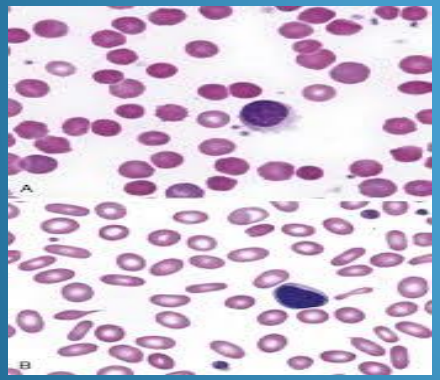
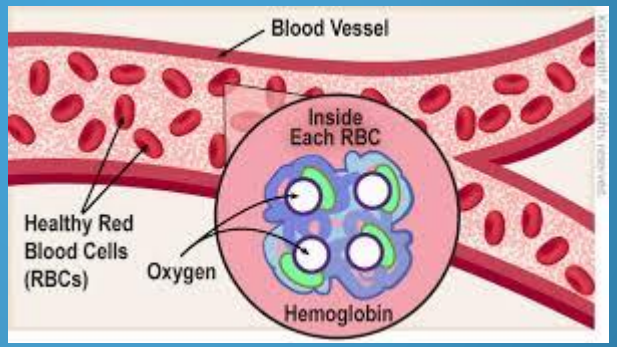
Congenital hemolytic anemias: Hemoglobinopathies





Reference: Current Diagnosis & Treatment Pediatrics by William Hay et al, 24th edition, 2018.... Pages 909-915

- The hemoglobinopathies are generally classified into two major groups:

caused by **quantitative def. in the production of globin chains** (e.g. thalassemia)→ These quantitative defects in globin synthesis cause microcytic and hypochromic anemias

caused by **structural abn. of globin chains** (e.g. sickle cell disease)→ The most important of these, hemoglobins S, C, and E, are all the result of point mutations and single a.a substitutions in β-globin

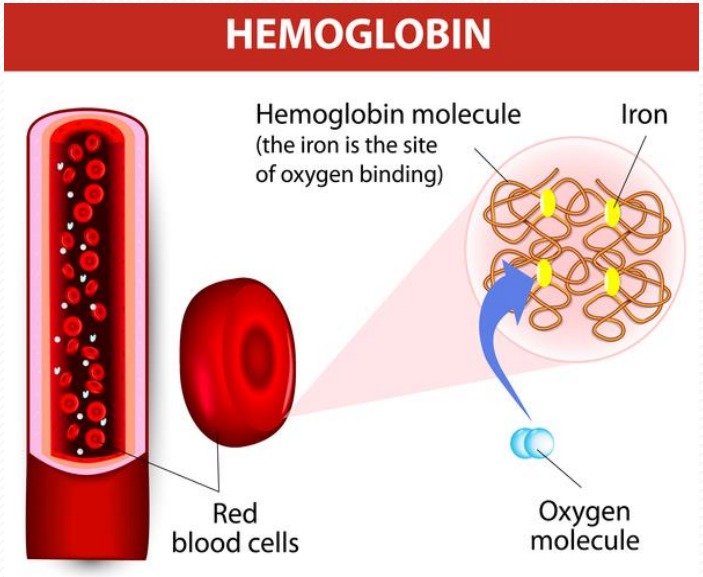
Types of hemoglobin in human

In the fetus:

- Hemoglobin F ($\alpha_2\gamma_2$)

After birth:

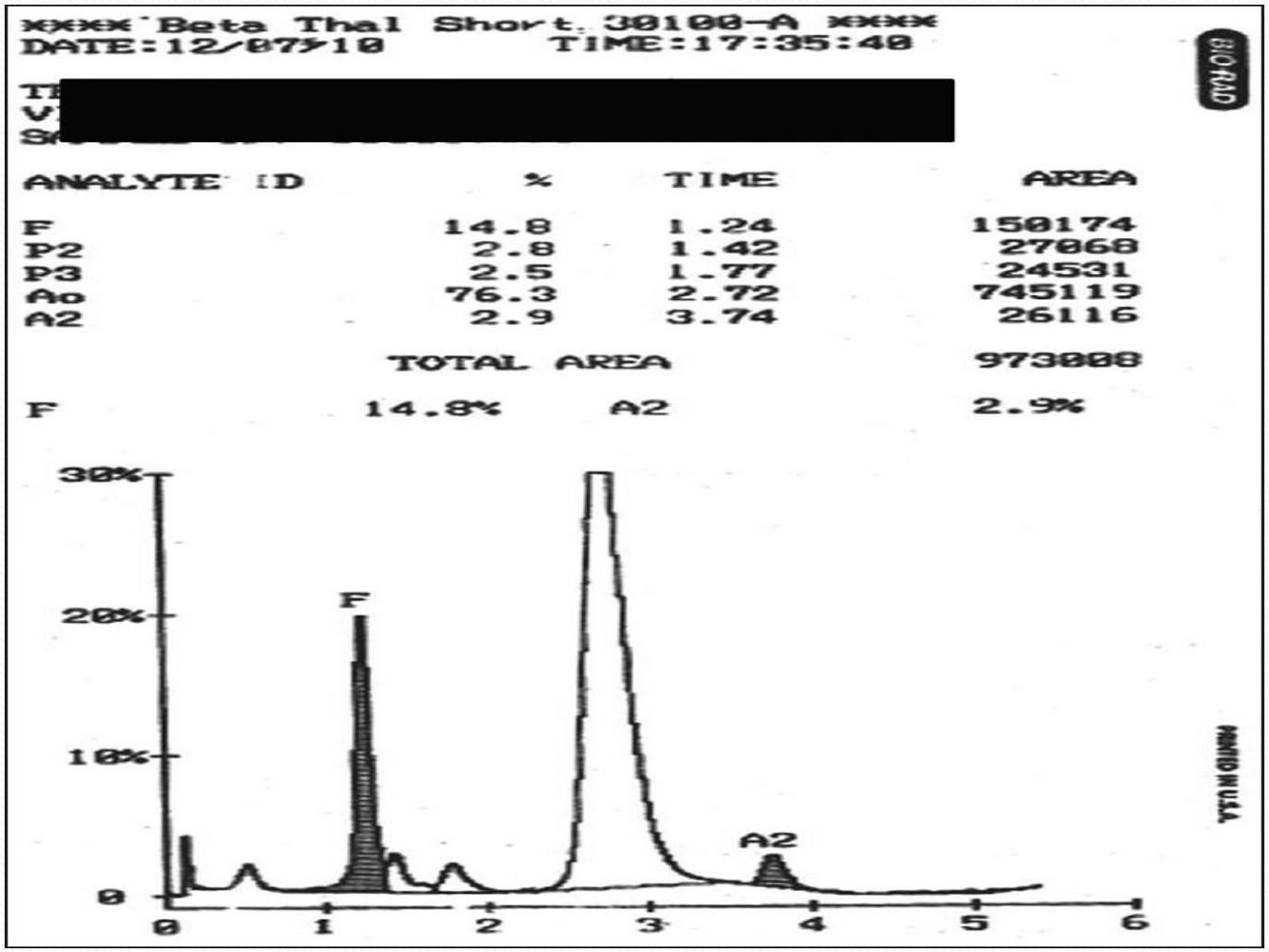
- Hemoglobin A ($\alpha_2\beta_2$)
- Hemoglobin A2 ($\alpha_2\delta_2$)
- Hemoglobin F ($\alpha_2\gamma_2$)



