Anemia 4:
Congenital Hemolytic Anemias

Fourth year Medical Students

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Abdallah Awidi Abbadi.MD.FRCP

Feras M Fararjeh, MD

Congenital Hemolytic Anemias: Subtypes

1- Membrane defects: HS

2- Enzymopathies: G6PD Deficiency, PK Def

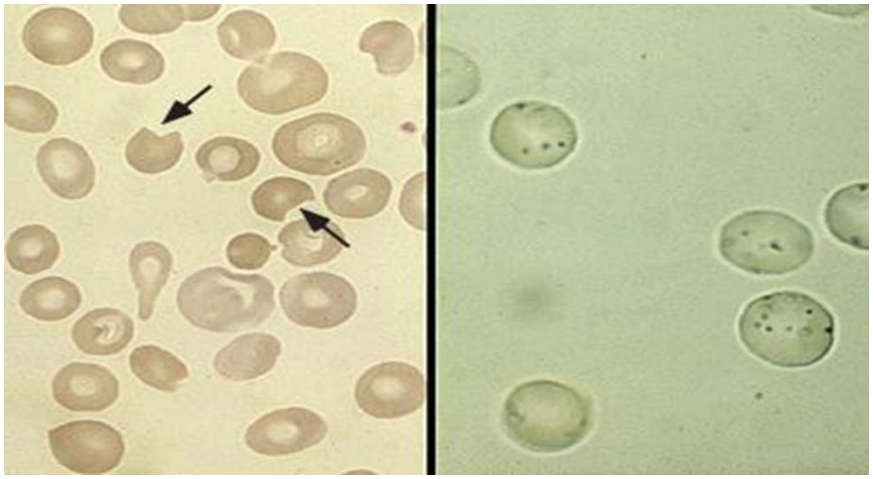
3- Hemoglobinopathies: B-Thal, SS

Anemia (4): Congenital Hemolytic Anemias **Case 4**

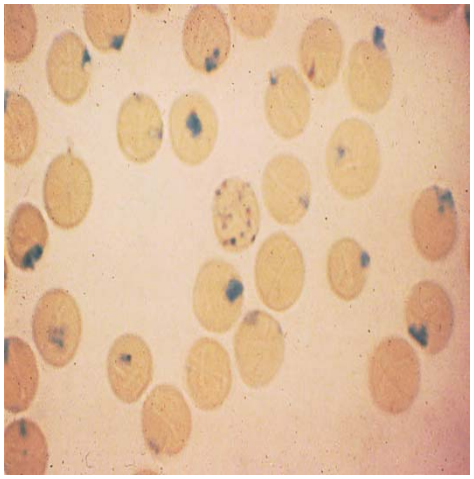
18 yr old male presented to ER with headches, dizziness, red urine and severe loin pain few hours after he ate fresh“fool” beans. He looked jaundiced and sweaty. His BP 90/60, Pulse rate 120.He had no splenomegaly. Hb 9 g/dl, WBC 16K, Plt 280K. Retics 9%.LDH 3000, Bilirubin 5 mostly indirect.

Urine

Bite cells (Bld film)

