Sickle cell anemia

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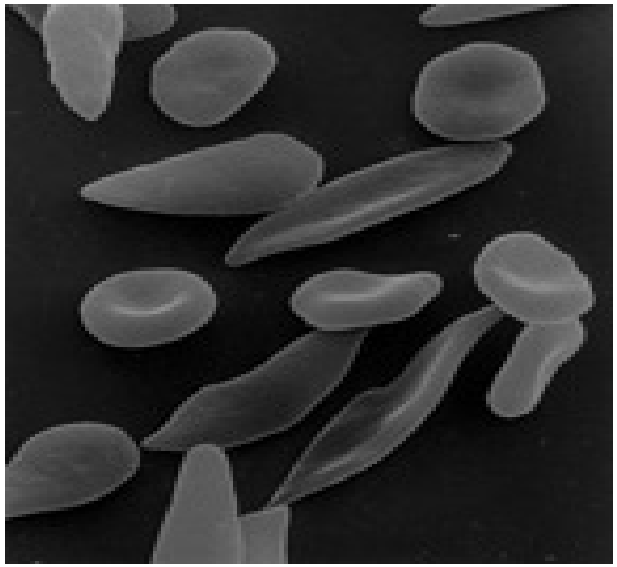


What is sickle cell?

- Sickle-cell anemia is caused by a point mutation in the β-globin chain
- The amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position
- The association of two wild-type α-globin subunits with two mutant β-globin subunits forms hemoglobin S (HbS).

What is sickle cell?

- Sickle cell anemia
- Anemia - sickle cell; Hemoglobin SS disease (Hb SS); Sickle cell disease.

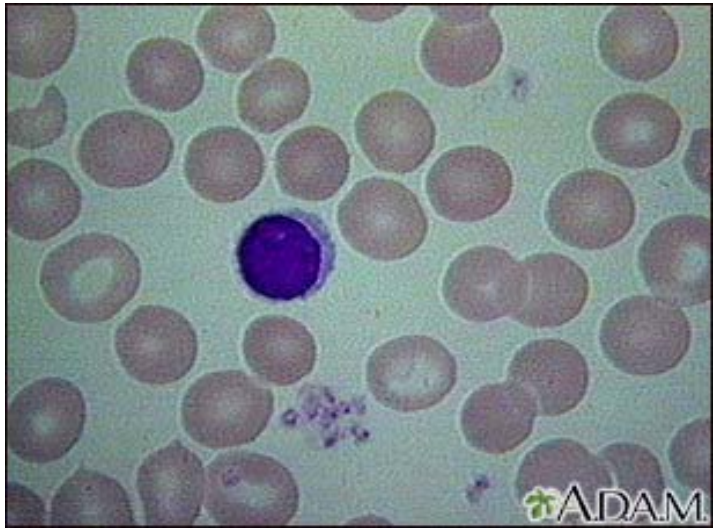
- Sickle cell anemia is a disease passed down through families in which red blood cells form an abnormal sickle or crescent shape.

- Red blood cells carry oxygen to the body and are normally shaped like a disc.

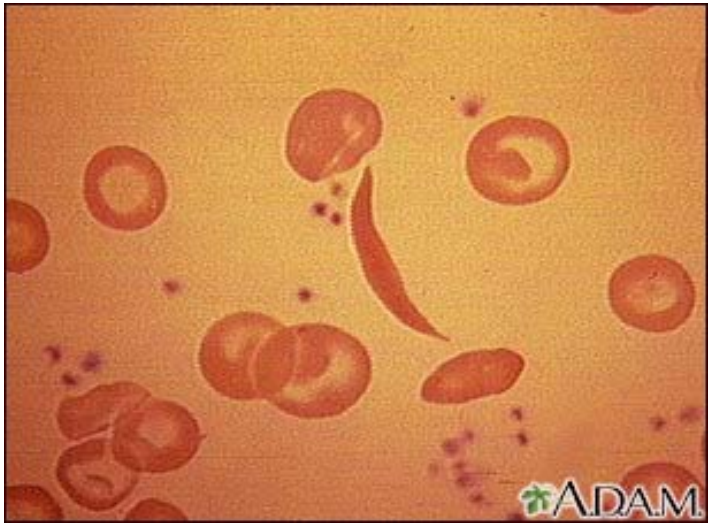
- Sickle cell anemia is inherited from both parents. If you inherit the sickle cell gene from only one parent, you will have sickle cell trait. People with sickle cell trait do not have the symptoms of sickle cell anemia.