Variant forms that cause disease:

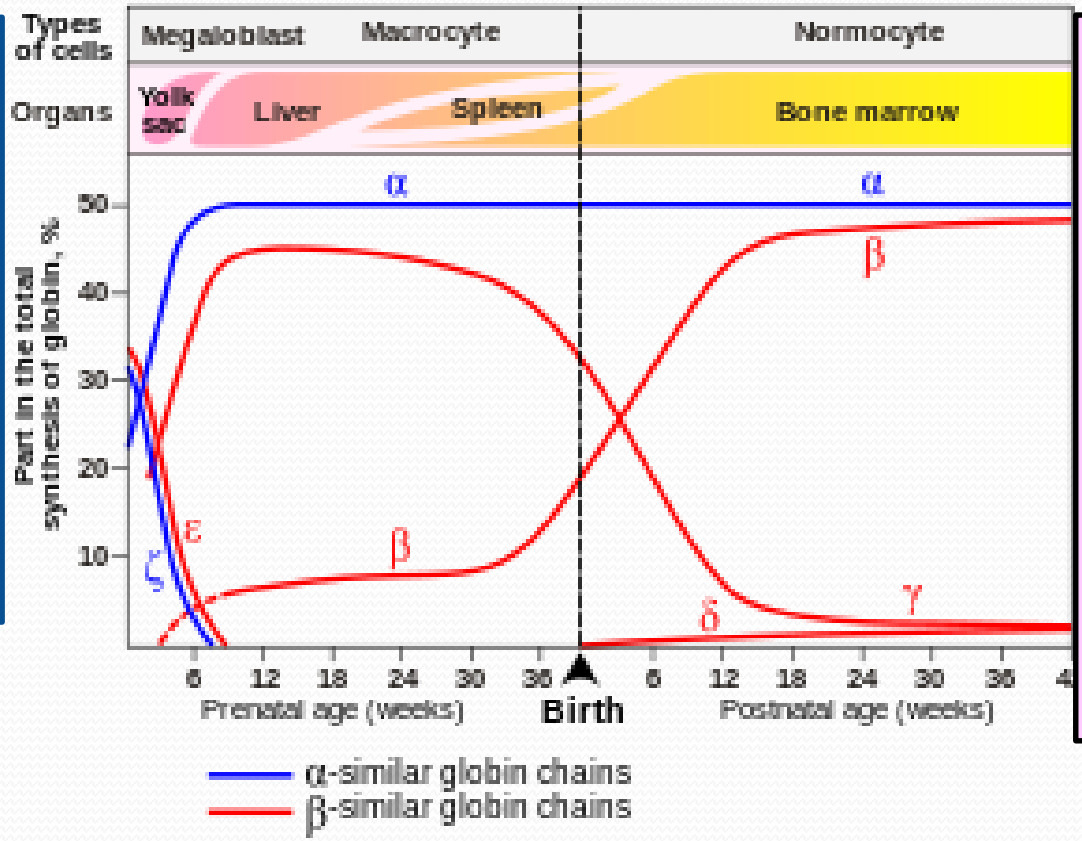
- Hemoglobin H (β_4)
- Hemoglobin Barts (γ_4)
- Hemoglobin S ($\alpha_2\beta^S_2$)
- Hemoglobin C ($\alpha_2\beta^C_2$)
- Hemoglobin E($\alpha_2\beta^E_2$)
- Hemoglobin D-Punjab ($\alpha_2\beta^D_2$).
- Hemoglobin SC disease

Blood electrophoresis



- Figure 30–3 shows the normal developmental changes that occur in globin-chain production during gestation and the first year of life.

At birth, the predominant hemoglobin is **fetal hemoglobin** (hemoglobin F), which is composed of two α-globin chains & two γ-globin chains.

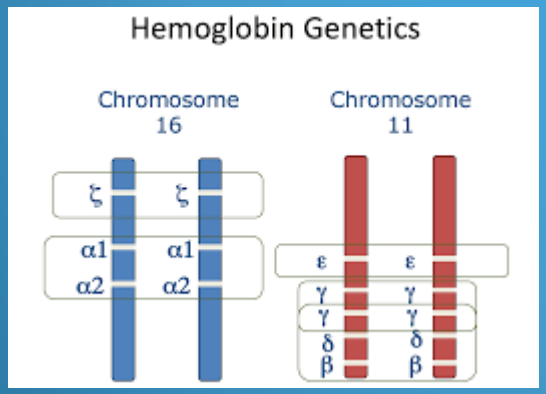


Subsequently, the production of γ-globin decreases & the production of β-globin increases so that **adult hemoglobin** (two α chains & two β chains) predominates after 2–4 months.

