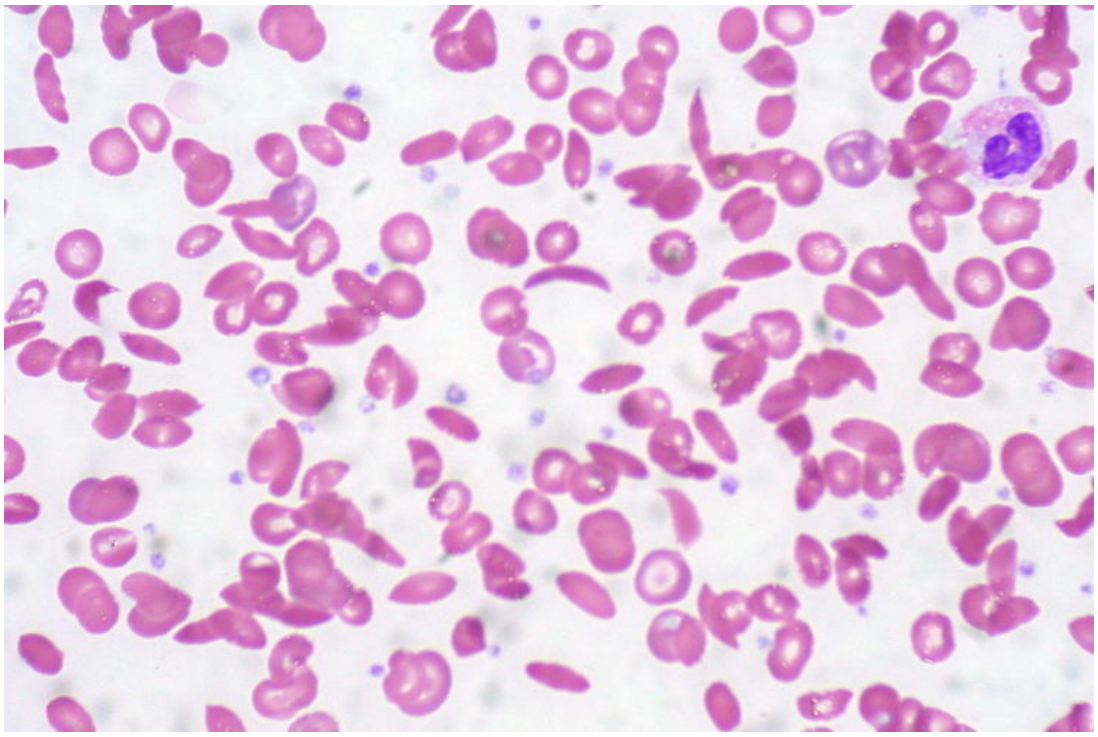
Sickle Cell Anemia

See online here



Sickle cell disease (SCD) is an inherited hemoglobinopathy with a mutation in the β-globin chain. Low oxygen tension results in sickling of the abnormal hemoglobin within the red blood cells, which presents as ischemia or hemolysis. As a chronic illness, patients depend on pain management. Disease management encompasses acute care, prevention, and screening for complications.

Epidemiology and Etiology

Epidemiology

- Most common in people of Sub-Saharan African, Mediterranean, and Middle Eastern heritage
- 1 in 500 inhabitants of Sub-Saharan Africa
- Equally present between males and females