- Sickle cell disease is much more common in people of African and Mediterranean descent. It is also seen in people from South and Central America, the Caribbean, and the Middle East.

Cell Morphology



Red blood cells, normal cell



Red blood cells, sickle cell

Sickle cell anemia

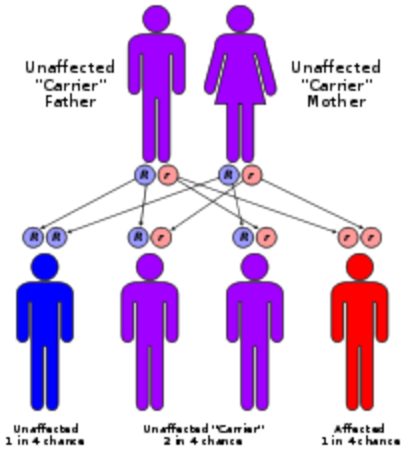
- Sickle cell is the most common inherited hemoglobinapathy in the world
- About 10% of African American carry a sickle cell gene
- Only about 1/500 AA have sickle cell anemia
- Most patient with sickle trait are asymptomatic

Inheritance

- Inheritance

- autosomal recessive genetic disorder.
- The presence of two defective genes (SS) is needed for sickle cell anemia.
- If each parent carries one sickle hemoglobin gene (S) and one normal gene (A), each child has a 25% chance of inheriting two defective genes and having sickle cell anemia
- 25% chance of inheriting two normal genes and not having the disease

- 50% chance of being an unaffected carrier like the parents.



Sickle-cell disease is inherited in the autosomal recessive pattern.

Incident of sickle cell

- Incidence

  Sickle cell anemia affects millions
- It is common among people whose ancestors come from sub-Saharan Africa; South America, Cuba, Central America
- Saudi Arabia; India; and Mediterranean countries such as Turkey, Greece, and Italy.
- In the Unites States, around 100,000 people most are of Africa decent.
- The disease occurs in about 1 in every 500 African-American births and 1 in every 1000 to 1400 Hispanic-American births.
- About 2 million Americans, or 1 in 12 African Americans, carry the sickle cell trait.

Sickle trait

- Rare complications
- S40:A60
- Most 98% are without symptoms
- Hematuria
- Pyelonephritis
- Splenic infarct at high altitudes
- Medullary cancer of the kidney

Sickle cell trait

Complications and Risks Associated with Sickle Cell Trait

- 1. Splenic infarction at high altitude, with exercise, or with hypoxemia
- 2. Isothenuria with loss of maximal renal concentrating abilitty
- 3. Hematuria secondary to renal papillary necrosis
- 4. Fatal exertional heat illness with exercise
- 5. Sudden idiopathic death with exercise
- 6. Glaucoma or recurrent hyphema
- 7. Bacteruria in women
- 8. Bacteruria or pyelonephritis associated with pregnancy
- 9. Renal medullary carcinoma in young people (ages 11 to 39 years)
- 10. Early onset of end stage renal disease from autosomal dominant polycystic kidney.

Sickle trait not so benign

- Observation study in listed recruits in US Armed Forces basic training.
- A military trainee with Hb AS suffered exercise related
- hypernatremia during physical training in the field.
-
- One of the trainee survived a critical illness that included acute renal failure requiring
- of dialysis.

  During a single summer, there were four exercise related deaths
- among recruits at Fort Bliss, all of whom were black and had sickle cell trait.
- No recruits with normal hemoglobin died.
- The recommendations for safe exercise by individuals with
- sickle cell trait.
- The excess morbidity and mortality is preventable by avoiding exertional
- heat illness.

