
بسم الله الرحمن الرحيم

sickle cell disease

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۲۰۲۵-۶-۲۲

Brief Medical History

١٩١٠ – First Description of Sickle-Shaped Blood Cells by Dr James Herrick.

١٩١٧ – Genetic basis for SCD were discovered by Dr. V. Emmel.

١٩٢٢ – Disease was named “sickle cell anaemia” by Vernon Mason .

١٩٢٧ –- Hahn and Gillespie explained by showing that the sickling effect is related to oxygen deficiency.

Distribution of the sickle-cell(Epidemiology)

Global Prevalence:

- One of the most common monogenic disorders.
- ~٣٠٠’٠٠٠ newborns affected annually (WHO).
- ٥% of global population carries hemoglobinopathy genes.

Geographical Distribution

- Sub-Saharan Africa: Nigeria, DR Congo, Ghana, Uganda.
- Indian Subcontinent, Middle East: Saudi Arabia, Bahrain, UAE.
- Mediterranean: Greece, Italy, Turkey.
- Central/South America: Brazil,Caribbean.

Distribution of the sickle-cell(Epidemiology)

Prevalence in Iran

- Concentrated in southern provinces: Khuzestan, Bushehr, Hormozgan, Sistan & Baluchestan, southern Fars.
- Carrier prevalence: ۱۰–۳۰%.
- Disease prevalence higher than national average.

Healthcare Burden

- Frequent hospitalizations.
- Severe complications.
- Need for specialized care.
- High strain on developing healthcare systems.

Distribution of the sickle-cell(Epidemiology)

Importance of Screening

- Newborn screening programs.
- Genetic counseling for at-risk couples.
- Reducing incidence of affected births.

Summary

- SCD remains a major global health challenge.
- High burden in endemic regions and expanding globally.
- Early screening and counseling remain crucial.

Pathophysiology

Loss of oxygen.

↓

Polymers or rigid rods

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leading to sickled RBCs

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RBCs Stick to blood vessels

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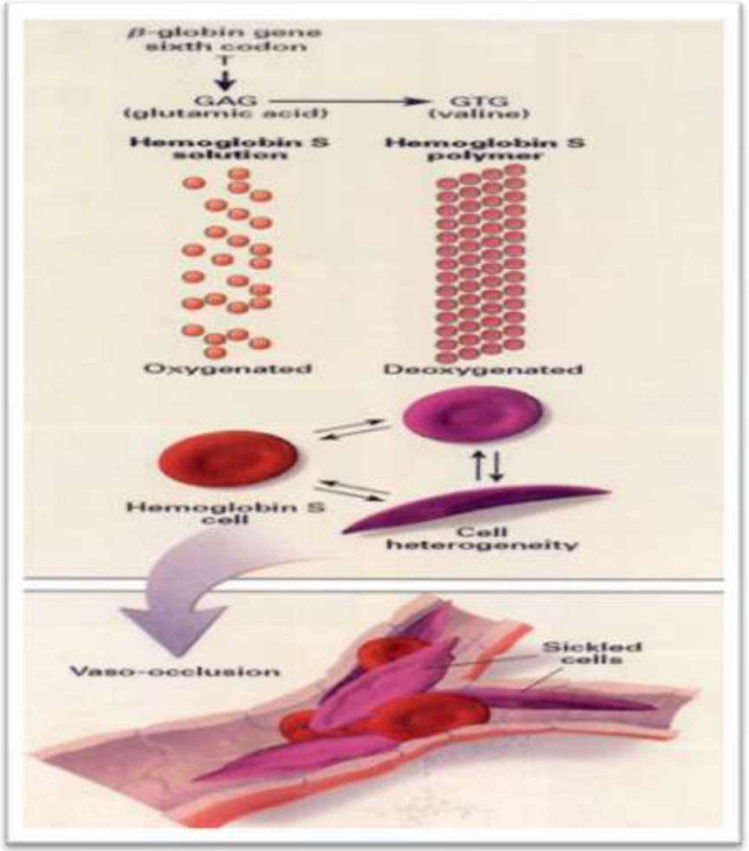
Stasis