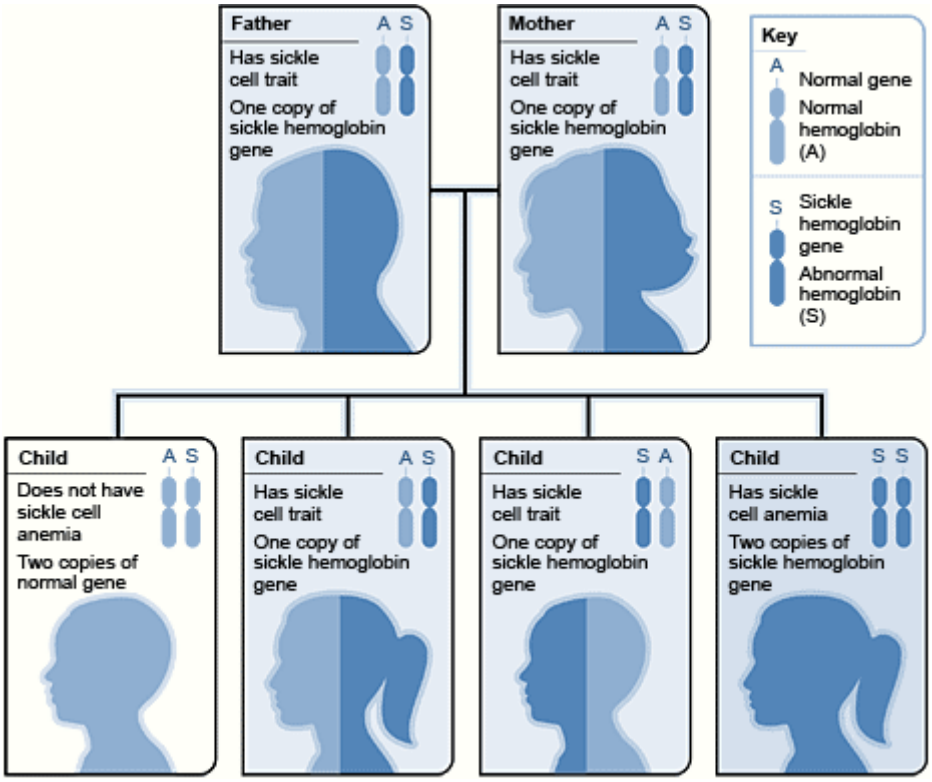


Image: “Mode of Inheritance in Sickle Cell Disease” by the National Heart Lung and Blood Insitute (NIH). License: Public Domain

Etiology

- Autosomal recessive inheritance pattern
- Mutation in the β-globin gene
- HbS gene is a point mutation
- Chromosome 11, codon 6 – position 15.5 – adenine → thymine (GAG → GTG)
- Amino acid substitution at position 6; glutamic acid → valine
- Homozygous: two HbS genes → sickle cell disease (HbSS)
- Heterozygous: one HbS gene → sickle cell trait (HbAS)
- Compound heterozygous: one HbS gene, one HbC gene (HbSC)
- HbC is a hemoglobinopathy where glutamic acid → lysine at the sixth position of the β-globin gene

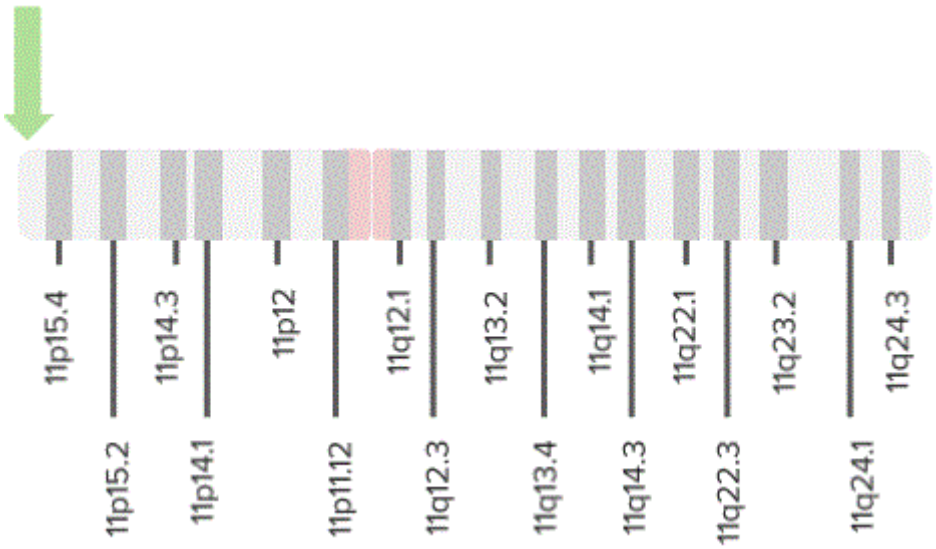


Image: “Sickle Cell Disease. Point mutation” By Lecturio.