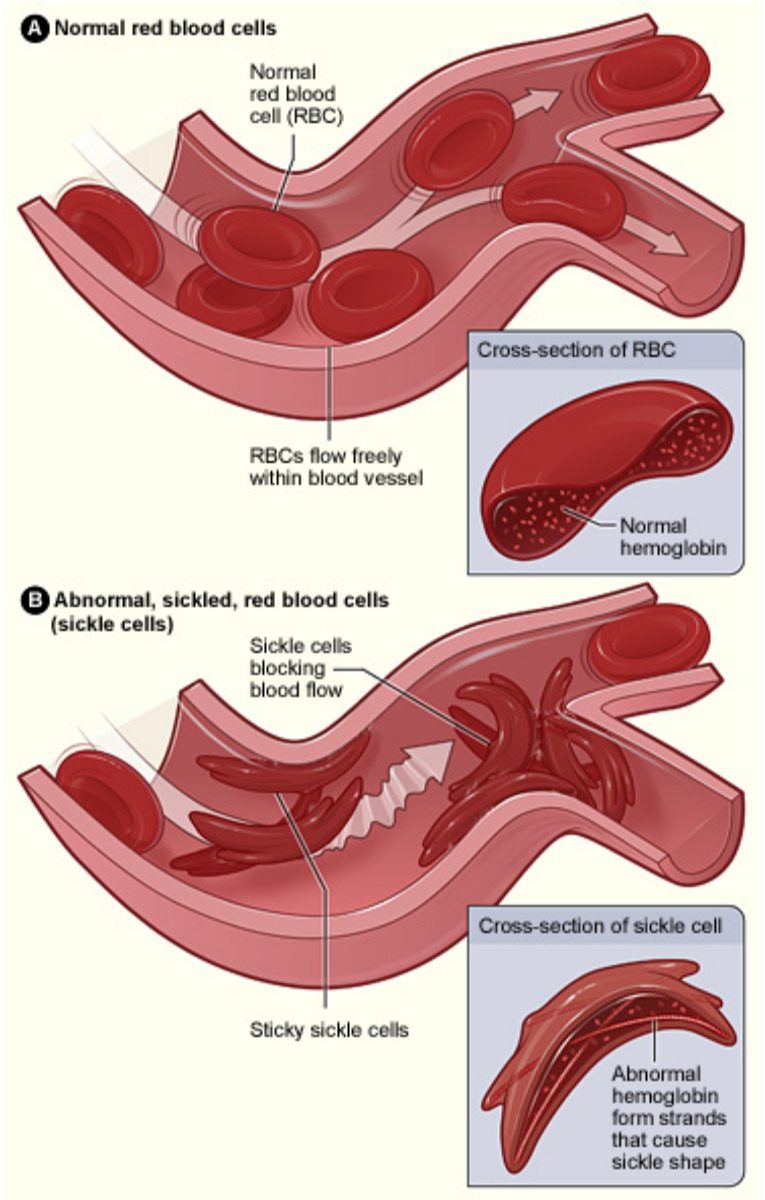
- At least half of these cases were proven to suffer from acute exertional heat illness, with rhabdomyolysis as the predominant component.
- The other half of cases died suddenly without a clear etiology,
- Splenic Infarction from sickle cell trait is more common with
- exercise at high altitude but has occurred with altitude exposure at

Sickle cell disease

- Variable expression
- Chronic hemolytic anemia
- Vasoocclussive crisis
- Risk of kidney disease
- CVA
- Heart failure
- Iron overload

Pathophysiology

- When the deoxygenated of hemoglobin S occurs the normal shape of the molecule changes
- It be comes less soluble (it aggregates and polymerizes)


A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

Structure of RBC

- loss of red blood cell elasticity

- In sickle-cell disease, low-oxygen cause red blood cell sickling and damage the cell membrane and decrease the cell's elasticity.

- The rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia

- The actual anemia of the illness is caused by hemolysis, the destruction of the red cells inside the spleen

Type of sickle cell

Variations of sickle cell

There are several types of sickle cell disease

Sickle Cell Anemia (SS)

Sickle-Hemoglobin C Disease (SC)

Sickle Beta-Plus Thalassemia

Sickle Beta-Zero Thalassemia

Sickle and thallassemia trait

The presence of alpha-thallassemia reduces the risk of hemolysis.