↓

Hypoxia

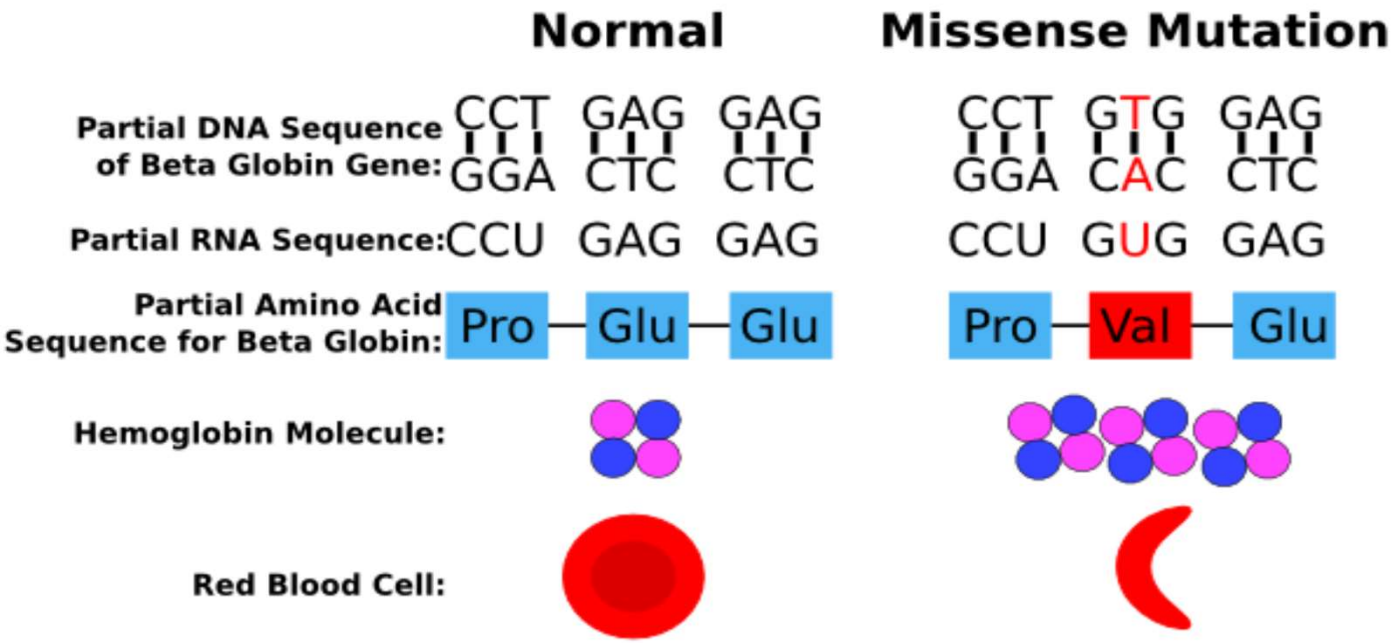
↓

Pain (vaso-occlusive crisis)



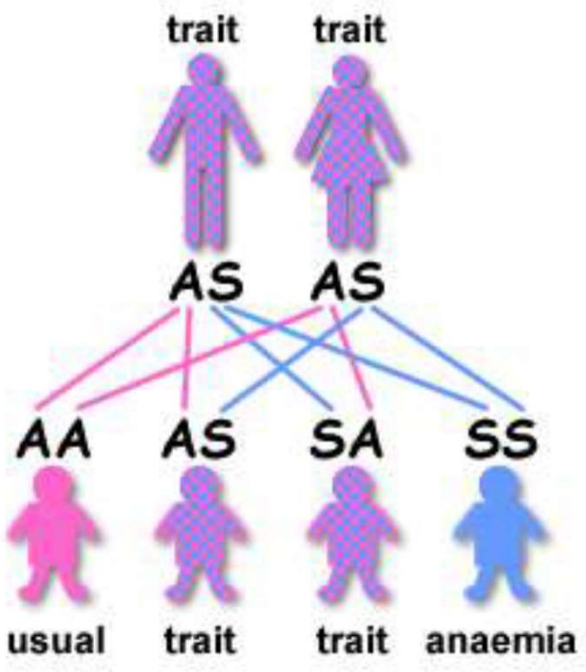
Genetics of SCD

- The change in cell structure arises from a change in the structure of hemoglobin.
- A single change in an amino acid causes hemoglobin to aggregate.



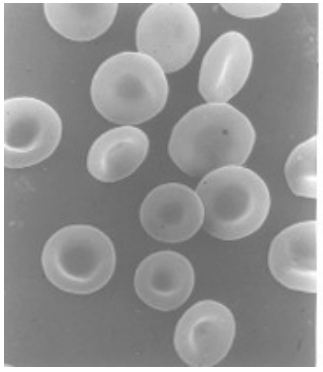
Genetics of SCD

•It’s autosomal recessive blood disease.
•You inherit it from your parents.
*The gene defect is a known mutation of a single nucleotide.
*The person who receives only one defective gene from either one of his parents will develop Sickle-cell trait.
*The person that receives the defective gene from both his parents will develop Sickle-cell disease.



Red Blood Cells from Sickle Cell Anemia

 Deoxygenation of SS erythrocytes leads to intracellular hemoglobin polymerization, loss of deformability and changes in cell morphology.



OXY-STATE

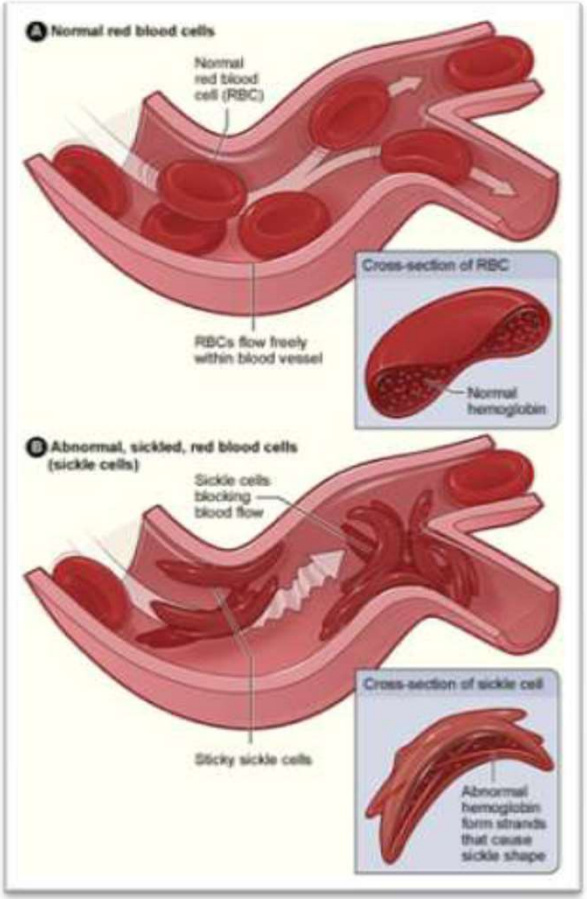
DEOXY-STATE

Vaso-oclusive crisis

- Ischemia
- Pain
- Necrosis
- Often leads to organ damage
- Management

– **Severe**: analgesics, Opioid
– **Mild**: NSAIDs
– New treatment involving

*__Adenosine A٢a receptor agonists:__
These medicines may reduce pain-related complications.



Symptoms

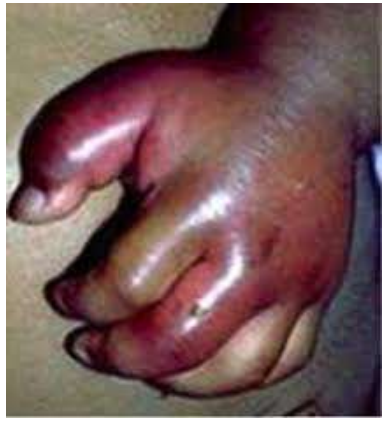
They vary from person to person and change over time,include:

Anemia.