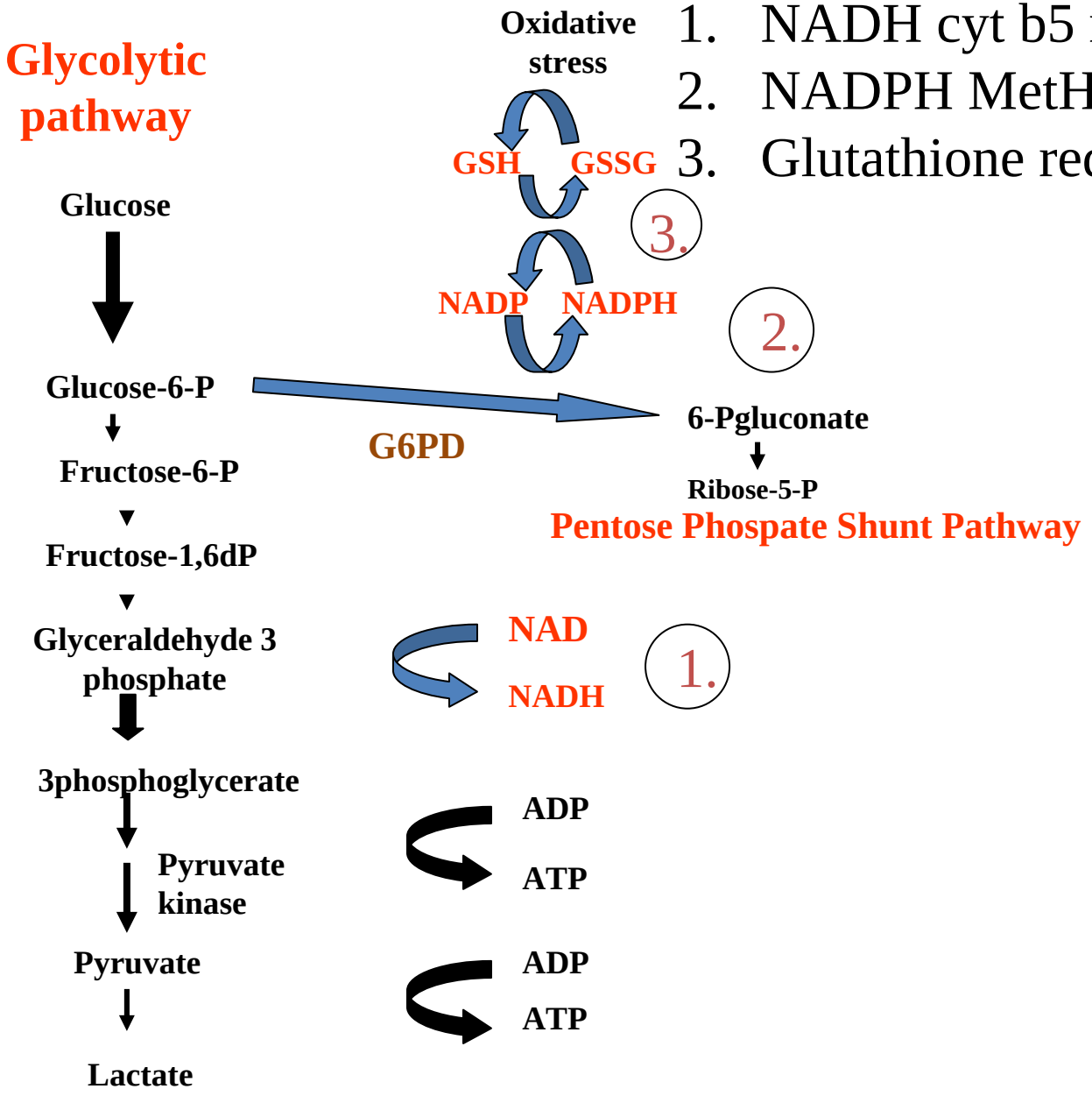


Heinz Bodies



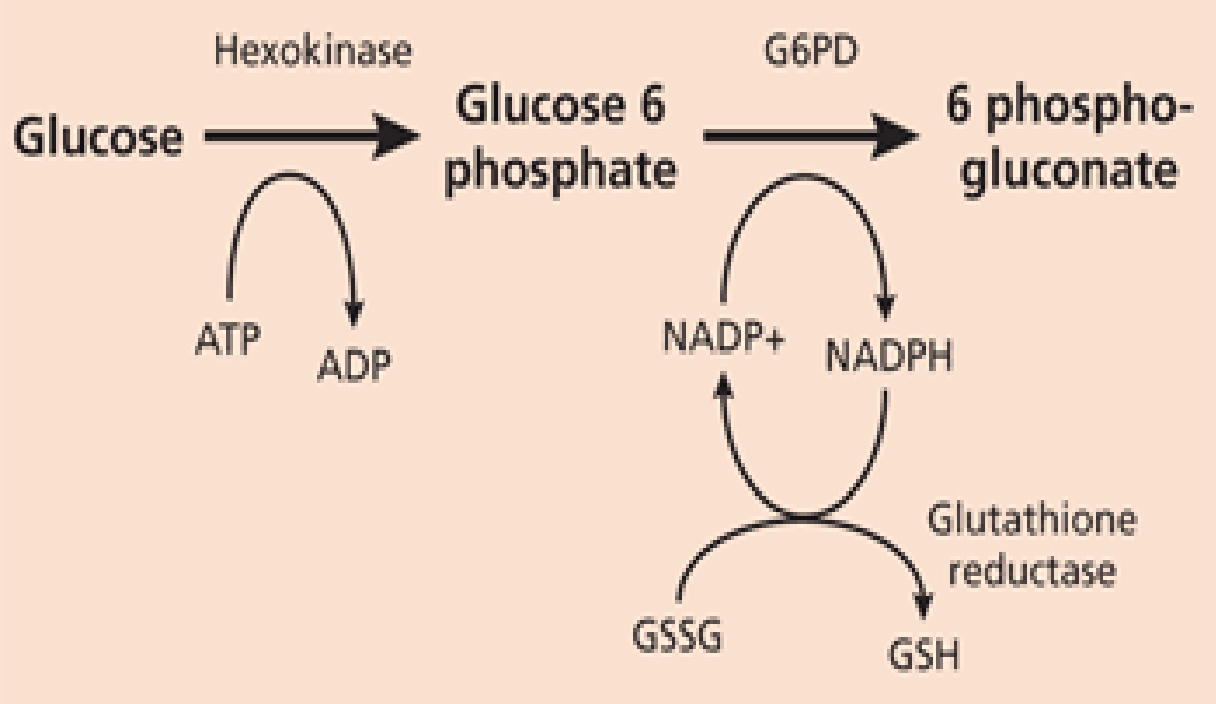
Pathways of MetHb reduction:

1. NADH cyt b5 reductase
2. NADPH MetHbreductase
3. Glutathione reductase

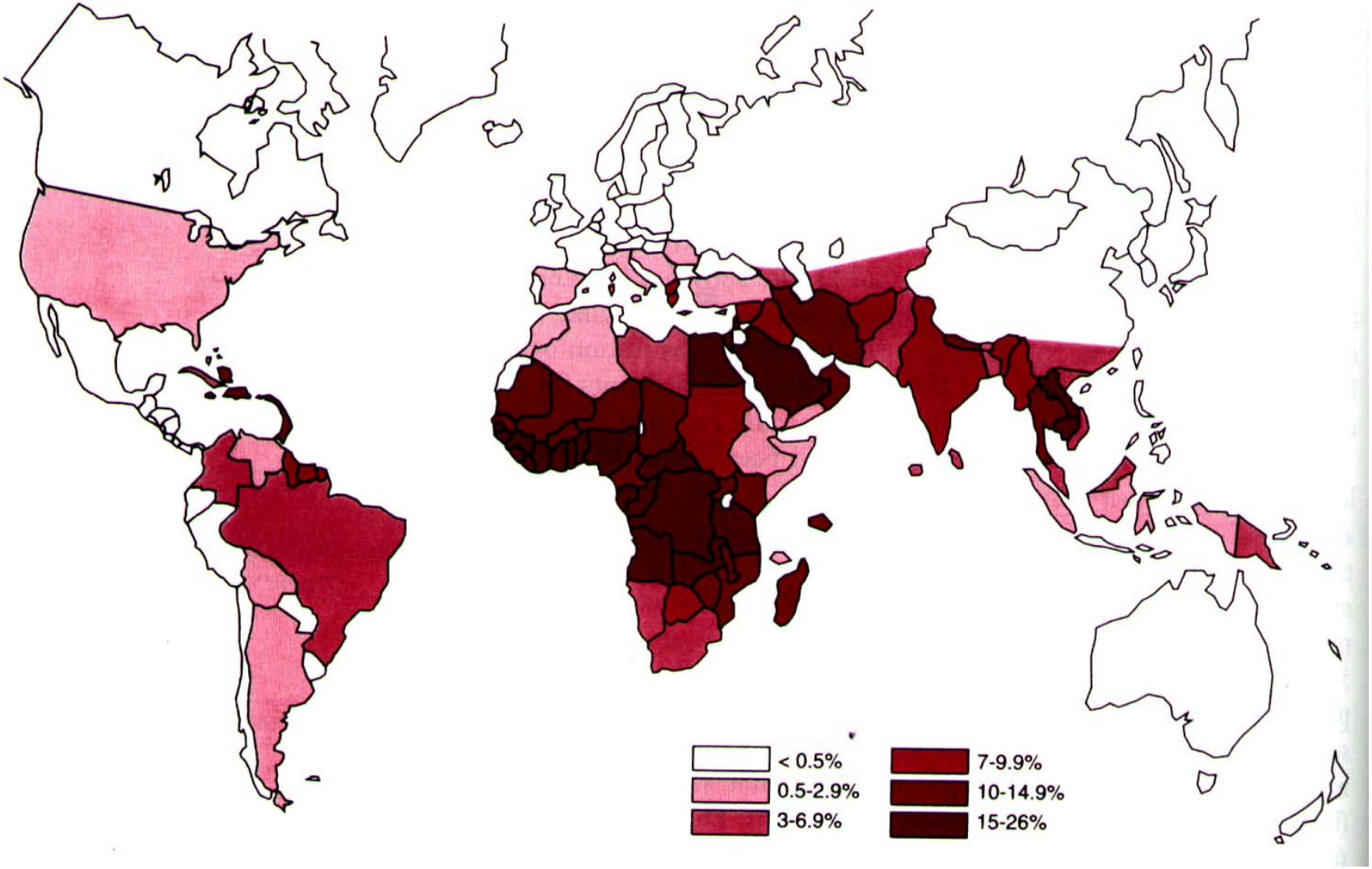


Diagnosis of case 4: G6PD deficiency: hemolytic anemia induced by fava(broad) beans (Favism)

Pentose Phosphate Pathway



Prevalence of G6PD: > 400 mill people/ Malaria belt



Clinical Features:

- **Disease from completely asymptomatic to severe intravascular hemolysis upon exposure to oxidant stress.**
- **Common precipitating factors:**
  - **Drugs: Primaquine – Methylene Blue – Nalidixic acid – sulpha drugs – pyridium and other.**
  - **Infections**
  - **Diabetic ketoacidosis**
  - **Favism: hemolysis after exposure to Fava beans, occurs in Gd^{Med} variant**

Clinical Syndromes: G6PD Deficiency

1- **Neonatal Jaundice**: severe/ Kernicterus /, 1-3 day after birth.