Thalassemia

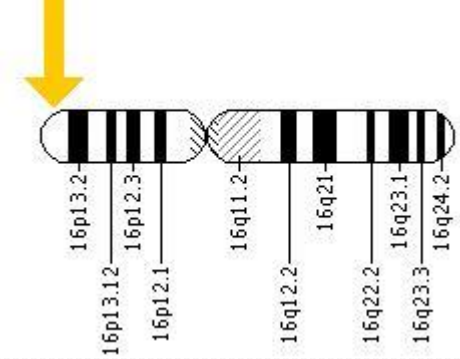
α-thalassemia

β-thalassemia



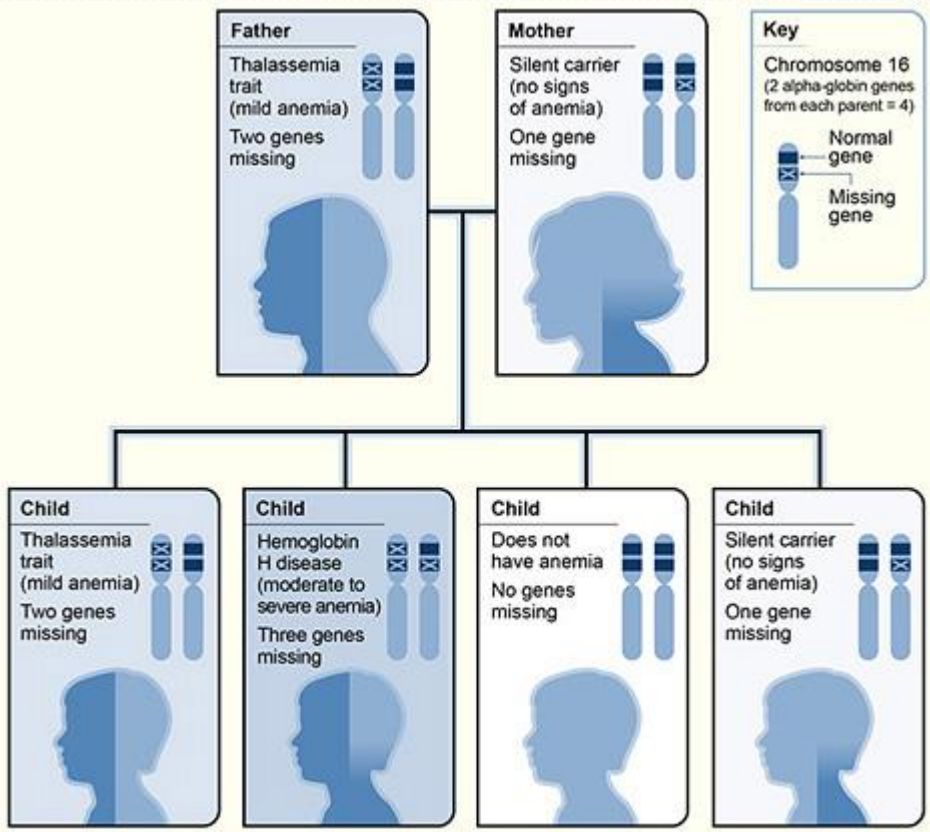
Basima A. Almomani

α-thalassemia



- Most of the α thalassemia syndromes are the result of deletions of one or more of the four **α-globin** genes on **chr. 16**.

- The variable severity of the α-thalassemia syndromes is related to the number of gene deletions (Table 30–1).



National Heart Lung and Blood Institute
http://www.nhlbi.nih.gov/health/health-topics/topics/thalassemia/causes.html

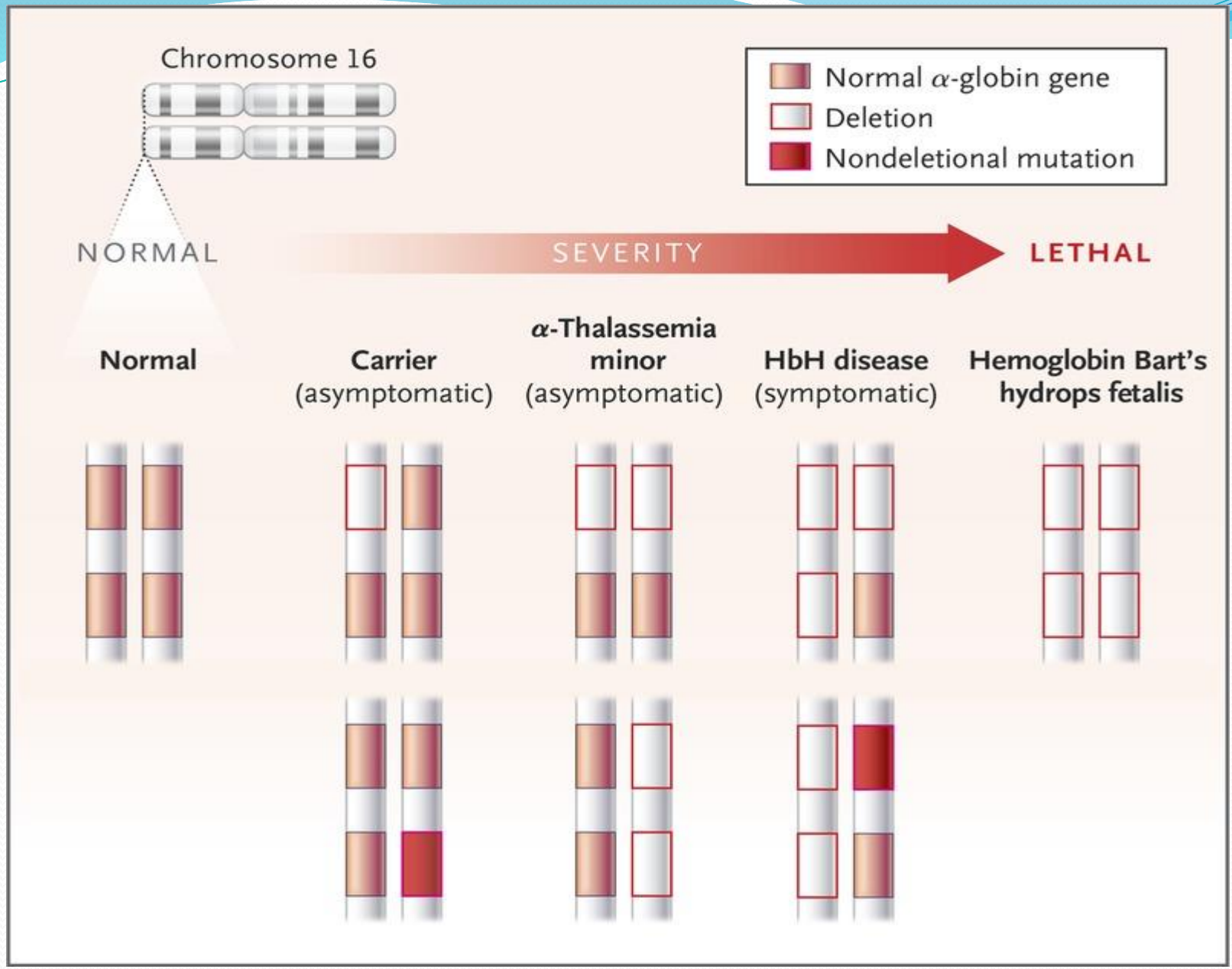
- The severity of the α-thalassemia syndromes varies among affected ethnic groups, depending on the genetic abnormalities prevalent in the population.

- In persons of African ancestry, α-thalassemia is usually caused by the deletion of only one of the two α-globin genes on each chromosome.
- In Asians, deletions of one or both of α-globin genes on the same chromosome are common.

Clinical findings

- The clinical findings depend on the # of α-globin genes deleted (Table 30-1).