- Sickle cells break apart easily and die, leaving you without enough red blood cells.
- Red blood cells usually live for about ١٢٠ days before they need to be replaced.
- But sickle cells usually die in ١٠ to ٢٠ days, leaving a shortage of red bloodcells (anemia).
- Without enough red blood cells, your body can't get the oxygen it needs to feel energized,causing fatigue.

Painful swelling of hands and feet.

The swelling is caused by sickle-shaped red blood cells blocking blood flow to the hands and feet.



Symptoms

 Delayed growth. Red blood cells provide your body with the oxygen and nutrients you need for growth. A shortage of healthy red blood cells can slow growth in infants and children and delay puberty in teenagers.

 Vision problems. Tiny blood vessels that supply your eyes may become plugged with sickle cells. This can damage the retina — the portion of the eye that processes visual images, leading to vision problems.

Complications

Complications Sickle cell anemia can lead to a host of complications, including:

 Stroke. A stroke can occur if sickle cells block blood flow to an area of your brain. Signs of stroke include seizures, weakness or numbness of your arms and legs, sudden speech difficulties, and loss of consciousness. A stroke can be fatal.
 Acute chest syndrome. This life-threatening complication causes chest pain, fever and difficulty breathing. Acute chest syndrome can be caused by a lung infection or by sickle cells blocking blood vessels in your lungs. It might require emergency medical treatment with antibiotics and other treatments.
 Pulmonary hypertension. People with sickle cell anemia can develop high blood pressure in their lungs (pulmonary hypertension). This complication usually affects adults rather than children. Shortness of breath and fatigue are common symptoms of this condition, which can be fatal.

Complications

- **Organ damage. Sickle cells that block blood flow through** blood vessels immediately deprive the affected organ of blood and oxygen. In sickle cell anemia, blood is also chronically low on oxygen. Chronic deprivation of oxygen-rich blood can damage nerves and organs in your body, including your kidneys, liver and spleen. Organ damage can be fatal.
- **Blindness. Sickle cells can block tiny blood vessels that** supply your eyes. Over time, this can damage the portion of the eye that processes visual images (retina) and lead to blindness.
- **Leg ulcers. Sickle cell anemia can cause open sores, called** ulcers, on your legs.
- **Gallstones. The breakdown of red blood cells produces a** substance called bilirubin. A high level of bilirubin in your body can lead to gallstones.

Diagnosis

 A blood test can check for hemoglobin S — the defective form of hemoglobin that u
United States, this blood test is part of routine newborn screening done at the hospita.. But older children and adults can be tested, too.

 In adults, a blood sample is drawn from a vein in the arm. In young children and babies, the blood sample is usually collected from a finger or heel.

 If the screening test is negative, there is no sickle cell gene present.

 If the screening test is positive, further tests will be done to determine whether one or two sickle cell genes are present.

 Check for a low red blood cell count (anemia) will be done.

Treatment

 Treatment is usually aimed at avoiding crises, relieving symptoms and preventing complications.

Babies and children age ٢ and younger with sickle cell anemia should make frequent visits to a doctor.

- **Antibiotics.**
  Children with sickle cell anemia may begin taking the antibiotic penicillin when they're about ٢ months old and continuetaking it until they're at least ٥ years old.
- Doing so helps prevent infections,such as pneumonia, which can be lifethreatening to an infant or child with sickle cell anemia.
- As an adult, if you've had your spleen removed or had pneumonia, you might need to take penicillin throughout your life.

Treatment

Assessing stroke risk

 Using a special ultrasound machine (transcranial), doctors can learn which children have a higher risk of stroke.

This painless test, which uses sound waves to measure blood flow, can be used on children as young as ٢ years.

Regular blood transfusions can decrease stroke risk.

Vaccinations to prevent infections

 Childhood vaccinations are important for preventing disease in all children.

 Vaccinations, such as the pneumococcal vaccine and the annual flu shot, are also important for adults with sickle cell anemia.

Treatment

Blood transfusions

 In a red blood cell transfusion, red blood cells are removed from a supply of donated blood, then given intravenously to a person with sickle cell anemia.

 Blood transfusions increase the number of normal red blood cells in circulation, helping to relieve anemia. In children with sickle cell anemia at high risk of stroke, regular blood transfusions can decrease the risk. Transfusions can also be used to treat other complications of sickle cell anemia, or they can be given to prevent complications.

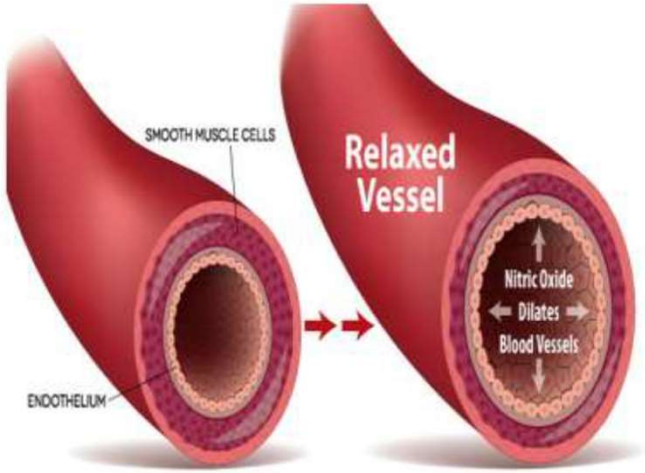
 Blood transfusions carry some risk, including infection and excess iron buildup in your body. Because excess iron can damage your heart, liver and other organs, people who undergo regular transfusions might need treatment to reduce iron levels.

Treatment

 Nitric oxide. People with sickle cell anemia have low levels of nitric oxide in their blood.

 Nitric oxide is a gas that helps keep blood vessels open and reduces the stickiness of red blood cells. Treatment with inhaled nitric oxide might prevent sickle cells from clumping together.

