestration crisis (autosplenectomy)
  Bone marrow infarct
  Bone aseptic necrosis, osteomyelitis
  Renal cortical necrosis
  hand-foot syndrome
  priapism
  CNS – stroke
  Retinal damage – blindness
  Skin ulcers
  Acute chest syndrome

Investigation

- Diagnosis is usually established in childhood,
- childhood history
- hemolytic anemia
- Granulocytosis
- RBC morphology -sickle cell, target cell, howell-jolly body
- intermittent episodes of ischemic pain
- Diagnostic test- Sickling test +ve with reducing substance as sodium metabisulfite
- Hb electrophoresis (HbS)

Factors associated with increased morbidity and reduced survival

- > three crises requiring hospitalization per year.
- chronic neutrophilia.
- a history of splenic sequestration or hand-foot syndrome, and second episodes of acute chest syndrome

Treatment

- Patient require ongoing continuity of care.
- Education and familiarity with pattern of symptoms provide the best safeguard.
- Treatment of ppt factors
- preventive measures- regular slit-lamp examinations
- **antibiotic prophylaxis** appropriate for splenectomized patients during dental or other invasive procedures; and
- vigorous oral **hydration** during or in anticipation of periods of extreme exercise, exposure to heat or cold, emotional stress, or infection.
- Pneumococcal and *Haemophilus influenzae* vaccines.

Treatment

- **management of acute painful crisis-** vigorous hydration, thorough evaluation for underlying causes (such as infection), and aggressive analgesia , blood transfusion should be reserved for extreme cases

- **Acute chest syndrome** medical emergency that may require management in an intensive care unit oxygen therapy, Hydration transfusion to maintain a hematocrit > 30, and emergency exchange transfusion if arterial saturation drops to <90%.

Treatment

- **Hydroxyurea**- (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial affects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000 per L

- **BMT**- definitive cures known to be effective and safe only in children .Prognostic features justifying bone marrow transplant are the presence of repeated crises early in life, a high neutrophil count, or the development of hand-foot syndrome.

- Gene therapy

Thalassemia syndrome

Hemoglobin consist of 2α &2β peptide chains

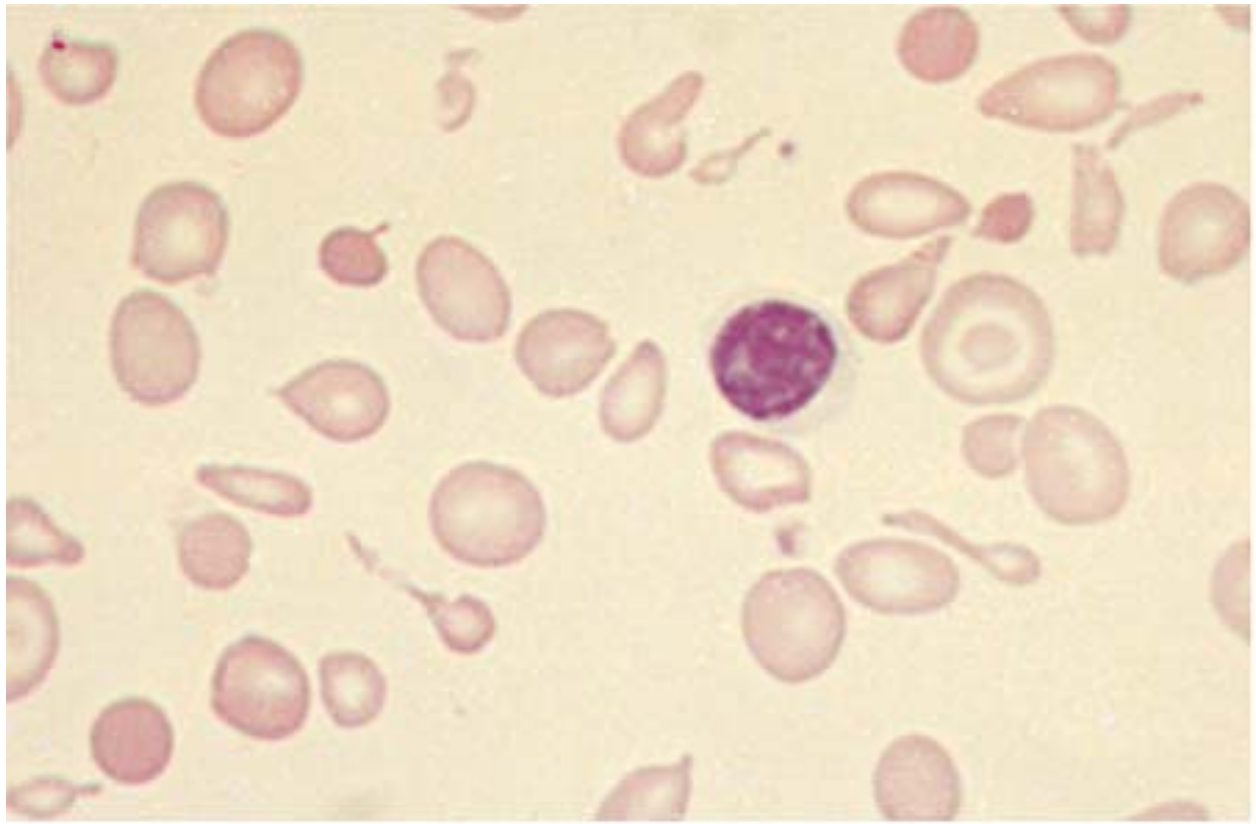
HbA	95% –	α2β2
HbA 2	5%	α2 δ2
Fetal HbF	-¯	α2 γ2
		(may persist in β thalassemia)