2- **Favism**: acute intravascular Hemolysis after exposure to broad bean (Vicia fava), the offending agent is divicine, it produces free Oxygen radicals on autoxidation.

3-**Infection** which promote the formation of H_2O_2 following oxygen burst in neutrophils and macrophage may result in hemolysis

4- **Drug induced hemolysis**

G6PD variants

Genotypes/Isoenzymes

G6PD B+ : wild type , whites > blacks

G6PD A+ : blacks > whites

G6PD A- : blacks with mild deficiency

G6PD Med : whites Mediterranean, Kurdish, severe def.

G6PD Canton : Thailand, Vietnam, Taiwan

WHO variants

WHO Variants

Class	Level of deficiency	Enzyme activity	Prevalence
I	Severe	<10% enzyme activity Chronic nonspherocytic hemolytic anemia in the presence of normal erythrocyte function	Uncommon; occurs across populations
II	Severe	<10% enzyme activity with intermittent hemolysis	Varies; more common in Asian and Mediterranean populations
III	Moderate	10–60% enzyme activity Hemolysis with stressors only	10% of black males in the United States
IV	Mild to none	60–150% enzyme activity No clinical sequelae	Rare
V	None	>150% percent of normal No clinical sequelae	Rare

G6PD - Glucose-6-phosphate dehydrogenase

Drug-Induced Acute Hemolysis

- Drugs that have been linked to G6PD
- Primaquine
- Sulphonamide antibiotics

  Sulphones e.g. dapsone used against leprosy
- Other sulphur-containing drugs: glibenclamide (an anti-diabetic drug

  Nitrofurantoin
- Vitamin K analogues
- Several others

  Henna can cause a hemolytic crisis in G6PD deficient infants

Genetics

- Majority of the variants - from a single point-mutation resulting in amino acid substitution in gene encoding for G6PD located at the Xq28 region on the tip of the long arm of the X- chromosome
- G6PD Mediterranean is caused by mutation (**563 C-->T**)

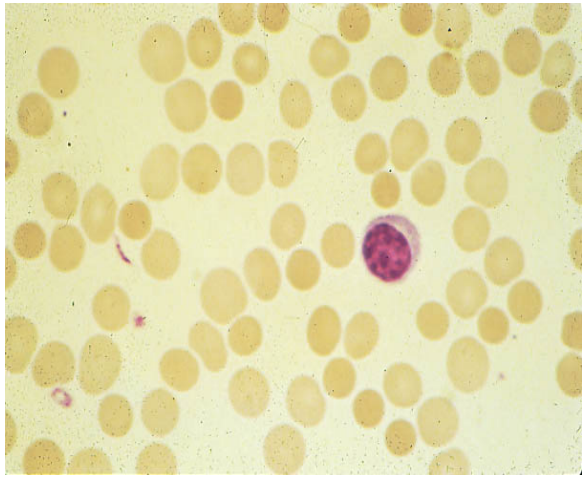
Therapy

- Avoid precipitating factors.
- Blood transfusion in severe hemolysis.
- Maintenance of good urine output during hemolytic episodes
- Folic acid.
- Exchange transfusion in newborn

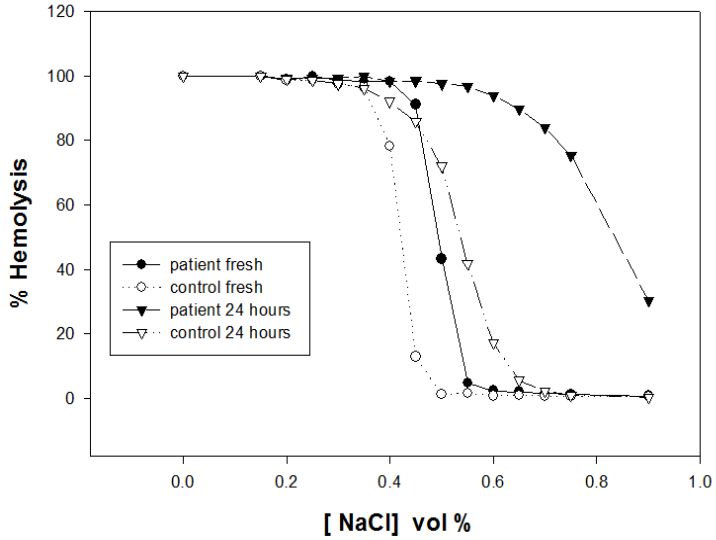
Case 4 B

36 yr old lady presented with “anemia syndrome” and splenomegaly. She was mildly jaundiced. Hb 8g/dl, retics 10%, WBC, Plt were normal. LDH 1160, Bilirubin 3mg/dl d 1.DAT –ve.