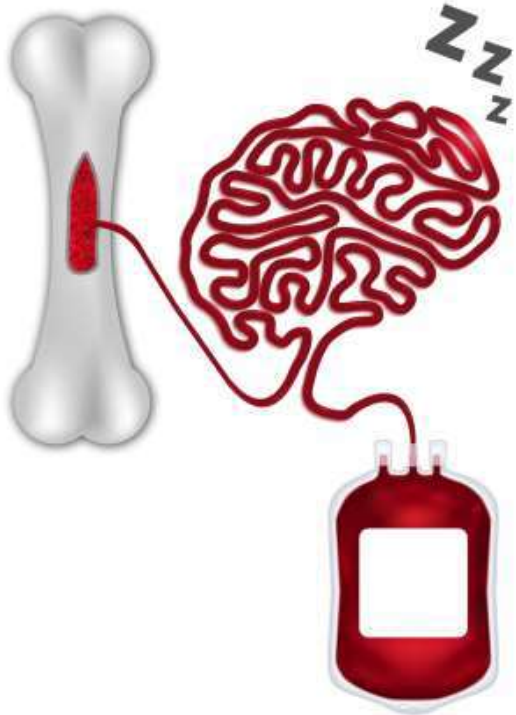
 Studies on nitric oxide have shown little benefit so far.



Bone Marrow Transplant

 Bone marrow transplant, also known as stem cell transplant, offers the only potential cure for sickle cell anemia. It's usually reserved for people younger than age ١٦ because the risks increase for people older than ١٦. Finding a donor is difficult, and the procedure has serious risks associated with it, including death.
 A bone marrow transplant involves replacing bone marrow affected by sickle cell anemia with healthy bone marrow from a donor. The procedure usually uses a matched donor, such as a sibling, who doesn't have sickle cell anemia. For many, donors aren't available. But stem cells from umbilical cord blood might be an option.

Bone Marrow Transplant



Bone Marrow Transplant

 Because of the risks associated with a bone marrow transplant, the procedure is recommended only for people, usually children, who have significant symptoms and problems from sickle cell anemia.

 If a donor is found, the person with sickle cell anemia receives radiation or chemotherapy to destroy or reduce his or her bone marrow stem cells. Healthy stem cells from the donor are injected intravenously into the bloodstream of the person with sickle cell anemia, where they migrate to the bone marrow and begin generating new blood cells.

 The procedure requires a lengthy hospital stay. After the transplant, you'll receive drugs to help prevent rejection of the donated stem cells. Even so, your body might reject the transplant, leading to life-threatening complications.

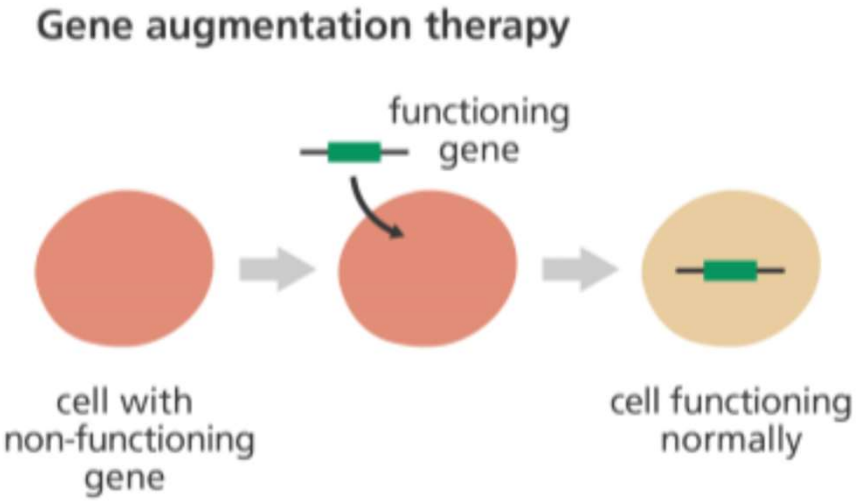
Experimental treatments

Scientists are studying new treatments for sickle cell anemia, including:

- **Gene therapy. Researchers are** exploring whether inserting a normal gene into the bone marrow of people with sickle cell anemia will result in normal hemoglobin.
- Scientists are also exploring the possibility of turning off the defective gene while reactivating another gene responsible for the production of fetal hemoglobin — a type of hemoglobin found in newborns that prevents sickle cells from forming. Potential treatments using gene therapy are a long way off, however.

Experimental treatments

- Although several of the initial hurdles to SCD gene therapy appear to have been overcome, it is prudent to recognize barriers that remain.
- Efficient transduction of HSCs with lentiviral vectors has become increasingly reliable, but the complicated components of many globin vectors present unique challenges for production of high-titer virus capable of robust transduction.



Experimental treatments

- Scaling up procedures to multiple patients is a nontrivial challenge.
- Safety and efficacy can only be established by careful clinical trials with extended patient follow-up.
- Gene engineering methods are rapidly evolving and should facilitate development of “secondgeneration” gene therapy approaches in the coming years. After many years of preclinical laboratory investigation, gene therapy options are now on the horizon for patients with SCD.

Prognosis

*New and aggressive treatments for sickle cell disease are prolonging life and
improving its quality.

*Recently as ١٩٧٣, the average lifespan for people with sickle cell disease was only ١٤ years.

*Currently, life expectancy for these patients can reach ٥٠ years and over.

*Women with sickle cell live longer than their male counterparts.

*The median age at death :

-Males : ٥٣years

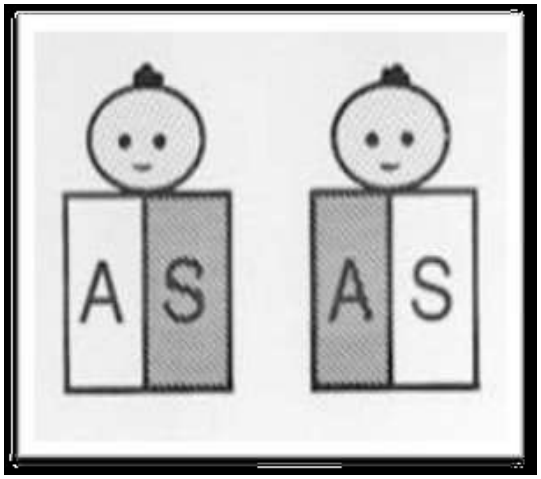
-Females: ٥٨ years

Treatment

- **Hydroxyurea.**
  - – Reactivates fetal Hb production
  - – Decreases severity of attacks
  - – Increases life span
  - – More effective with Erythropoietin.
- **Bone marrow transplant during childhood.**
- **♢-HMF. This natural compound binds to red blood cells and** increases their oxygen. This helps prevent the red blood cells from sickling.