Thalassemia syndrome

- At birth, Hgb F appx. 80 %
  and Hgb A -20 %.

- By approximately six months of age, healthy infants will have transitioned to mostly Hgb A,a small amount of Hgb A2, and negligible Hgb F

Blood film of thalassemia



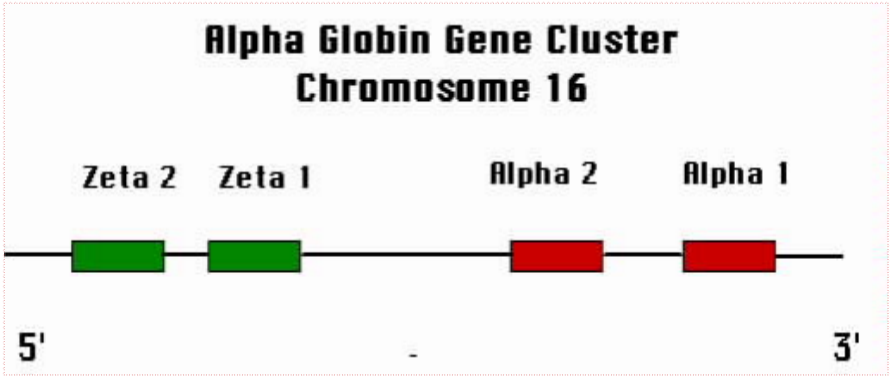
Epidemiology

- Affects men and women equally and occurs in approximately 4.4 of every10,000 live births
- Alpha thalassemia occurs most often in persons of African and Southeast Asian descent
- Beta thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent
- Thalassemia trait affects 5 to 30 percent of persons in these ethnic groups.

Alpha Thalassemia

- Alpha thalassemia is the result of deficient or absent synthesis of alpha globin chains, leading to excess beta globin chains.

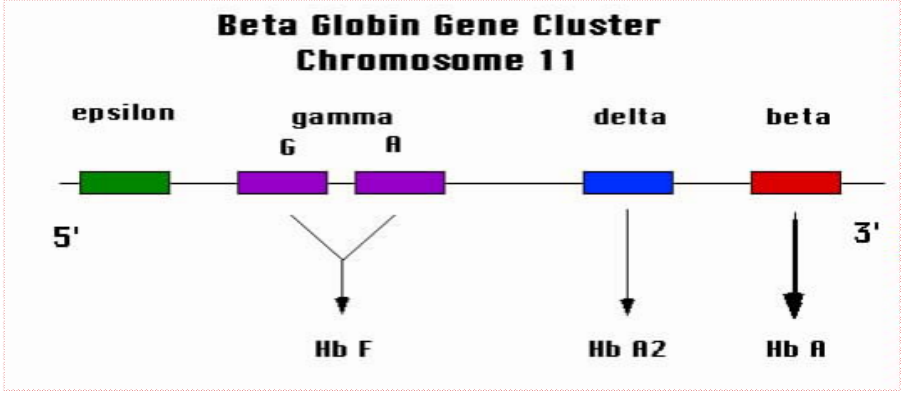
- Alpha globin chain production is controlled by two genes on each chromosome 16