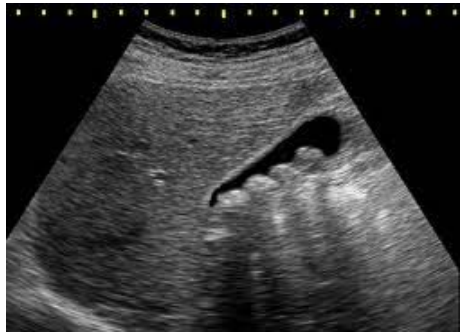
Bld film



Osmotic fragility test



Abd. US



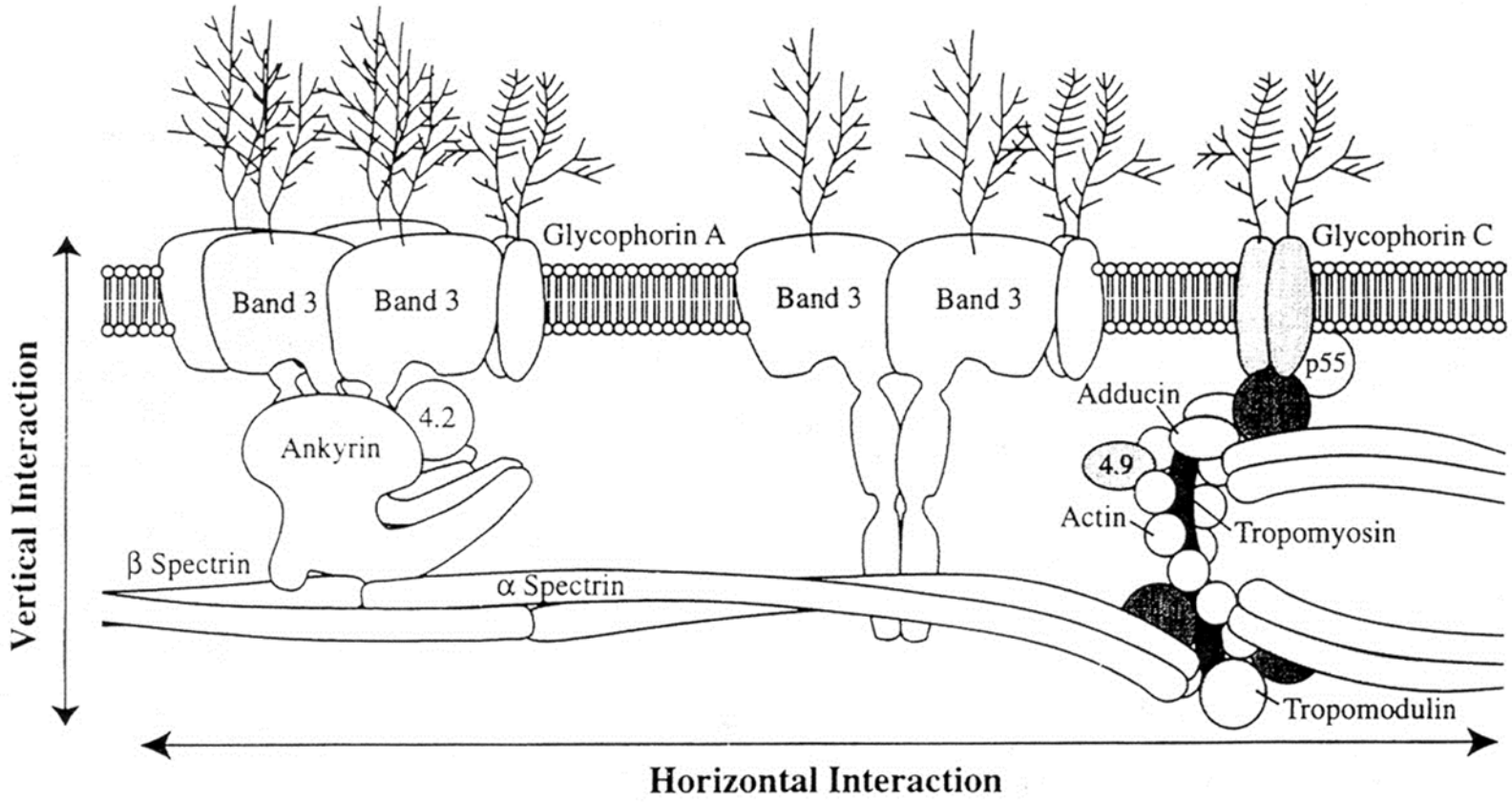
Hereditary Spherocytosis

- Prevalence and inheritance
  - In Northern Europeans prevalence is about 1 in 5,000
  - Clinical severity is **highly variable**, but uniform within a given family
  - Typically the autosomal dominant *homozygous is very severe or lethal*
  - some recessively inherited
  - No consensus for splenectomy indications

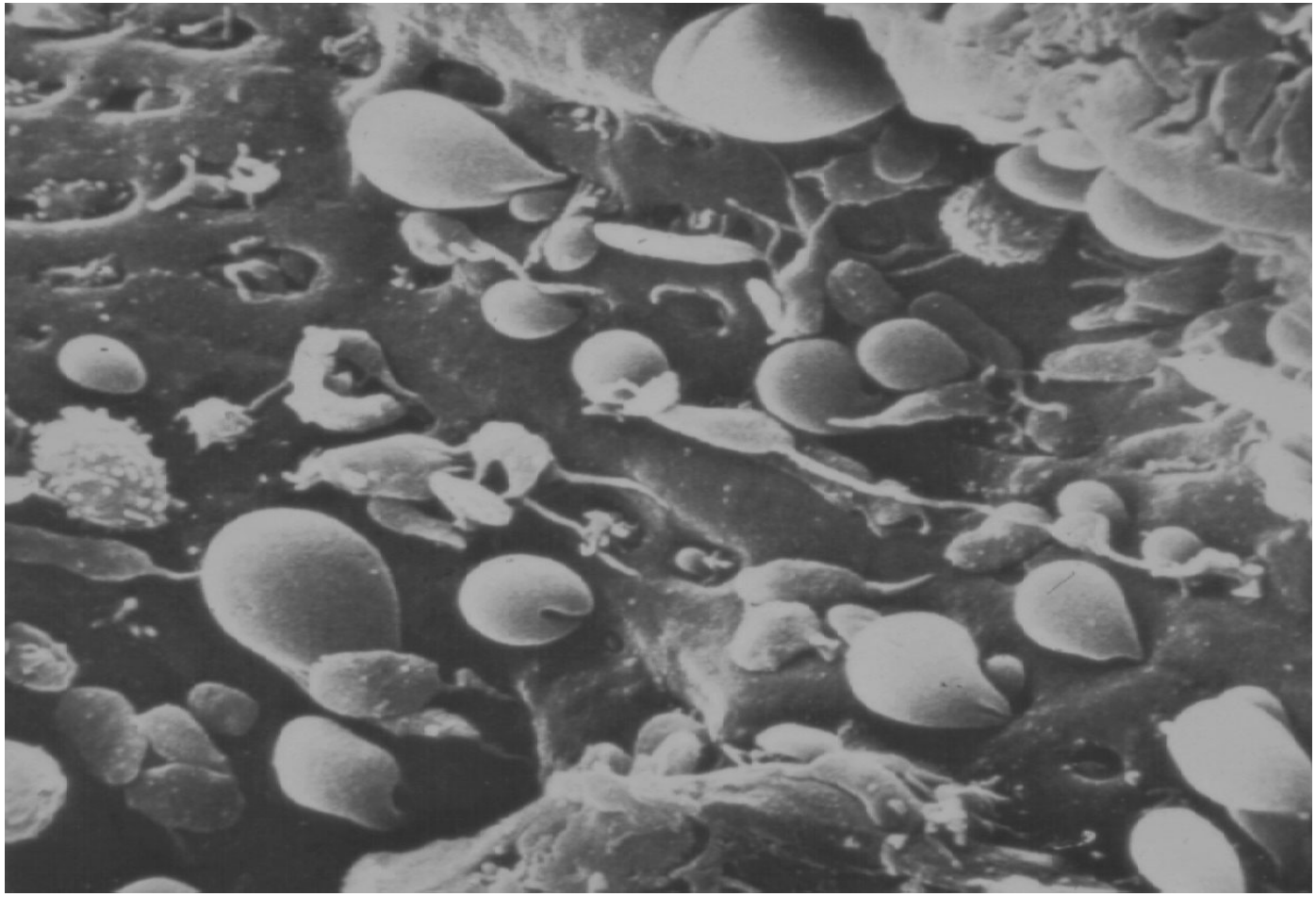
Hereditary Spherocytosis

- Molecular pathology
  - Partial deficiency of spectrin
  - Combined deficiency of spectrin and ankyrin
  - Molecular Defects:
    - mutations of **ankyrin: most common**
    - mutations of band 3 protein
    - mutations of protein 4.2 (common in Japanese)
    - Others: β & α spectrin, protein 4.9 are rare