Sickle Cell Trait (AS)

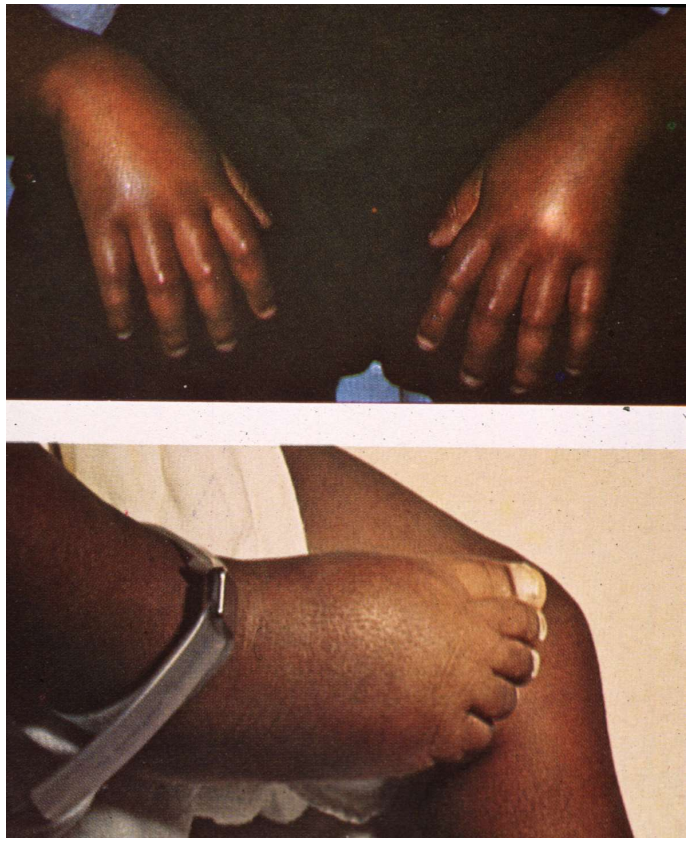
*A person has one abnormal allele of the hemoglobin beta gene.
*Those who are heterozygous for the sickle cell allele produce both normal **“HbA” and abnormal hemoglobin “HbS” (the two alleles are co-dominant).**
*Asymptomatic :Don’t show severe symptoms as in Sickle cell Anemia.
* **HbA : ٦٠%, HbS: ٤٠% , HbF:<٢%**
*They act as carriers and can transmit the disease to their off springs.
*People with sickle cell who exercise heavily, such as athletes and those who are exposed to dehydration or altitude extremes, may sometimes experience sickle cell anemia symptoms.



The most important demonstrations

- Acute pain attack: The first manifestation is dactylitis or hand-foot syndrome.
- Thigh attack in ٥٠%
- Stroke in ١٠% of patients
- Osteonecrosis in ٥٠%
- Increased pulmonary artery pressure in one-third of patients
- Growth and puberty delay in ٣٠%

- Leg
- Ulcers
- Priapism
- Nephropathy
- Retinopathy
- Liver complications
- Infection
- Splenomegaly in early infancy



Prognostic syndrome of disease severity

- Hemoglobin less than ٨ grams per deciliter
- White blood cell count more than ٢٠٬٠٠٠ per cubic millimeter
- Dactylitis attack less than one year of age
- First blood transfusion less than one year of age

Acute Splenic Sequestration

- The patient should be treated immediately.
- The Opening the patient's vein and injecting fluids and blood is the main treatment.
  volume of blood given should be small.
- The patient's hemoglobin should be stored in the range of ٨ to ٩ grams per deciliter
  As the spleen shrinks, ١ to ٢ grams per deciliter is added to the patient's hemoglobin.
- Splenectomy is the main treatment for this syndrome.

Aplastic attack

- Parvovirus B١٩ is mainly responsible for transient suppression of erythroid production.
- Anemia with reduced rethrocyte count is seen.
- Neutropenia and thrombocytopenia are also occasionally seen.
- Increased IgM antibodies to parvovirus B١٩ indicate recent infection.
- Isolation of the infected individual from pregnant women is essential.
- A decrease of ٢٥% or more in hemoglobin and symptomatic anemia require blood transfusion.

Hyperhemolysis

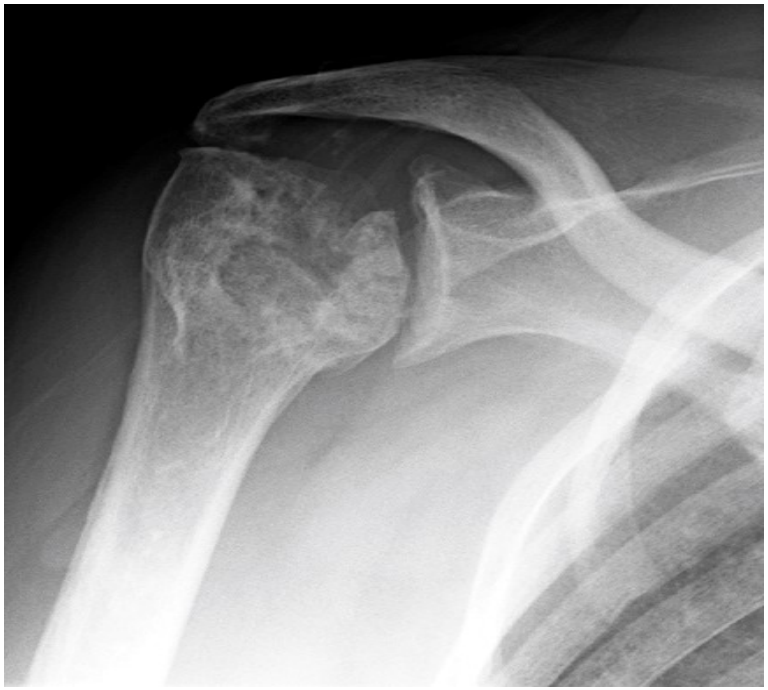
- Hyperhemolysis is characterized by a greater than normal decrease in hemoglobin, an increase in reticulocyte count, and an increase in LDH.
- The presence of G۶PD anemia in patients and immunization in some patients following blood transfusions (alloimmunization and autoantibodies) are among the causes of this syndrome.
- Intravenous gammaglobin and steroid injections can help reduce the blood's adverse load and blood selection.