Table 28-1 α-thalassemia				
Usual genotypes	α- gene number	Clinical feature	Hb electrophoresis at birth Birth	 > 6 mo
αα/αα	4	normal	N	N
-α/αα	3	Silent carrier	0-3% Hb Bart's	N
-α/-α -/αα	2	α-thal trait	2-10% Hb Bart's	N
-/-α	1	Hb H disease	15-30% Hb Bart's	Hb; H present
-/-	0	fetalhydrops	>75% Hb Bart's	-



Basima A. Almomani

The thalassemias: Genetic, clinical, and laboratory findings

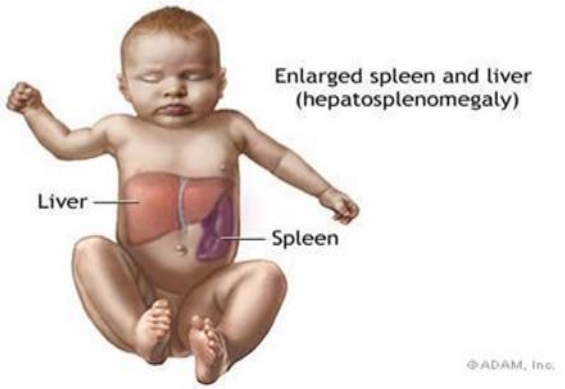
Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Minor	α α / - - or α - / α -	Low	Mild	Normal 3 to 8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5 to 30 percent HbH present in adults 20 to 40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA_2 are absent
Beta thalassemia				
Minor (trait)	β / $β^0$ or β / $β^+$	Low	Mild	HbA_2 increased (3.5 to 7 percent)
Intermedia	$β^+$ / $β^+$ and others*	Low	Moderate	HbF increased in about 50 percent of patients
Major	$β^0$ / $β^0$	Low	Severe	HbA absent Only HbA_2 and HbF are present

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; $β^+$: thalassemic gene producing some β-chain; $β^0$: thalassemic gene producing no β-chain.
* See text for multiple other genotypes.

Courtesy of Stephen A Landaw, MD, PhD.

UpToDate®

- Persons with one α-globin gene (three-gene deletion)
  - ✓ have a mild to moderately severe microcytic hemolytic anemia (Hg level of 7–10 g/dL),
  - ✓ which may be accompanied by hepatosplenomegaly and some bony abnormalities



- The deletion of all four α-globin genes
- ✓ causes severe intrauterine anemia →hydrops fetalis
- ✓ Extreme pallor & massive hepatosplenomegaly.
- ✓ Hg electrophoresis reveals a predominance of Bart's hemoglobin.

Differential Diagnosis

- α-Thalassemia trait (two-gene deletion) must be differentiated from other mild microcytic anemias.

α-thalassemia trait children show normal or increased levels of ferritin and serum iron.

Iron Def Decreased ferritin & serum iron

α-thalassemia trait
normal Hg electrophoresis after age 4–6 months

β-thalassemia minor
Abnormal Hg electrophoresis after age 4–6 months

The history of a low MCV at birth or the presence of Bart's hemoglobin on the neonatal hemoglobinopathy screening test suggests α- thalassemia.

Complication

- The principal complication of α-thalassemia trait →is the needless administration of iron.

- Persons with hemoglobin H disease →may have intermittent exacerbations of their anemia in response to oxidant stress or infection.

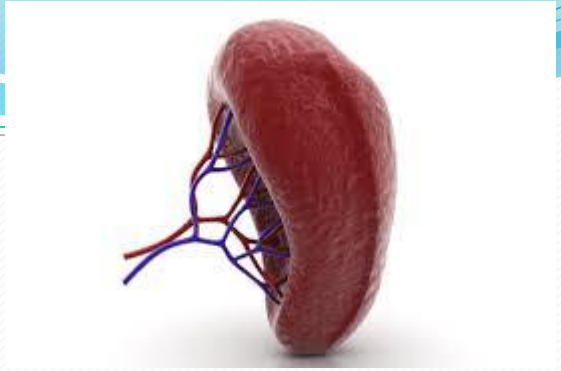
- Splenomegaly →may exacerbate the anemia and may require splenectomy.

- Women pregnant with hydropic α-thalassemia fetuses → increased complications of pregnancy, particularly toxemia and postpartum hemorrhage.

Treatment

- Persons with α-thalassemia trait → no treatment.
- Those with hemoglobin H disease →should receive supplemental folic acid and avoid oxidant drugs that cause hemolysis.

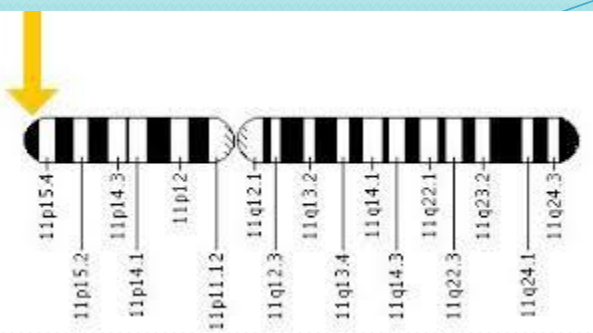
- The anemia →may also be exacerbated during periods of infection, and transfusions may be required.



- Hypersplenism →may develop later in childhood and require surgical splenectomy.

- Genetic counseling and prenatal diagnosis should be offered to families at risk for hydropic fetuses.

β-thalassemia



- β-globin genes are present in diploid cells, one on each chromosome 11.
- **β◦** thalassemia → no globin chains
- **B+** thalassemia→ some β-globin chain are produced

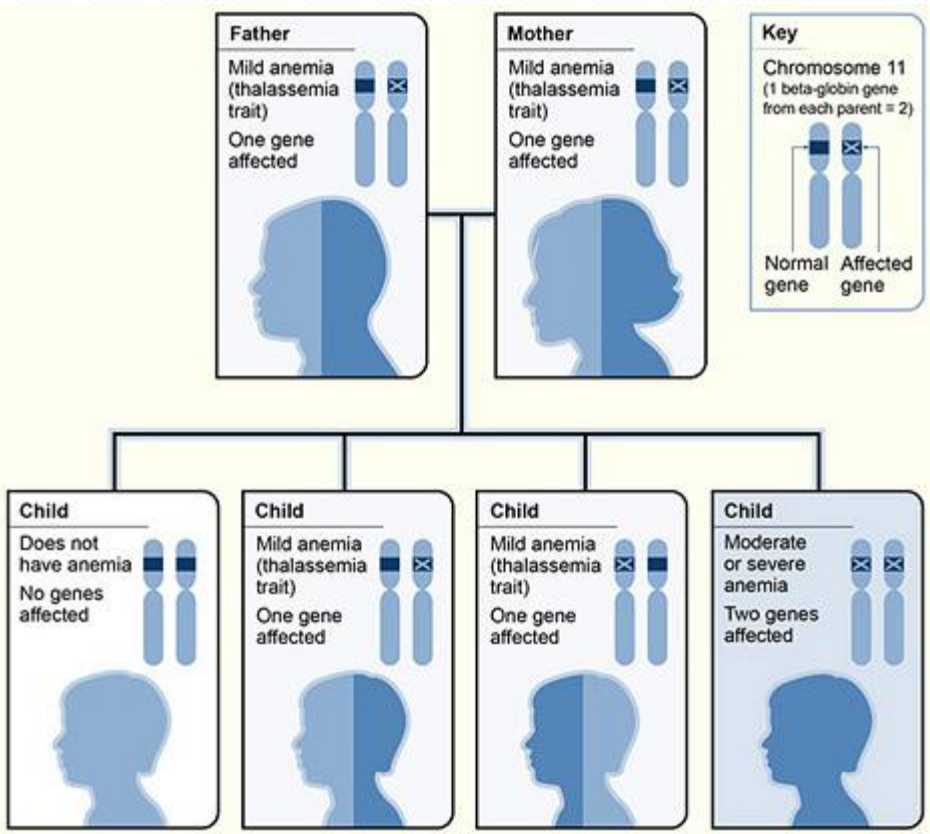
✓heterozygous for β-thalassemia gene→β- thalassemia minor