Beta Thalassemia

- 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



Classification of thalassemia

type	Hb g/dl	Hb-Electrophoresis	Clinical Syndrome
α- thalassaemias			
Hydrops foetalis	3-10	Hb Barts(γ4)100%	Fatal in utero/early pregnency
Hb-H disease	2-12	HbF(10%)	Hemolytic anaemia
α- thalassaemias	10-14	N	No anemia(RBC-MH)
β- thalassaemias			
β- thalassaemias major	<5	HbA(0-50%) HbF(50-98%)	Severe congenital HA/require BT
β- thalassaemias minor	10-12	HbA2(4-9%) HbF(1-5%)	Mostly asymtomatic

α- thalassemias

Hb Barts- Hydrops foetalis

- deletion of all four **α** chain genes
- Total suppression of α globin chain synthesis
- Most severe form(Homozygous state)
- Incompatible with life
- Diagnosis-lab picture of severe HA
- Hb-Electrophoresis- Hb Barts - diagnostic

Hb-H disease

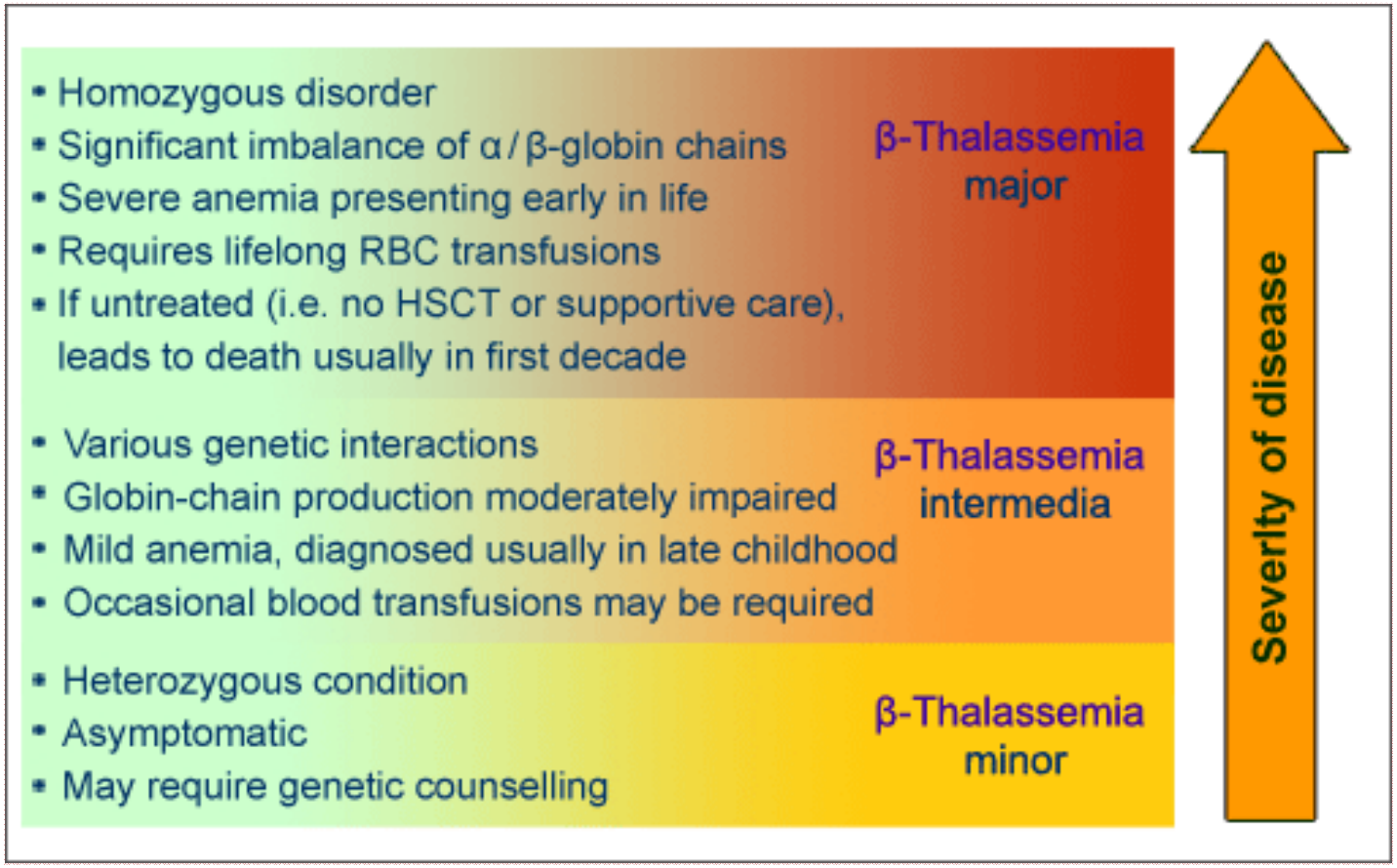
- Deletion of three α-chain genes
- Hb-H β-globin chain tetramer(β4)
- Markedly impaired α-chain synthesis
- Clinical feature- s/o HA
- Lab- hemolytic anemia, Heinz bodies(brilliant cresyl blue stain)
- Diagnostic-Hb-Electrophoresis