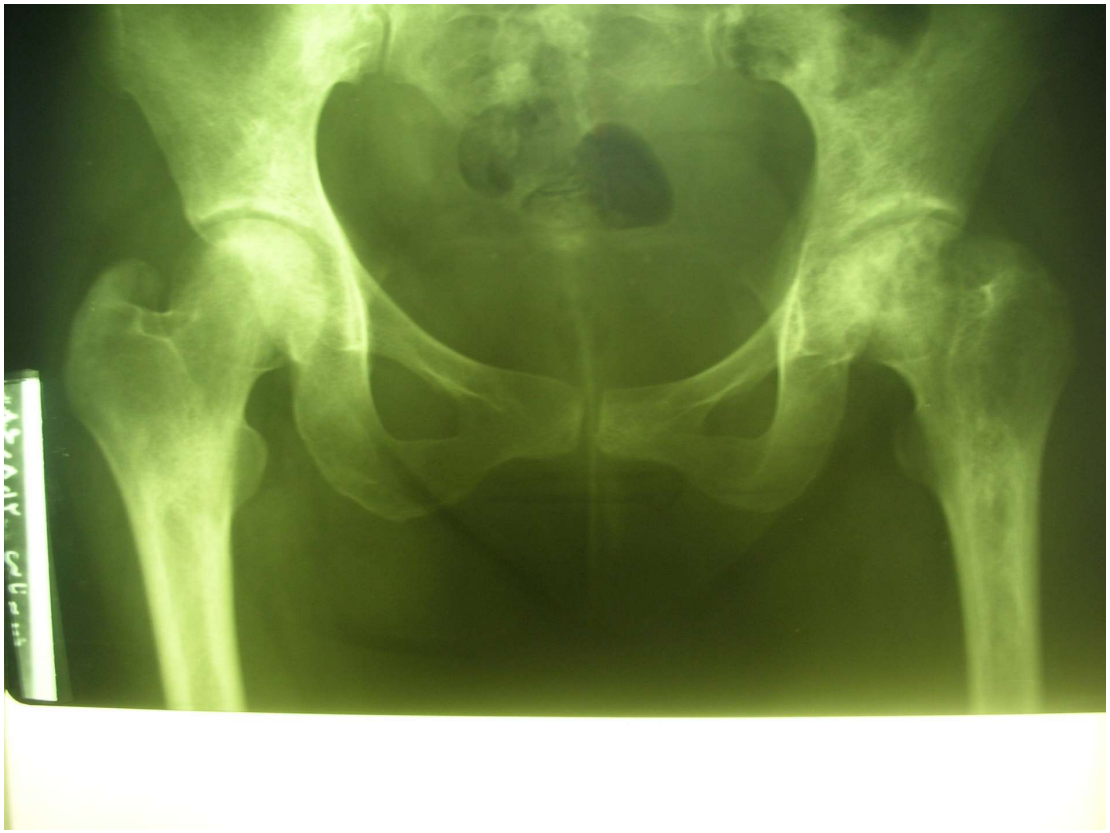
Infection in the tuberculosis cycle and the thalassemia cycle:

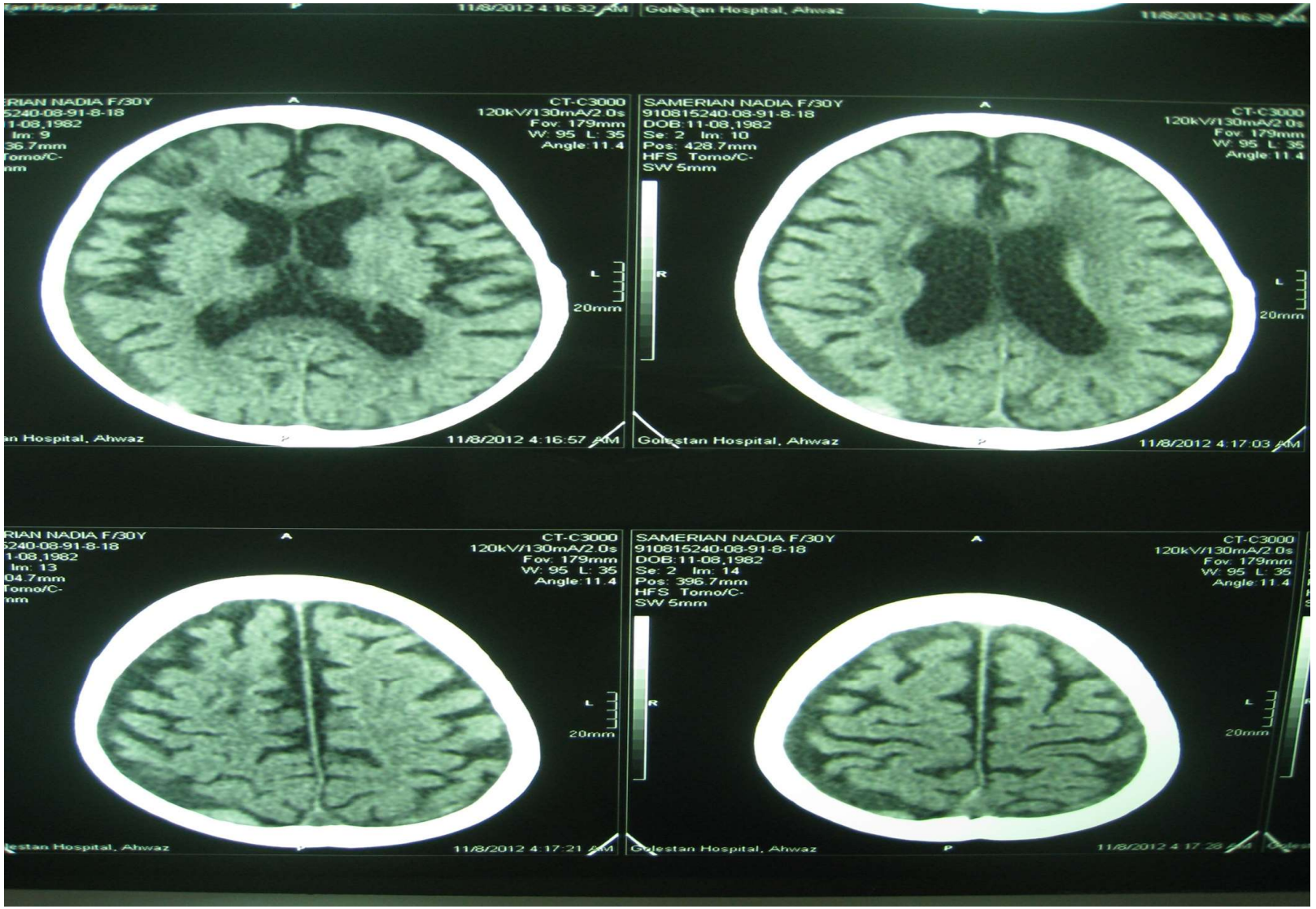
- Due to hyposplenism and impaired opsonization, they are susceptible to infections with pneumococci, Haemophilus influenzae, Staphylococcus aureus, and Salmonella.
- As patients age, the infection shifts from pneumococci to gram-negative infections such as Escherichia coli, Klebsiella, and Salmonella.
- Any febrile event in a sickle cell or sickle cell thalassemia patient should be considered serious.
- Infection is the most common cause of death in these patients

- All patients should receive vaccinations against Haemophilus influenzae, pneumococcus, meningococcus, and influenza in addition to routine vaccinations. Patients should receive penicillin from ٢ months of age.
- Any sickle cell or sickle thalassemia child with fever should be treated as if he or she had pneumococcal septicemia unless proven otherwise (preferably ceftriaxone).
- In patients with suspected pneumonia, an additional antibiotic such as azithromycin, erythromycin, or clarithromycin should be used in addition to ceftriaxone to cover mycoplasma and chlamydia.

- By the age of ۳۵, ۵۰% of sickle cell and sickle thalassemia patients have hip and shoulder osteonecrosis.
- Three-quarters of patients with shoulder osteonecrosis also have hip osteonecrosis.
- Patients with elevated hematocrit and alpha thalassemia are at higher risk of osteonecrosis.
- Treatment: Conservative therapy.Transfusion has not been proven to reduce pain and disease progression.