✓Homozygous for β-thalassemia gene →β- thalassemia major or β- thalassemia intermedia

The thalassemias: Genetic, clinical, and laboratory findings

Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Minor	α α / - - or α - / α -	Low	Mild	Normal 3 to 8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5 to 30 percent HbH present in adults 20 to 40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA_2 are absent
Beta thalassemia				
Minor (trait)	β / β° or β / $β^+$	Low	Mild	HbA_2 increased (3.5 to 7 percent)
Intermedia	$β^+$ / $β^+$ and others*	Low	Moderate	HbF increased in about 50 percent of patients
Major	β ° / β °	Low	Severe	HbA absent Only HbA_2 and HbF are present

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; $β^+$: thalassemic gene producing some β-chain; β°: thalassemic gene producing no β-chain.
* See text for multiple other genotypes.



National Heart Lung and Blood Institute
http://www.nhlbi.nih.gov/health/health-topics/topics/thalassemia/causes.html

- Homozygous individuals generally have β-thalassemia major (Cooley anemia), a severe transfusion dependent anemia.

- β-thalassemia intermedia→ which is more severe than thalassemia minor but is not generally transfusion-dependent.

- β-thalassemia genes interact with genes for structural β-globin variants, such as Hg S and Hg E to cause serious disease in compound heterozygous individuals.

Clinical findings
A. Symptoms and Signs

- β-thalassemia minor →asymptomatic with a normal physical examination

- β-thalassemia major are normal at birth but develop significant anemia during the first year of life.

- If the disorder is not identified and treated with blood transfusions, such children

- grow poorly
- develop massive hepatosplenomegaly
- enlargement of the medullary space with thinning of the bony cortex.

- The skeletal changes cause:
- characteristic facial deformities
- predispose the child to pathologic fractures

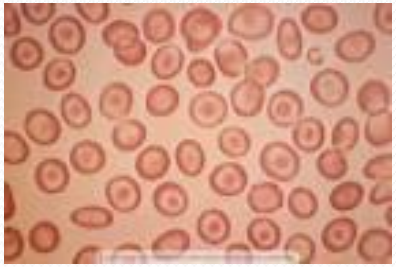
B-Lab findings

- **β- thallassemia minor**

✓ normal neonatal screening but subsequently develop a decreased MCV with or without mild anemia.

✓ bld smear: mild microcytic, hypochromic anemia

✓ after 6-12 mon: HbF, A2 or both elevated



The thalassemias: Genetic, clinical, and laboratory findings

Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Minor	α α / - - or α - / α -	Low	Mild	Normal 3 to 8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5 to 30 percent HbH present in adults 20 to 40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA_2 are absent
Beta thalassemia				
Minor (trait)	β / β° or β / $β^+$	Low	Mild	HbA_2 increased (3.5 to 7 percent)
Intermedia	$β^+$ / $β^+$ and others*	Low	Moderate	HbF increased in about 50 percent of patients
Major	β° / β°	Low	Severe	HbA absent Only HbA_2 and HbF are present

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; $β^+$: thalassemic gene producing some β-chain; β°: thalassemic gene producing no β-chain.
* See text for multiple other genotypes.

❑β-thallasemia major

- ✓ Hb A is absent on neonatal screening (shows Hb F only)
- ✓ Such infants are hematologically normal at birth, but develop severe anemia after the first few months of life
- ✓ Bld smear: severe hypochromic, microcytic anemia
- ✓ Hb level falls to 5-6 g/dl or less

The diagnosis of homozygous β-thal may be suggested by the finding of β-thal minor in both parents.

The thalassemias: Genetic, clinical, and laboratory findings

Disorder	Genotype	MCV	Anemia	Hemoglobin electrophoresis
Alpha thalassemia				
Silent carrier	α α / α -	NL	None	Normal <3 percent Hb Barts at birth
Minor	α α / - - or α - / α -	Low	Mild	Normal 3 to 8 percent Hb Barts at birth
Hb H disease (deletional)	α - / - -	Low	Moderate	5 to 30 percent HbH present in adults 20 to 40 percent Hb Barts at birth
Major (fetal hydrops)	- - / - -	Low	Fatal	Hb Barts, Hb Portland, and HbH present HbA, HbF, and HbA_2 are absent
Beta thalassemia				
Minor (trait)	β / β° or β / $β^+$	Low	Mild	HbA_2 increased (3.5 to 7 percent)
Intermedia	$β^+$ / $β^+$ and others*	Low	Moderate	HbF increased in about 50 percent of patients
Major	β° / β°	Low	Severe	HbA absent Only HbA_2 and HbF are present

MCV: mean corpuscular volume; Hb: hemoglobin; NL: normal; $β^+$: thalassemic gene producing some β-chain; β°: thalassemic gene producing no β-chain.
* See text for multiple other genotypes.

Courtesy of Stephen A Landaw, MD, PhD

Differential Diagnosis

- β-Thalassemia minor must be differentiated from other causes of mild microcytic, hypochromic anemias.

β-thalassemia minor children have abnormal hemoglobin electrophoresis after age 4–6 months.

α-thalassemia trait children have a normal hemoglobin electrophoresis after age 4–6 months.

β-thalassemia minor

- ✓ elevated RBCs,
- ✓ elevated hemoglobin A2 level

Iron deficiency anemia

- ✓ Reduced RBC
- ✓ reduced hemoglobin A2 level

- β-Thalassemia major is rarely confused with other disorders.