Clinical and lab

Disease group	**severity**	S(%)	F(%)	Hgb
SS(α–/–α), ($-\alpha$,$-\alpha$)	severe	>90	<10	6-8
Sickle beta($S\beta^0$)	Mod-severe	>80	<20	7-9
Sickle Beta +($S\beta+$)	Mild-moderate	>60	<20	9-12
Sickle C dz(SC)	Mild-moderate	50	<5	10-15

Clinical manifestation

- Shorten red cell survival from the 120 days
- To 15-25 days
- Moderate to severe hemolysis
- Splenic sequestration
- Vasoocclusion results in severe joint and muscle pain
- Bone infarct
- Precipitated by infection, dehydration, cold temp, stress, pregnancy and exercise

Complications

- Acute dactylitis- necrosis of bone marrow in the hands and feet
- Osteomylitis/leg ulcers
- AVN
- Lung dysfunction (infarcts, htn, hypoxemia, ILD)
- Acute chest syndrome
- Stroke/seizure
- CV: heart failure,
- Retinopathy
- GN
- Aplastic crisis

Acute dactylitis- necrosis of bone marrow in the hands

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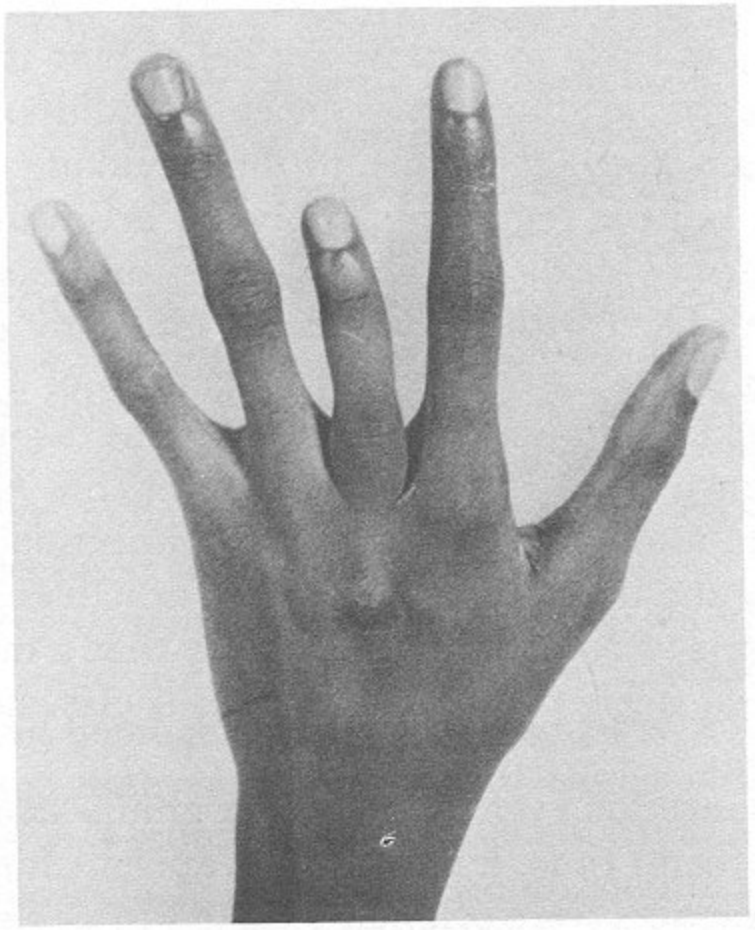

Complications

- Younger children with sickle cell anemia have attacks of abdominal pain.
- The following symptoms may occur because small blood vessels may become blocked by the abnormal cells:
- Painful and prolonged erection (priapism)
- Poor eyesight or blindness
- Problems thinking or confusion caused by small strokes
- Ulcers on the lower legs (in adolescents and adults)
- Over time, the spleen no longer works. As a result, people with sickle cell anemia may have symptoms of infections such as:
- Bone infection (osteomyelitis)
- Gallbladder infection (cholecystitis)
- Lung infection (pneumonia)
- Urinary tract infection
- Other symptoms include:
- Delayed growth and puberty
- Painful joints caused by arthritis

Sickle affects all organ system

- Avascular Necrosis is the death of bone tissue.
- In very advanced cases replacement of the hip joint may be necessary.
- The condition causes extreme pain and can result in the flattening or collapsing of the bone.
- Leg Ulcers:

  chronic damage to the BV in the legs.