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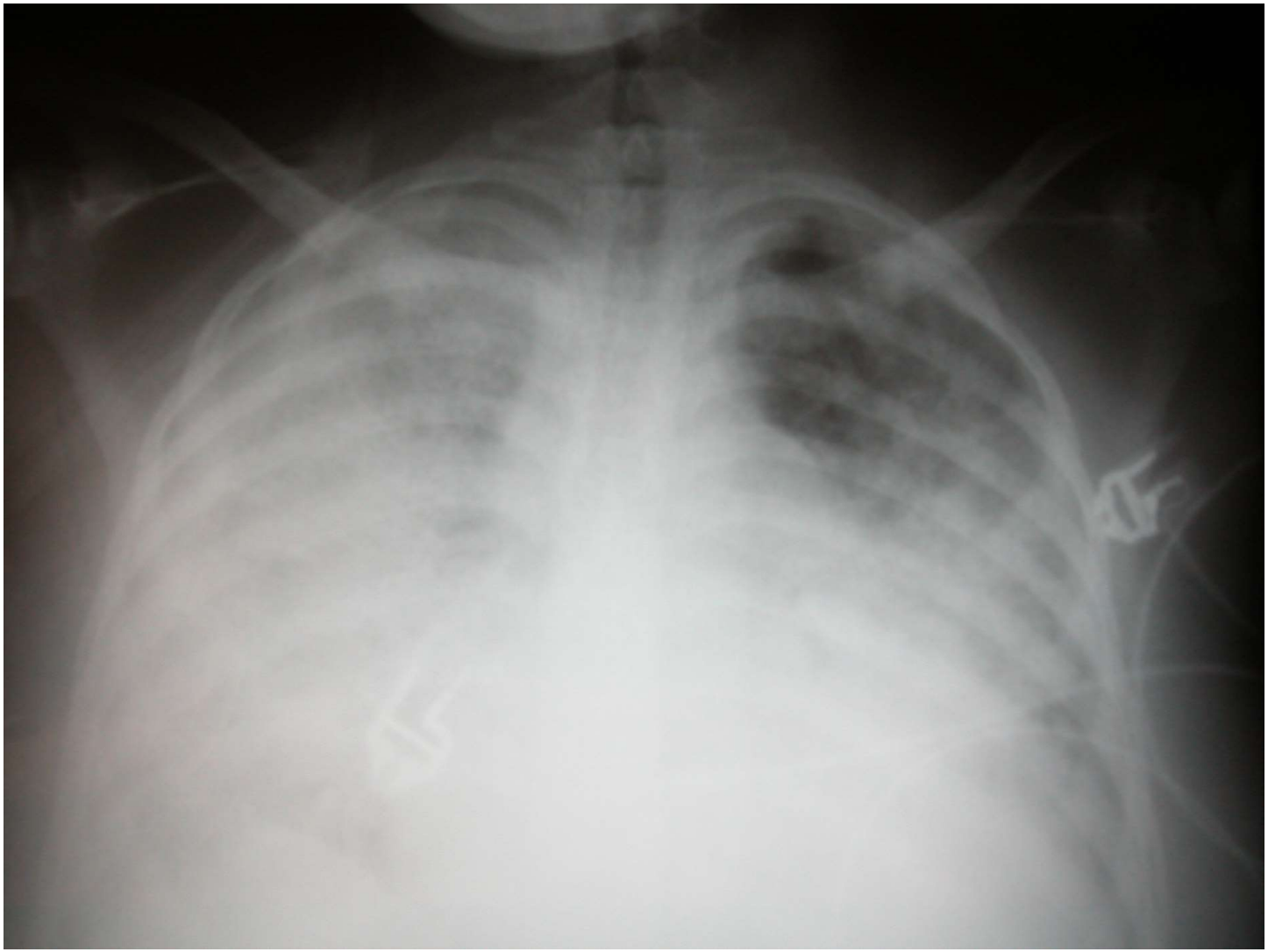
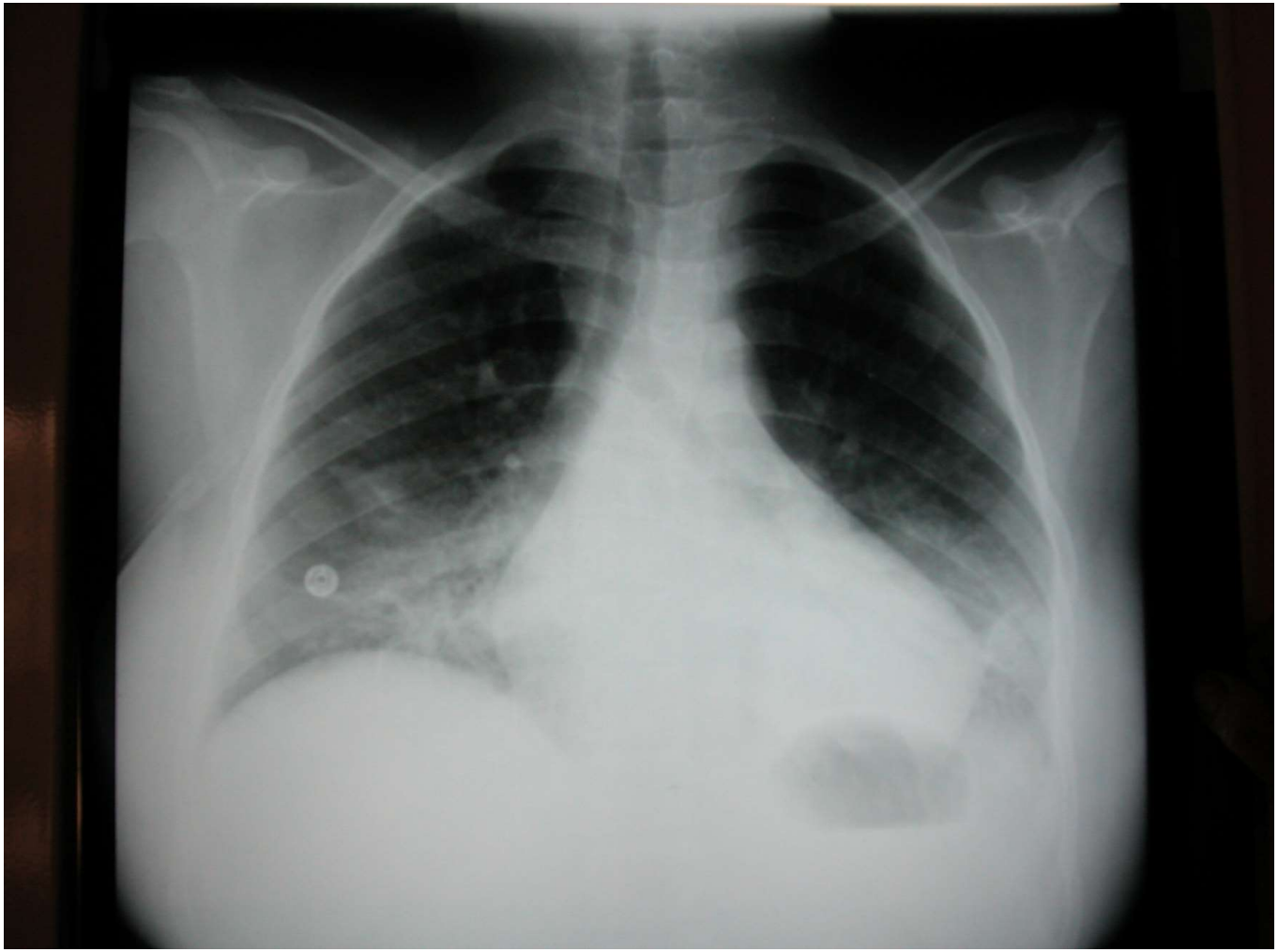
Severe Acute Chest Syndrome with Respiratory Distress



Acute Chest Syndrome ۴۸ hr after Exchange Transfusion



Increase in pulmonary artery pressure

- Definition: The velocity of blood returning from the tricuspid valve is equal to or greater than ۲٫۵ ml/s
- In acute painful attack and acute chest attack, the severity of the increase in pulmonary artery pressure increases.
- The main cause is the decrease in NO gas

Treatment of pulmonary arterial hypertension

Blood transfusion
Hydroxyurea
Warfarin
Sildenafil
Oral arginine (NO gas precursor)Important note:
Sickle cell and sickle cell thalassemia patients from adolescence onwards should undergo annual echocardiography due to increased pulmonary artery pressure

Kidney disease

Hematuria.
Decreased urine concentrating ability.
Focal segmental glomerulosclerosis,
Papillary necrosis.
Impaired urine acidification.
Reduced glomerular filtration rate.
Microalbuminuria.
Distal tubulointerstitial acidosis.
Impaired potassium excretion.
Early initiation of ACE inhibitor or ACE receptor antagonist drugs is helpful.