RBC Membrane



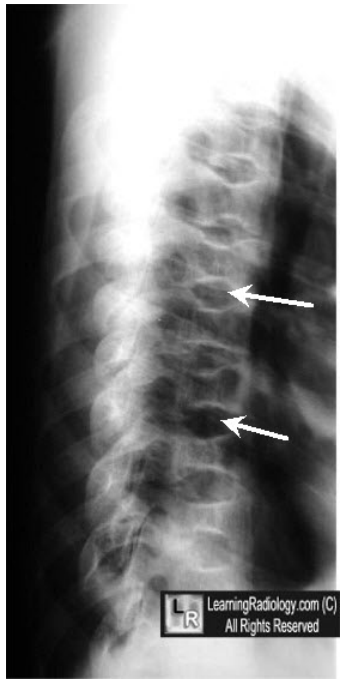
Splenic Conditioning

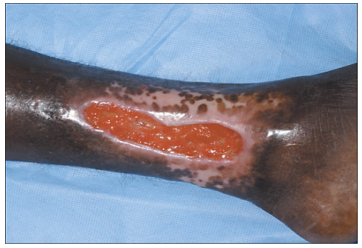


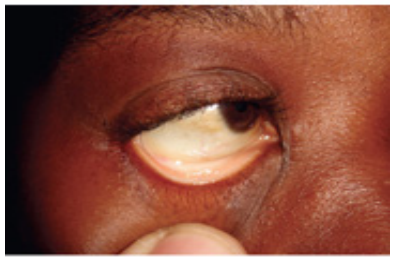
Case 4 C

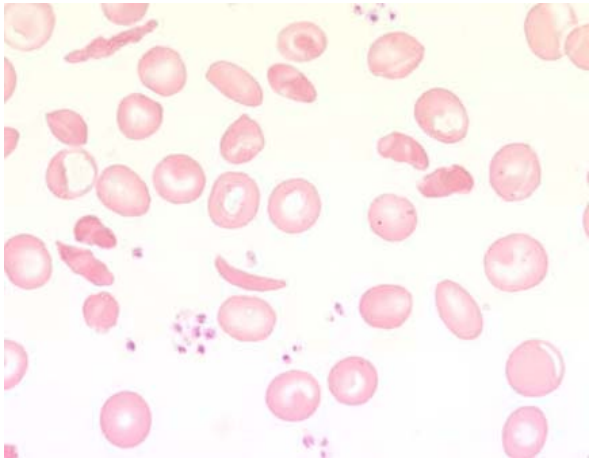
18 yr old male complains of acute pain in his back, Dizziness, Fatigue, Shortness of breath and Headaches for the last 6 hours. He has had similar attacks. P/E