  some pt need blood transfusions every 4-6 weeks to allow the ulcers to heal.
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Life threatening complications

- Acute chest syndrome
- Sepsis/meningitis (encapsulated organisms)
- Aplastic crisis (parvo B-19)
- CVA
- Acute cholecystitis(pigmented gallstones)
- Transfusion induce hemolysis

Life expectancy

- SS: severe anemia, frequent pain crisis
- More long term complications
- life expectancy is 52-55
- SC higher fetal Hgb and less bone and ocular complications (60)
- Better life expectacy
- ACS increase risk of M/M

Treatment

- Preventive and supportive care
- Treatment of complications
- Pentavalent/hepatitis vaccine
- PCN (pediatric)
- Folic acid
- Rest/ hydration/ pain medications
- Selective RBC transfusion
- O2(hypoxemia)

When is transfusions indicated?

- Splenic sequestration
- CVA
- Aplastic crisis
- Acute ocular events
- Acute chest syndrome
- High output cardiac failure
- Children with abnl transcranial Doppler's
- Pulm Htn
- Nonhealing foot ulcers
- priapism

Acute chest syndrome

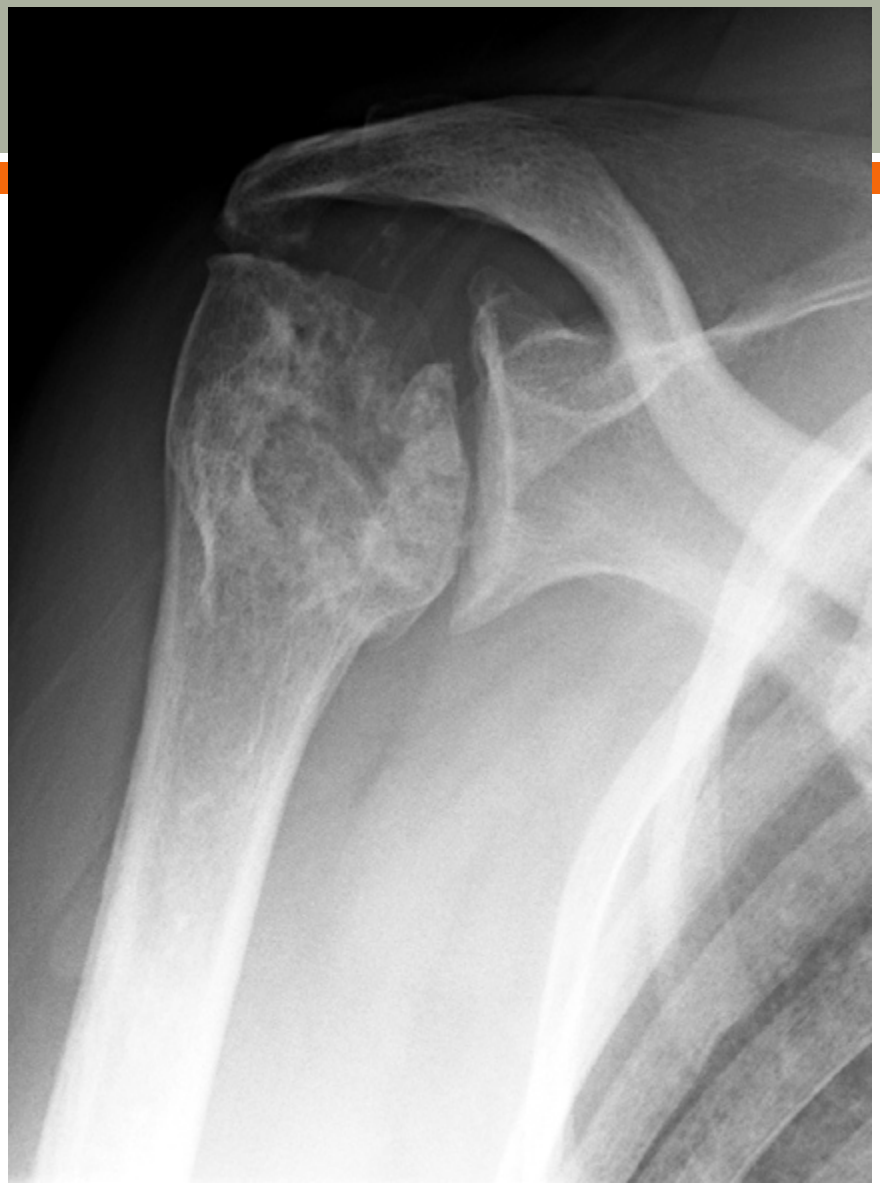
- Acute lung injury secondary to fat emboli,B. infection and viral
- Hypoxemia, chest pain , fever,
- Tachypnea, +/ infiltrate on CXR-
- May see a drop in Hgb
- Acute chest syndrome is the most common cause of morbidity and mortality
- MCC of death
- Highest incident in 2-4 yo, lowest in adults
- Hydrea lowers the incident of ACS
- $O_{2,}$ inhaled $NO_{2,}$? Steroid, exchange transfusion, or transfusion 3-4 u PRBC in anemic pts