Complication

β-thalassemia minor

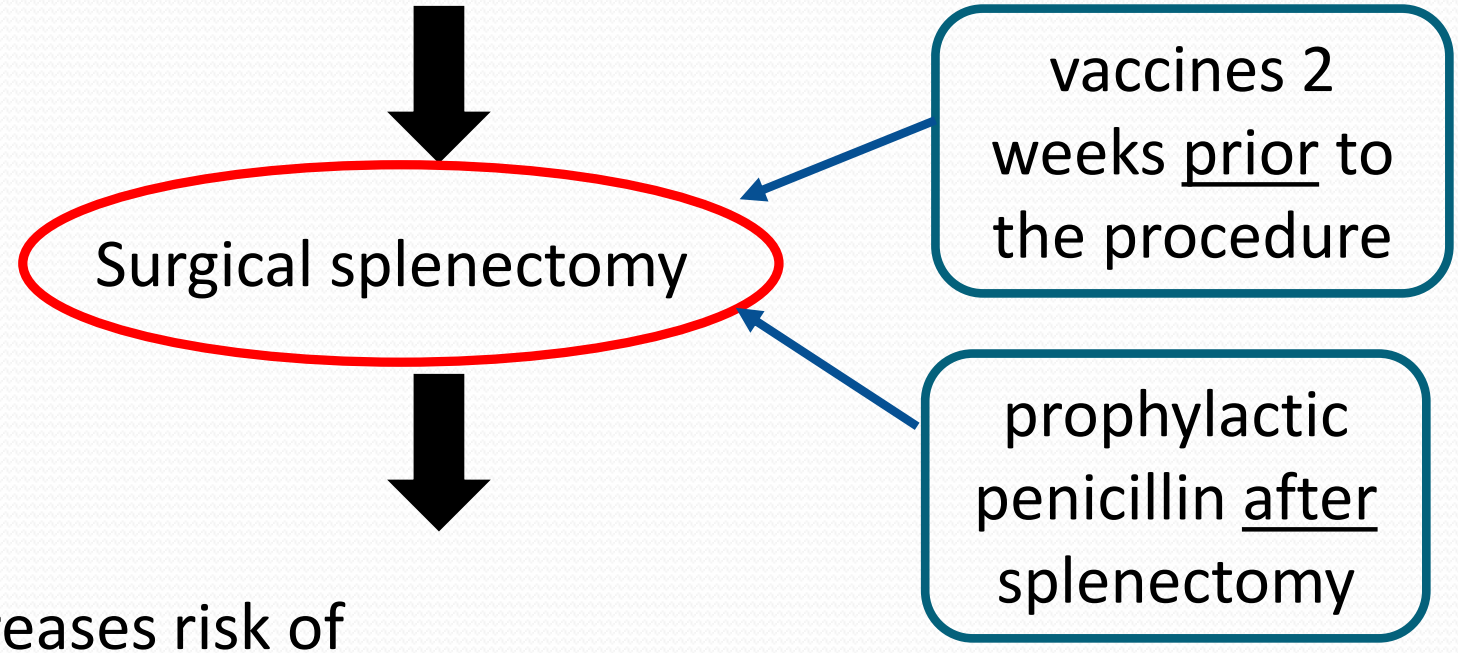
- Unnecessary use of iron therapy

Complication

β-thallasemia major

Without treatment	• most children die within the first decade of life
Inadequately transfused	•experience poor growth and recurrent infections and may have hepatosplenomegaly, thinning of the cortical bone, and pathologic fractures.
Transfused children	• hemosiderosis, splenomegaly, and hypersplenism.

- Patients → splenomegaly & hypersplenism



Increases risk of

- ✓ thrombosis,
- ✓ pulmonary hypertension,
- ✓ overwhelming septicemia.

Treatment

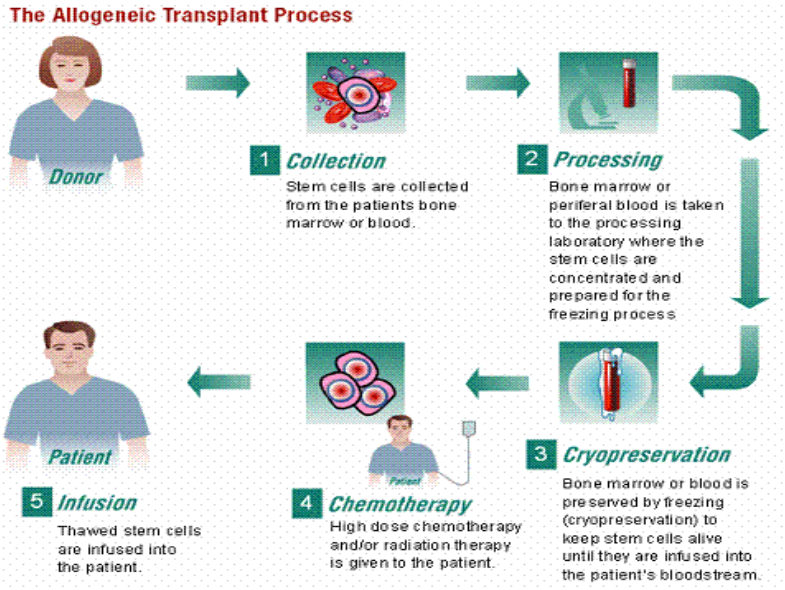
- β-minor thalassemia → No specific therapy

- β-major thalassemia:

Chronic transfusion with iron chelation

Stem cell transplantation

Gene therapy



- Programs of blood transfusion are generally targeted to maintain a nadir hemoglobin level of 9–10 g/dL.

- Chronic transfusion therapy is infrequently indicated for individuals with β-thalassemia intermedia.

- Transfusion-related hemosiderosis require chelation therapy (to prevent cardiac, hepatic, and endocrine dysfunction)with:

Agent	Route	Clearance
Deferoxamine (Desferal)	Slow infusion: intravenous or subcutaneous	Renal, hepatic
Deferasirox (Exjade)	Oral 	Hepatobiliary
Deferiprone (FERRIPROX®)	Oral	Renal, cardiac


Desferal
500 mg/vial
NOVARTIS
4 vials


EPOWER
CE
ISO
Portable Syringe Pump XB-500

Deferasirox (Exjade)

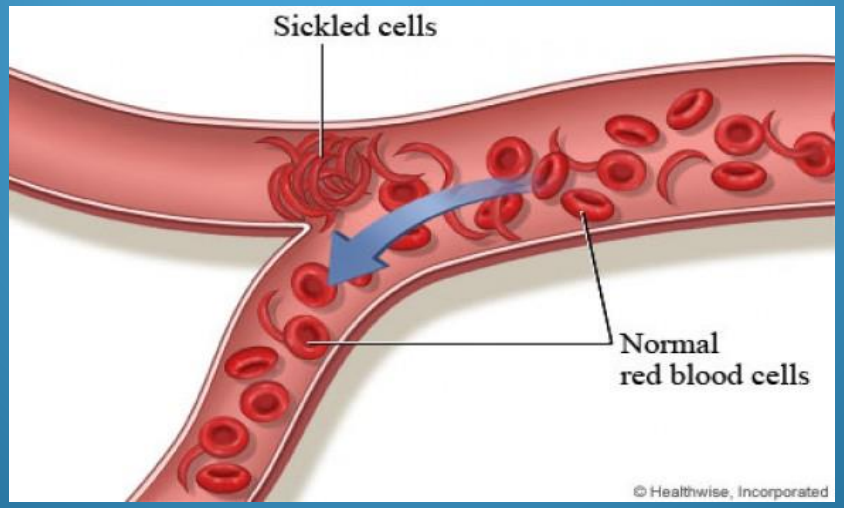
How is this drug best given?