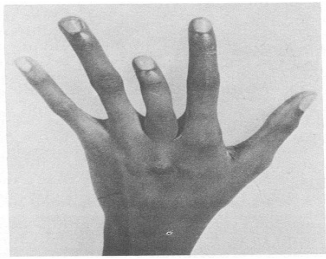
Xray spine









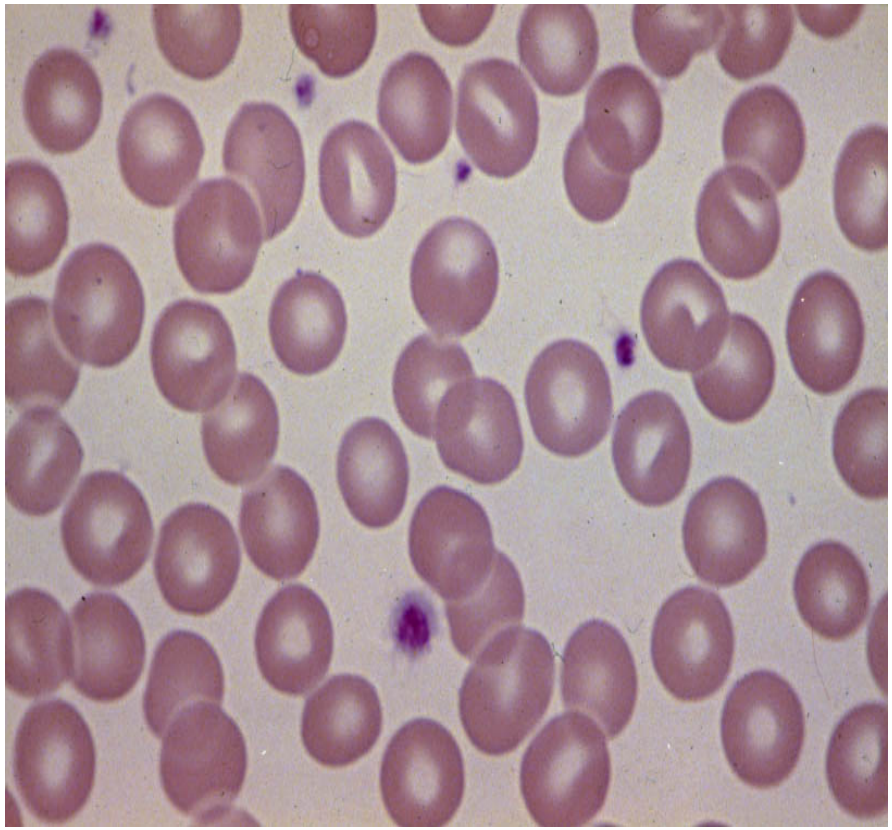


Sickle Cell Disease

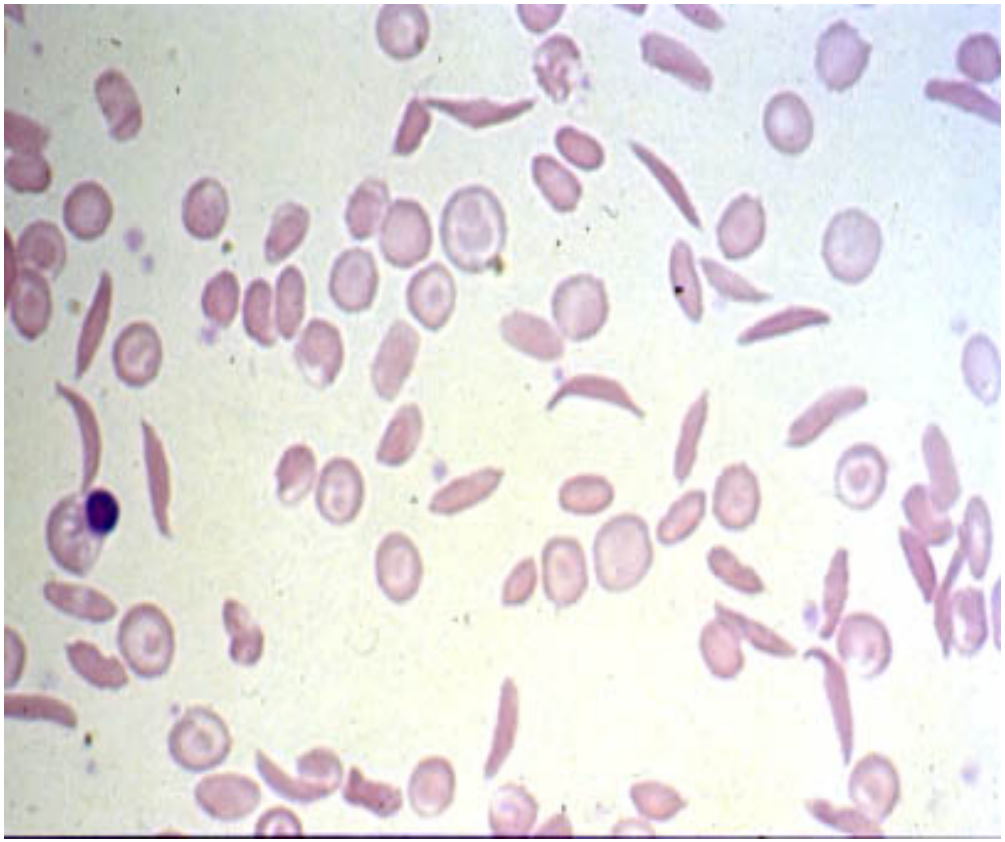
- Inherited as autosomal recessive
- Point mutation in beta globin gene (β6 Glu $\longrightarrow$ Val)
- Gene occurs in 8% of African-Americans

Peripheral Blood Smear

Normal



S-S



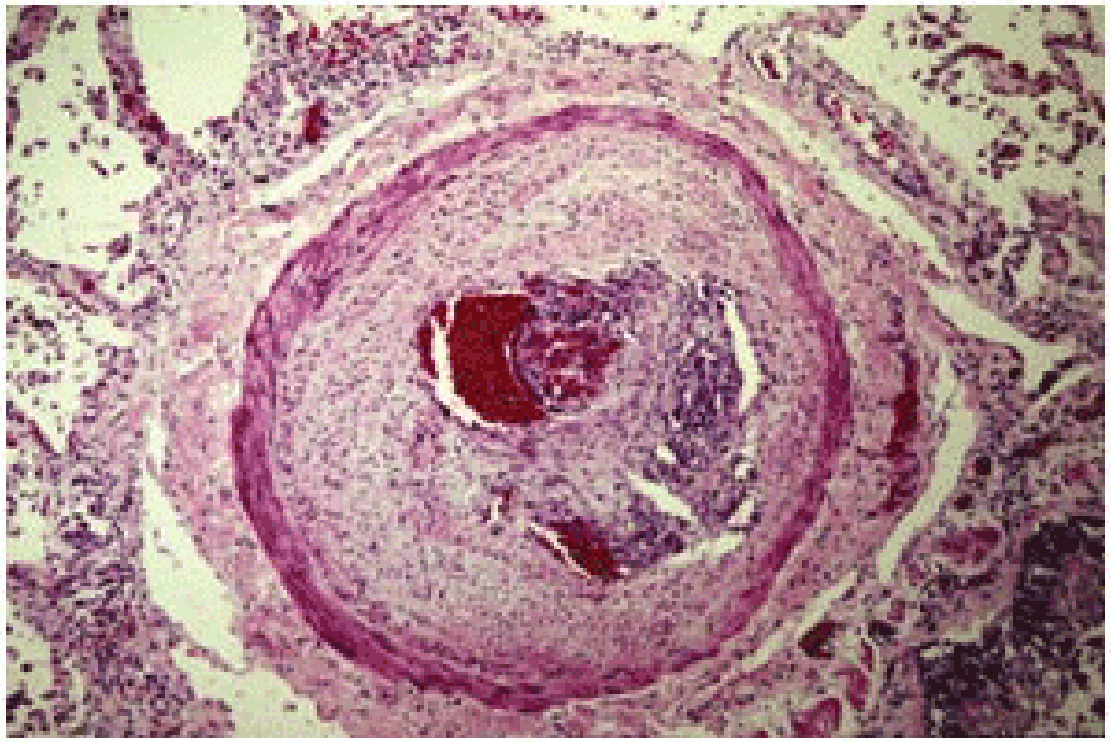
Sickle Cell Anemia Clinical Effects

- Chronic hemolytic anemia
  - Gallstones (bilirubin)
  - Risk of red cell aplasia (Parvovirus)
  - Decreased vascular tone
- Susceptible to infection
  - Functional asplenia
  - Infarcted tissue
  - Numerous manipulations
- Vaso-occlusion