Acute splenic sequestration

- 6/100 patient yrs
- Leading cause of death in children
- Leads to hypovolumic shock
- Left side upper quardrant pain
- Drop in hgb of 2g/dL
- Mild to moderate thrombocytopenia
- Erythrocytosis
- spleen usually palpable

Management

- Restore intravascular volume
- Transfuse PRBC
- No role for emergency spleenectomy
- Consider transfusion maintainance
- If reoccurs consider partial splenectomy
- *prophylactic PCN, and pneumococal
- vaccine



Aplastic Crisis

Most common in Sickle cell DZ

Parvo B19 virus

- Increase fatique , fever,pallor,thrombocytopemia
- arthralgia., Headache (rash)
- No compensatory reticulocytosis
- Most recover spontaneously
- 87% will require transfusion

Infectious complications

- Sepsis/meningitis (encapsulated organisms)
- Aplastic crisis (parvo B-19)
- Chronic leg ulcers
- pneumonia

Infection

- The function of the spleen varies
- As a child ages they loose spleen function
- Howell-jolly bodies
- Px PCN therapy can reduce 80% od S.pneumonia infections
- There is a 400 fold increase in the incident of sepsis in children <5
- The course is fulminant and often fatal

Prophylactic PCN

- All newborn with SS,SC,SB
- Start early at 2-3m old
- PCN 125MG PO bid
- d/C pcn AFTER age 5
- Other pathogens that can case sepsis
- H. influenza, E. coli, samonella
- People with sickle cell disease must reduce their risk of infections. This includes receiving certain vaccinations, including:
- Haemophilus influenzae vaccine (Hib)
- Pneumococcal conjugate vaccine (PCV)
- Pneumococcal polysaccharide vaccine (PPV)

When to use antibiotics

- Fever w/o source
- Menigitis or if suspicious
- Osteomylitis/septic arthritis
- UTI
- Toxic appearing
- T>39.9, and WBC>30 or less< 5

Stokes/clots

- CVA
- Risk of stroke by age 20 is 11%, by 30yrs 15%, 45 yo 25%
- Hemmoragic vrs ischemic
- Ischemic more common in younger pts
- 25% mortality ofter a hemmoragic stroke, may occur after splenic sequestration, priapism,aplasia,viral illness, TIA
- Pulmonary emboli/Port- DVT

Management of strokes in Sickle cell

- 2 eligible trials. One compared a chronic transfusion regimen for maintaining sickle hemoglobin lower than 30% with standard care in 130 children with SCD judged (through transcranial doppler ultrasonography) as high-risk for first stroke.
- During the trial, 11 children in the standard care group suffered a stroke compared to one in the transfusion group.
- This 92% relative risk reduction meant the trial was terminated early.
- Thirty months treatment was planned, but median follow up was 21.1 months.
- The transfusion group had a high complications rate: iron overload; alloimmunisation; and transfusion reactions.
- The second trial investigated risk of stroke when transfusion was stopped after at least 30 months.
- The trial closed early due to a significant difference in risk of stroke between participants who stopped transfusion and those who continued.
- Risk of CVA was measured by abnormal velocities on Doppler examinations, OR 0.02 (95% CI 0.00 to 0.43). No trials were identified investigating transfusion for preventing recurrence of stroke.