- Give this drug at the same time of day.
- Give on an empty stomach. Give 30 minutes before a meal.
- Mix the tablet with fruit juice (orange, apple) or water until melted and have your child drink right away. Do not let your child chew or swallow it whole.
- After drinking, rinse the rest of the drug in the glass with more juice or water and have your child drink.

- Small doses of supplemental ascorbic acid may enhance the efficacy of iron chelation.

- Noncompliance with chelation in adolescents and young adults may lead to death from congestive heart failure, cardiac arrhythmias, or hepatic failure.

Sickle cell disease



Basima A. Almomani

General Considerations

- The manifestations secondary to the propensity of deoxygenated sickle hemoglobin (S) to polymerize.

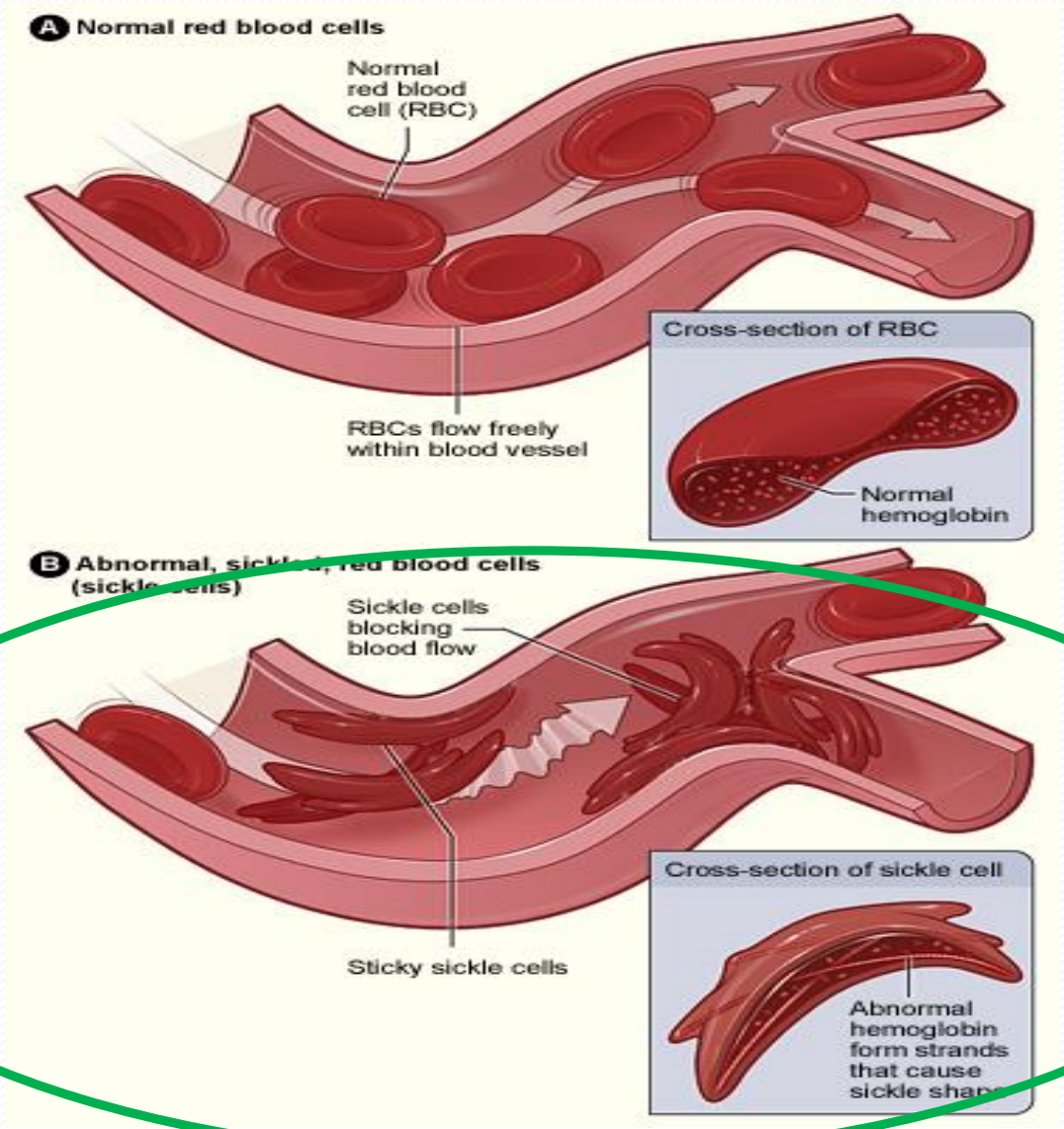
- Polymerization of sickle hemoglobin

- distorts erythrocyte morphology;
- decreases red cell deformability;
- causes a marked reduction in red cell life span;
- increases blood viscosity;
- predisposes to inflammation, coagulation activation, and episodes of vaso-occlusion.

Heterozygous carrier of sickle gene→ Sickle cell trait

Homozygosity for the sickle gene→ Sickle cell anemia

- the most severe sickling disorder & the most common form of sickle cell disease



Basima A. Almomani

Clinical Findings
A. Symptoms & Signs

- Physical findings are normal at birth, and symptoms are unusual before age 3–4 months because …

- A moderately severe hemolytic anemia may be present by age 1 year.

this causes pallor, fatigue, and jaundice, and predisposes to the development of gallstones during childhood and adolescence.

- Intense congestion of the spleen with sickled cells may cause splenomegaly in early childhood and results in functional asplenia

risk for overwhelming infection

- Acute splenic sequestration:

➢ sudden enlargement of the spleen with pooling of red cells,

➢ acute exacerbation of anemia,

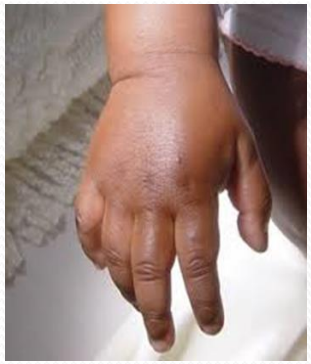
➢ in severe cases, shock and death.

- Aplastic crises

Acute exacerbation of anemia, usually caused by infection with human parvovirus and other viruses.

- Recurrent episodes of vaso-occlusion and tissue ischemia cause acute and chronic problems.

Dactylitis, or hand-and-foot syndrome, is the most common initial symptom of the disease



- Recurrent episodes of abdominal and musculoskeletal pain may occur throughout life.

- Overt strokes occur in about 11% of children with sickle cell anemia and tend to be recurrent.

Recurrence is significantly reduced with chronic red cell transfusions.