Vascular beds susceptible to injury

- Brain
- Lung
- Ankle
- Erectile vasculature of the penis

End-stage vascular lung disease



Infectious complications of Sickle cell anemia

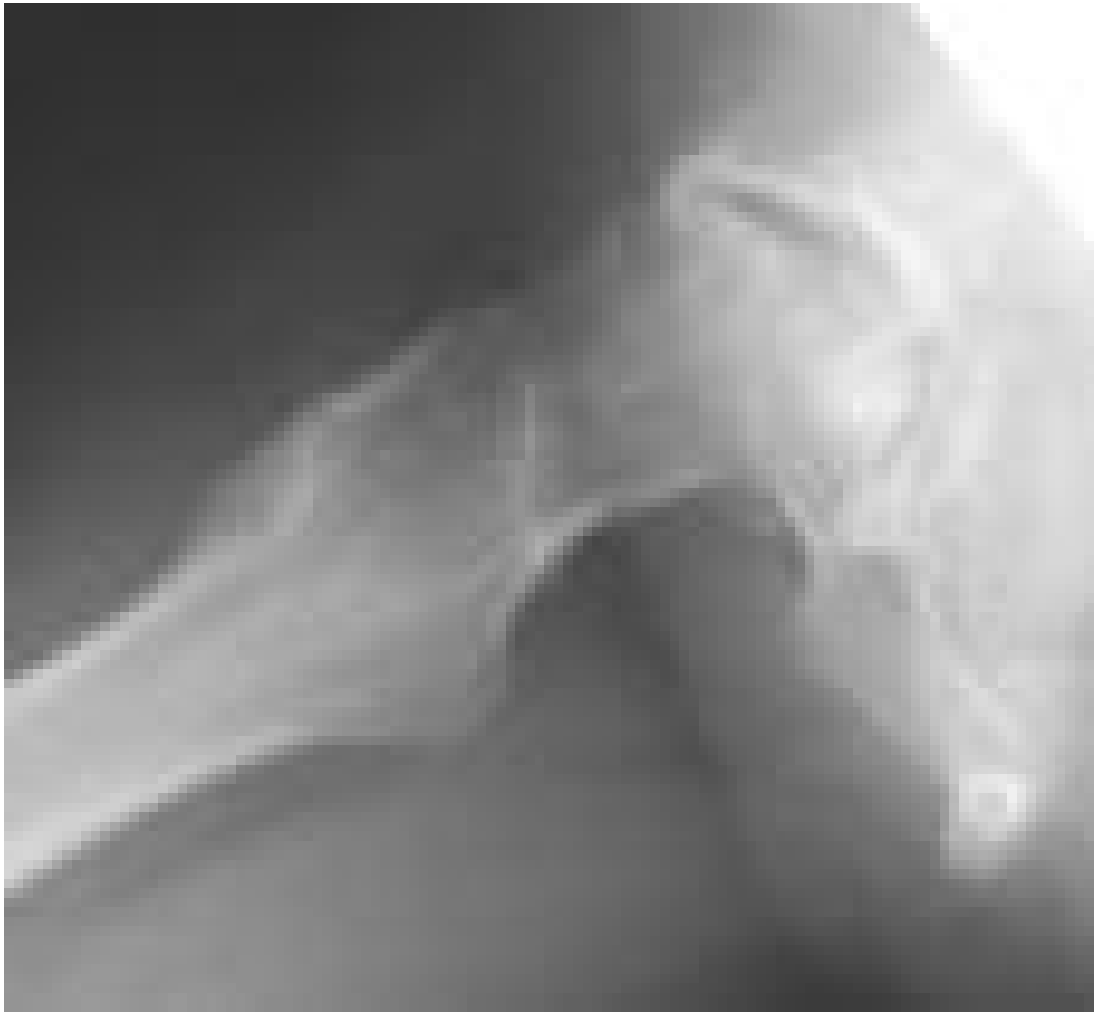
- Related to absent spleen
  - Pneumococcus infections
  - Hemophilus infections
  - Dramatically improved with the use of prophylactic penicillin in childhood
- Related to frequent instrumentation
  - Staphyloccocal infections
- Related to tissue infarction
  - Osteomyelitis

Auto-splenectomy
occurs in sickle cell disease

Sickle Cell Anemia Vaso-occlusion: Unique pathophysiologic feature

- Causes acute and chronic organ damage
- Acute complications
  - Sickle cell vaso-occlusive pain crisis
  - Hepatic crisis
  - Splenic crisis
  - Priapism
- Chronic organ damage
  - Stroke
  - Chronic lung disease with pulmonary hypertension
  - Renal failure
  - Avascular necrosis of bone

Sickle cell: avascular necrosis of the hip



Sickle cell vaso-occlusive crisis

- Serious complication of sickle cell anemia
- Risk of acute event (<48 hours)
  - Acute chest syndrome
  - Splenic sequestration
  - Massive hemolysis
  - Risk of sudden death

Sickle Cell Anemia Painful Events: Management Principles

- Correct fluid/electrolyte abnormalities; use hypotonic fluid and limit volume to avoid overhydration
- Treat any underlying illness
- Opioid analgesics (meperidine is not recommended)
- Blood transfusion is not indicated for an uncomplicated pain episode
- Incentive spirometry should be used during waking hours

Prevention of Painful Episodes

- Hydroxyurea increases Hgb F
  - Reduces the frequency of painful episodes, acute chest syndrome, RBC transfusions and hospitalizations
- Non-pharmacologic approaches have not been fully evaluated
- Prophylactic transfusions showed a decreased incidence of painful crisis in pregnancy

Sickle Cell Pain Episodes

- Average duration 5-7 days
- 30-50% of patients seen in ER are admitted
- Pain episodes account for ~90% of admissions
- Account for most of the cost of care

Addiction and pseudo-addiction

- Addiction (abuse)
  - Overwhelming involvement with obtaining and using mind-altering drug
- Pseudo-addiction
  - Relief seeking behavior misidentified as addictive behavior

Acute Chest Syndrome: Clinical Findings

- Etiology - multifactorial
  - Rib infarct causing splinting/atelectasis
  - Pulmonary fat embolism
  - Infection (mycoplasma, chlamydia, viral)
- Indistinguishable from pneumonia
  - Pleuritic chest pain, fever, cough, tachypnea, hypoxia
- Laboratory diagnosis
  - Worsening anemia
  - Infiltrate on chest radiograph

Acute Chest Syndrome: Outcome

- Complete recovery 91%
  - Weaned of supplemental O_2 3.1±1.9 days
  - Hospital discharge 5.4±2.3 days
- Chronic respiratory disease 3%
- Death 6%

Acute Chest Syndrome: Prevention and Treatment

- Incentive spirometry
- Treat possible underlying infection
- Bronchodilators and supplemental oxygen
- RBC transfusion therapy

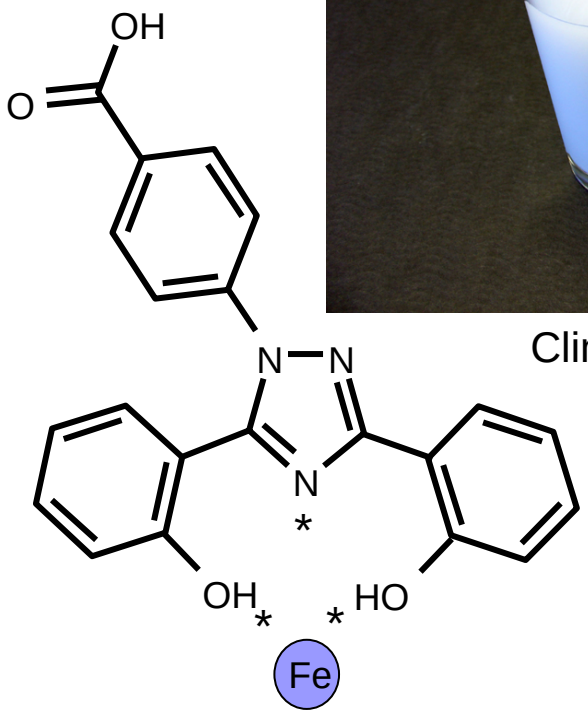
Indications for RBC transfusions in sickle cell disease