β- thalassemias

β- thalassemia major

- Common form of congenital anemia
- Homozygous form characterized by complete absence of β chain synthesis
- Diagnosis-lab picture of severe HA
- Hb-Electrophoresis-HbF & HbA2 - diagnostic

Severity of β–Thalassemia



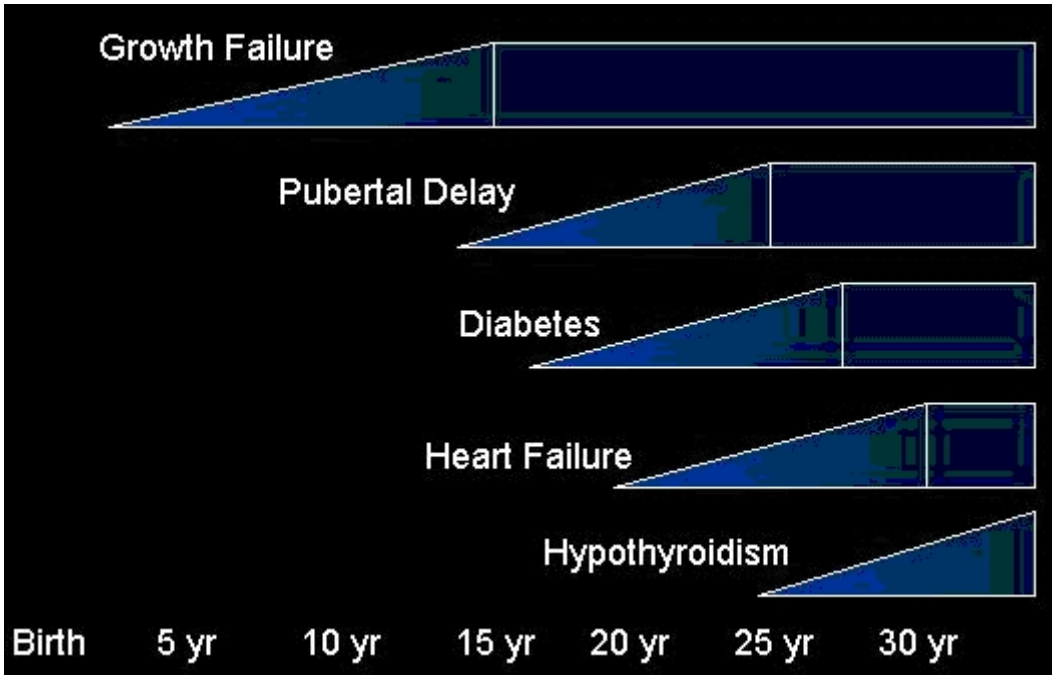
Clinical features

- Anemia
- Marked hepatosplenomegaly
- Marrow hyperplasia frontal bossing & prominent malar eminence
- Chipmunk facies, thalassemic facies
- Iron overload
- Growth retardation
- Delayed puberty, DM
- Cardiomegaly

Chipmunk facies, thalassemic facies

maxillary marrow hyperplasia and frontal bossing

Time of complications of Thalassemia



Diagnosis

- Most persons with thalassemia trait are found incidentally when their complete blood count shows a mild microcytic anemia

Microcytic anemia can be caused by:

1. Iron deficiency
2. Thalassemia
3. Lead poisoning
4. Sideroblastic anemia
5. Anemia of chronic disease.

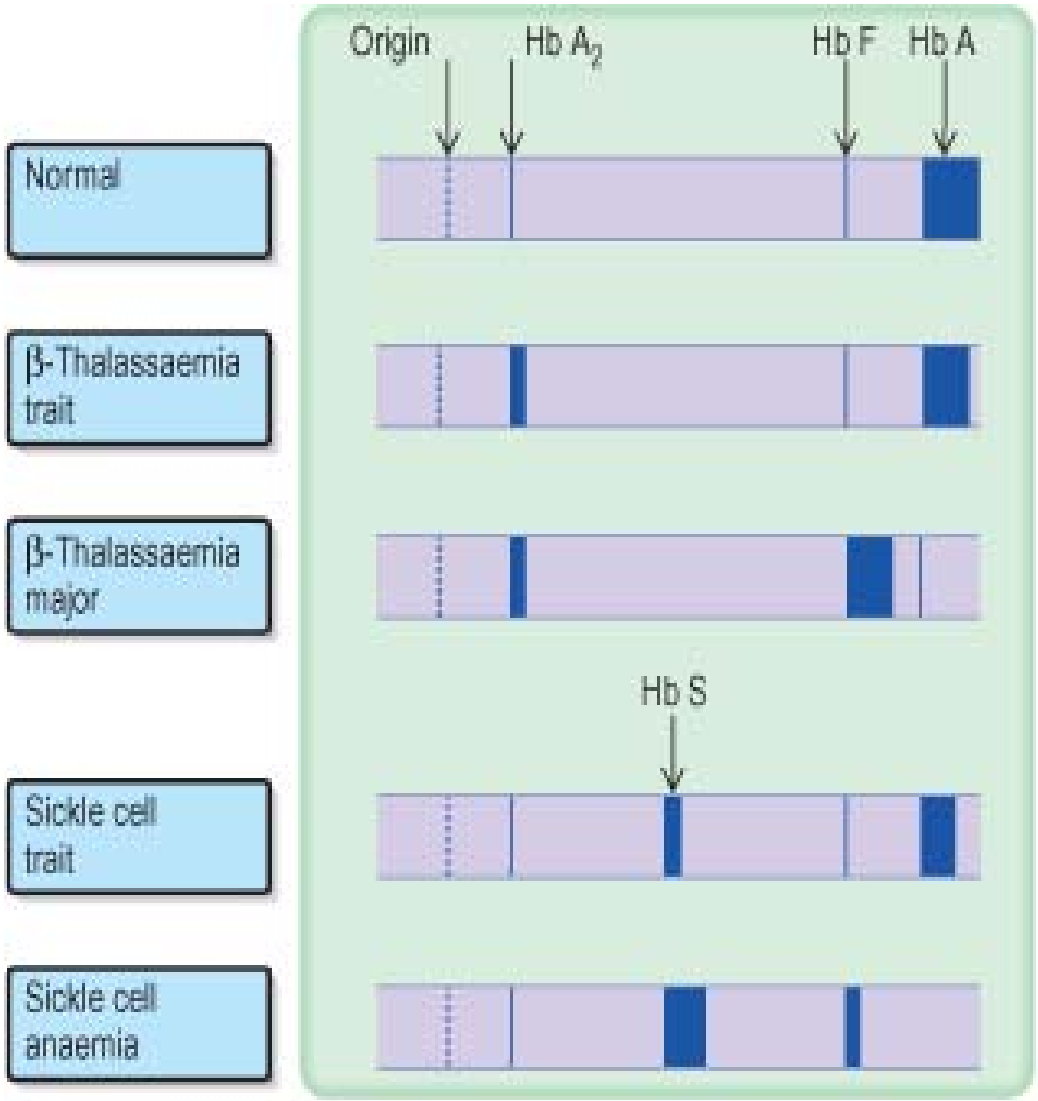
Use of RDW Values in the Diagnosis of Thalassemia

Microcytic Anemia **Children 6 months -6 years of age: MCV <70fl** **Children 7 to 12 years of age: MCV <76fl**		
↓		
RDW		
↓	↓	
Normal	Elevated (>15)	
↓	↓	
Favors Thalassemia	Ferritin level	
	↓	↓
	Normal(>100ng/mL)	Low(<10ng/mL)
	↓	↓

Supplemental tests

- Include:
  - Serum ferritin
  - The peripheral smear
  - Hemoglobin electrophoresis
  - Serum lead level
  - Rarely bone marrow aspirate

The hemoglobin electrophoresis



Treatment

- Blood transfusion to maintain hematocrit
- Folate supplementation
- Avoid iron therapy
- Desferrioxamine for iron chelation
- Splenectomy
- Allogenic bone marrow transplantation
- Gene therapy
- Antenatal diagnosis of thalassemia syndromes is now widely available.
- DNA diagnosis is based on PCR amplification of fetal DNA, obtained by amniocentesis or chorionic villus biopsy .

Prevention

- Blood tests and family genetic studies can show whether an individual has thalassemia or is a carrier.

- A genetic counselor can detail the family background, discuss risks.