- The acute chest syndrome is caused by pulmonary infection, infarction, or fat embolism from ischemic bone marrow.

- All tissues are susceptible to damage from vaso-occlusion, and multiple organ dysfunction is common by adulthood.

- Table 30-2: common clinical manifestations of sickle cell disease

	Acute	Chronic
Children	Bacterial sepsis or meningitis[a] Splenic sequestration[a] Aplastic crisis Vaso-occlusive events Dactylitis Bone infarction Acute chest syndrome[a] Stroke[a] Priapism	Functional asplenia Delayed growth and development Avascular necrosis of the hip Hyposthenuria Cholelithiasis
Adults	Bacterial sepsis[a] Aplastic crisis Vaso-occlusive events Bone infarction Acute chest syndrome[a] Stroke[a] Priapism Acute multiorgan failure syndrome[a]	Leg ulcers Proliferative retinopathy Avascular necrosis of the hip Cholecystitis Chronic organ failure[a] Liver Lung Kidney Decreased fertility

[a]Associated with significant mortality rate.

Lab findings

- Baseline Hb level of 7-10 g/dL → fall to life-threatening levels at the time of a splenic sequestration or aplastic crisis
- Baseline Reticulocyte is elevated
- The anemia is usually normocytic or macrocytic
- Peripheral bld. smear typically shows sickle cells

Electrophoretic patterns in common hemoglobinopathies

Condition	Hb A	Hb S	Hb C	Hb F	Hb A2
Normal	95-98*	0	0	<1	2.5 ± 0.2
Beta thal minor	90-95	0	0	1-3	>3.5
Sickle cell trait	50-60	35-45•	0	<2	<3.5
Sickle-beta(+) thal	5-30	65-90	0	2-10	>3.5
Sickle-beta(0) thal	0	80-92	0	2-15	>3.5
Sickle-Hgb C disease	0	45-50	45-50	1-8	<3.5
Homozygous sickle cell disease	0	85-95	0	2-15	<3.5

Hb: hemoglobin; Thal: thalassemia.

* Numbers indicate the percent of total hemoglobin for an untransfused adult patient. Ranges are approximate and may vary depending upon the particular laboratory and method of determination. There may be overlap of levels between the various sickle cell variants.

• Percent Hb S can be as low as 21 percent in patients with sickle cell trait in conjunction with alpha thalassemia.

Basima A. Almomani

Differential Diagnosis

Hemoglobin electrophoresis

Hematologic studies of the parents

DNA testing

Complication

- Repeated tissue ischemia & infarction → damage to every organ sys
- Patients who require multiple transfusion → are at risk of developing transfusion-related hemosiderosis and infections as well as red cell alloantibodies.
- Guidelines for routine evaluation for stroke risk

Treatment

Prophylactic antibiotic/ vaccines/ acute infection

Treatment of painful vaso-occlusive episodes

Red cell transfusions

Administration of hydroxyurea

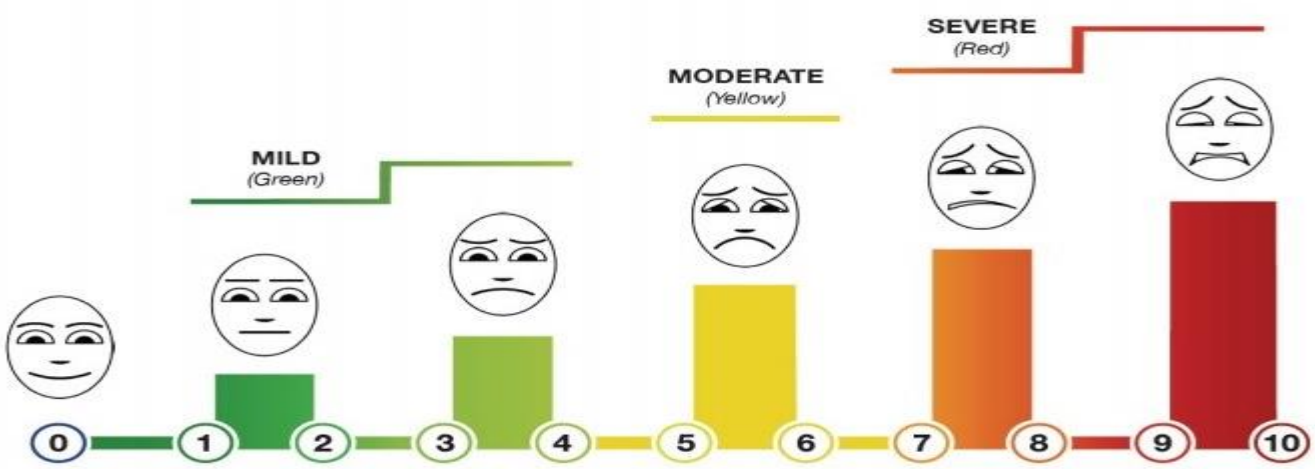
Stem cell transplant

Daily prophylactic penicillin

Vaccines

Management of acute infection

- Treatment of painful vaso-occlusive episodes includes :
  - the maintenance of adequate hydration (with avoidance of overhydration),
  - correction of acidosis if present,
  - administration of adequate analgesia,
  - maintenance of normal oxygen saturation,
  - the treatment of any associated infections.



- Red cell transfusions play an important role in management.
  - are indicated to improve oxygen-carrying capacity during acute severe exacerbations of anemia, as occurs during episodes of splenic sequestration or aplastic crisis.
  - are not indicated for the treatment of chronic steady-state anemia, which is usually well tolerated, or for uncomplicated episodes of vasoocclusive pain.

- Simple or partial exchange transfusion to reduce the percentage of circulating sickle cells is indicated for some severe acute vaso-occlusive events and may be lifesaving.

These events include:

- ✓ stroke,
- ✓ moderate to severe acute chest syndrome,
- ✓ acute life-threatening failure of other organs.

- Some patients with severe complications may benefit from **chronic transfusion therapy**.

The most common indications for transfusions are stroke or an abnormal transcranial Doppler assessment indicating an increased risk for stroke.

- Daily administration of oral hydroxyurea
  - increases levels of fetal hemoglobin,
  - decreases hemolysis,
  - reduces episodes of pain and dactylitis in young children with sickle cell anemia,
  - Reduces acute chest syndrome, hospitalization rates, and transfusions.

- Successful stem cell transplant cures sickle cell disease, but to date its use has been limited because of:

❖ the risks associated with the procedure,

❖ the inability to predict in young children the severity of future complications,

❖ the paucity of HLA-identical sibling donors.

Sickle cell trait

- Infants with sickle cell trait are identified by neonatal screening (Hb FAS)
- No anemia or hemolysis is present, and the physical examination is normal.
- Persons with sickle cell trait are generally healthy with normal life expectancy.
- Sickle trait erythrocytes are capable of sickling, with acidemia and hypoxemia.

Important counseling points