Indication	Outcome
Stroke	Initial recovery; decreased recurrence by 90%
Acute chest syndrome improvement	Rapid
Aplastic crisis	May be life saving
Pre-operative treatment (Hgb ~10 g/dl)	Decrease post-operative complications
Symptomatic anemia	Clinical improvement
Splenic or hepatic sequestration	Clinical improvement

Deferasirox :Oral Iron Chelator in chronic blood transfusion

- Tridentate* iron chelator
  - An oral, dispersible tablet
  - Administered once daily
  - Highly specific for iron
- Chelated iron excreted mainly in feces (< 10% in urine)

Clinical trial formulation or preparation

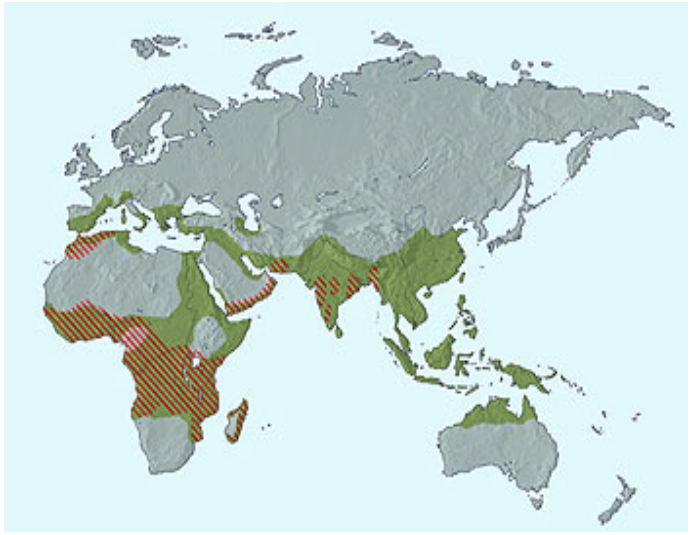


*3 polar interaction sites in the binding pocket.

Nick H, *Current Medicinal Chemistry.* 2003;10:1065-1076.

Sickle Cell Trait

- Protection against malaria
- Genitourinary complications
    - Hyposthenuria/ papillary sloughing
    - Painless hematuria
    - UTI during pregnancy
- Vaso-occlusive complications
    - Splenic infarction with hypoxia
    - Sudden death
    - Rhabdomyolysis



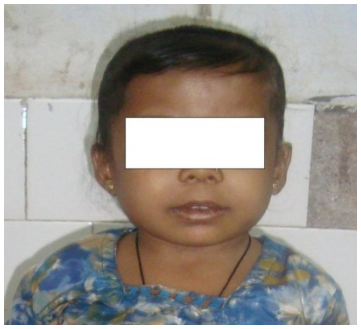
Sickle cell trait areas shown in orange stripes

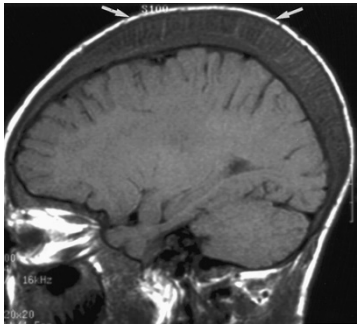
Case 4 D

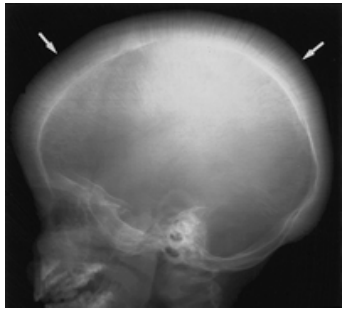
13 yr old male complains of skin pigmentation, abdominal swelling and pallor. He has been receiving blood transfusions since the age of 9 months. Stunted growth. Hb 6, MCV 55, retcs16%,s.Ferritin 5000.

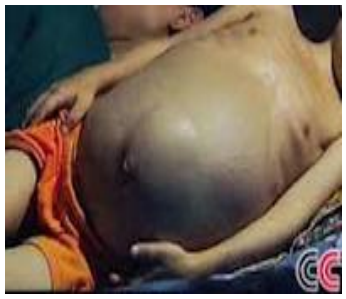
P/E

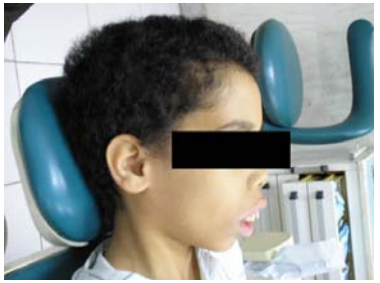
Xray











Clinical Syndrome	Genotype	Hb	Hb analysis
Minor (Trait)	β/β^{+} or β/β°	10-13	↑ Hgb A2, ↑ Hgb F
Intermedia	β^{+}/β^{+}	7-10	↑ Hgb A2, ↑↑ Hgb F
Major (Cooleys)	β^{+}/β° or $\beta^{\circ}/\beta^{\circ}$	< 7	↑ Hgb A2, ↑↑↑ Hgb F

Most commonly reported mutations in the B-globin gens in Jordanians

- **Eight mutations constituted about 86% of the Jordanian thalassemic mutations**
- **These mutations were IVS1-110 (G>A) (25%), IVS2-1 (G>A) (15%),**
- **IVS2-745 (C>G) (14.2%), IVS1-1 (G>A) (10%), IVS1-6 (T>C) (8.3%), codon 37 (G>A) (6.3%),**
- **codon 39 (C>T) (4.6%), and codon 5 (-C) (3.8%)**

Type of Mutation and severity of defect in B-Thal globin gene

Mutation	Phenotype	Ethnic Origin
Promoter Region Mutants		
-101 (C to T)	B(+)	Turkish
-88 (C to A)	B(+)	Mediterranean
-87 (C to G)	B(+)	Black American
Chain Terminator Mutants		
Codon 1 (-1 bp)	**B(0)**	Chinese
Codon 6 (-1 bp)	**B(0)**	Mediterranean
Codon 114 (-2, +1 bp)	B(+)	French
Splice Junction Mutants		
IVS-1, position 1 (G to A)	**B(0)**	Mediterranean
IVS-1, position 2 (T to G)	**B(0)**	Indian, Chinese
New Splice Site		
IVS-1 110 (G to A)	B(+)	Mediterranean
RNA Cleavage Defect		
AATAAA to AACAAA	B(+)	Black American

Beta Thalassemia: Clinical Manifestations/ complication

Osteoporosis

Extramedullary erythropoiesis/ tumor effect

Iron overload: skin, heart, liver, endocrine organs

Dilated cardiomyopathy secondary to severe anemia

Growth and development delayed

Large splenomegaly

Treatment/ Prevention of B thal major

- Blood Transfusion
- Iron chelation: deferroxamine (parenteral)
- ?splenectomy
- Allo-BMT
- Supportive
- **Prevention**

Oral deferasirox