Cardiovascular events

- Cardiomegaly , murmur, S3, suprasternal thrill
- Atherosclerosis is rare
- Increase size in the aortic root and left atrium
- Significant wall thickening in the septum changes due to in SV 2nd to Anemia
- Arrthymia is common during acute pain crisis

Transfusion induce hemolysis

- Life threating complications
- Secondary to alloantibodies and autoantibodies
- Hemolysis
- TRALI-acute lung injury/ARDS
- Hypoxemia
- Hypovolumic shock

Gallstones/liver dz

- Bilirubin stones are common 12% in 2-4yo and 42% in 15-18yo
- This lead to gallstones/cholecytitis
- Better to have an elective Lap chole that an emergent cholecystectomy which may be life threatning
- Intrahepatioc sickling can be life threating
- Cause RUQ pain, fever, jaundice and elavated LFT

Iatrogenic complications

- Recurrent clots
- Hemolytic complications
- Iron overload
- Constipation
- Port infections
- Heart failure
- Kidney failure

Complication of transfusion

- Delayed transfusion reaction
- Alloimmunization
- Hyperviscousity in pt with SC

** recurrent Tx can lead to life threatening hemolysis and shock

Pregnancy

- Spontaneous abortions occur in 5%
- Higher rate of preecclampsia
- Preterm labor and premature labor
- For routine pregnancy prophylactic transfusions are not recommended
- High risk management

Risk of pregnancy

65% ↑ in Anaemia

↑Risk of stroke

Folate deficiency

↑Cerebral complications

61% ↑ infection

25% ↑ Miscarriage

↑ Still birth rate

↑ Pelvic inflammation

Thrombophlebitis

Papillary necrosis

↑ Rate of meningitis

↑ Perinatal mortality

↑ Bone crisis

↑ Rate of amnionitis

↑ Caesarean section rate

↑ Sickle chest syndrome

↑ Pulmonary complications

13% ↑ Premature birth

25% ↑(IUGR)

Splenic sequestration

↑ Infertility

5% ↑ Hypertension

↑ Painful crisis

↓ Placenta weight/

↑Placenta praevia rate

↑Maternal Mortality

Treatment

Hydrea

- Decrease the rate of ACS, pain crisis and transfusion
- Increases fetal hemoglobin
- Reduce mortality

Stem cell transplant (cure)

- Children with strokes
- HLA match sibling

Treatment for pain crisis

- IVF
- Pain medication
- -oral
- -IV
- Transfusion(sparingly)
- Oxygen
- Iron chelation

Treatment for sickle cell disease

- Treatments that may be needed to manage complications of sickle cell anemia include:
- Dialysis or kidney transplant for kidney disease
- Counseling for psychological complications
- Gallbladder removal in people with gallstone disease
- Hip replacement for avascular necrosis of the hip
- Surgery for eye problems
- Treatment for overuse or abuse of narcotic pain medicines
- Wound care for leg ulcers
- Bone marrow or stem cell transplants can cure sickle cell anemia. However, they are currently not an option for most patients. Sickle cell anemia patients are often unable to find well-matched stem cell donors.
- People with sickle cell disease must reduce their risk of infections. This includes receiving certain vaccinations, including:
- Haemophilus influenzae vaccine (Hib)
- Pneumococcal conjugate vaccine (PCV)
- Pneumococcal polysaccharide vaccine (PPV)

Economical complications

- Enormous(frequent hospitalization)
- Lack of education
- Unemployed
- Poverty
- Neglect
- Disability

Emergency Department Visits of Sickle Cell Disease Patients by Age, 1999–2007

0–9 years	12.2%
10–19 years	15.0%
20–29 years	31.1%
30–45 years	34.6%
45+ years	7.0%

Drug dependency

- Common
- Difficult to manage
- Hard to separate physical from psychological dependency
- Early intervention/avoiding narcotics
- Alternative to narcotics
- Abuse/depression

Narcotic dependency

- The physical craving for pain meds

- Withdrawl symptoms
- Sweats, abd pain, n/v, headache,
- Tachycardia, anxiety and agitation
- Seizure and the shakes
- Narcotics should be withdrawn slowly

Narcotic abuse

- Unfortunate consequence

  Demerol/ dilaudid/morphine
- Recurrent admission
- Dishonesty about level of pain
- Medical personnel mistrust