Video Gallery

Sickle Cell Anemia by Kevin Ahern, PhD
Sickle Cell Anemia: Etiology by Carlo Raj, MD
Pediatric Sickle Cell Disease by Brian Alverson, MD

Pathophysiology

- HbS is prone to polymerization with other hemoglobin molecules under conditions of low oxygen tension.
- Polymerization results in a rigid structure that distorts the membrane.
- Membrane damage results in calcium influx and efflux of potassium and water, which dehydrates the RBC giving it the characteristic sickle shape.
- Sickling is aggravated by:
    - Infection
    - Dehydration
    - Hypoxia
    - Fever
    - Acidosis
- The fragile cell leads to hemolysis and vessel occlusion
- Hemoglobin released from hemolyzed cells readily binds to NO
- Depletion of NO results in vascular smooth muscle cell contraction and platelet aggregation
- There is a shortened half-life of the HbS containing RBCs to 12 days (average is 120 days)
- The sickle-shaped cell and shortened half-life renders immunity to malaria

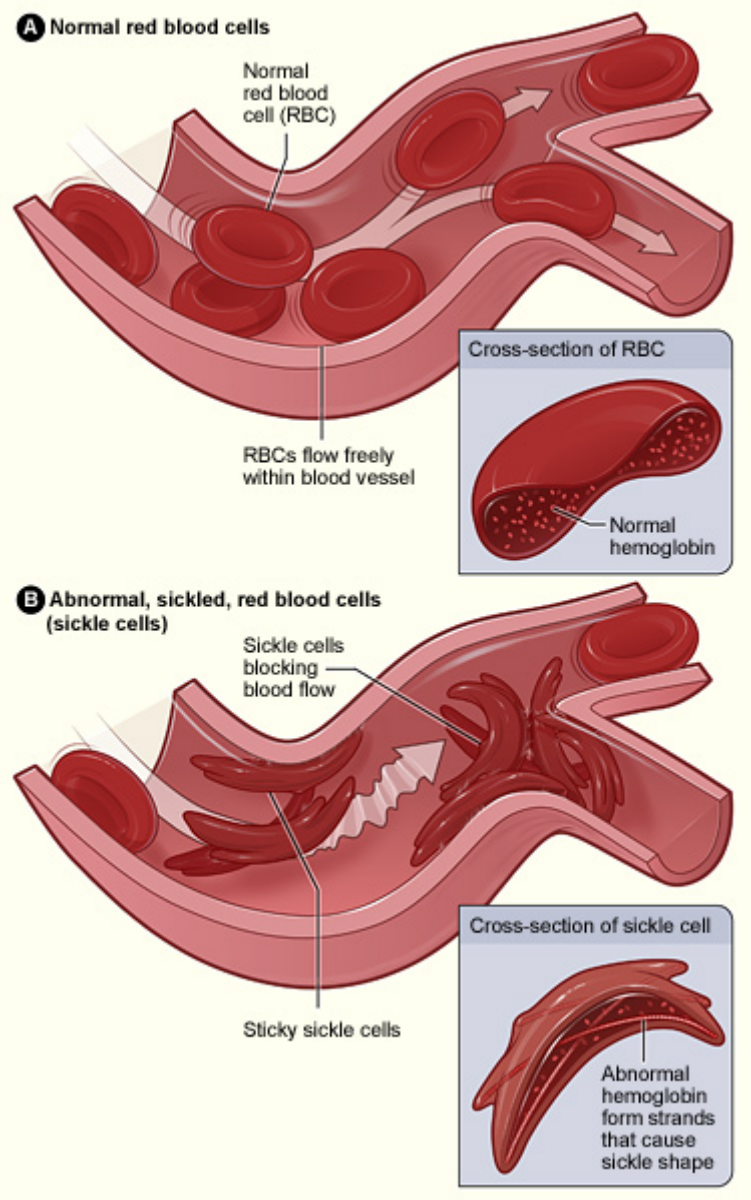


Image: “Abnormal Hemoglobin results in Sickling” Figure A shows normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin. Figure B shows abnormal, sickled red blood cells blocking blood flow in a blood vessel. The inset image shows a cross-section of a sickle cell with abnormal (sickle) hemoglobin forming abnormal strands. By The National Heart, Lung, and Blood Institute. License: Public Domain

Clinical manifestations

Mechanism	Symptoms
Chronic hemolysis (intravascular/extravascular)	• Anemia ◦ SOB ◦ Fatigue ◦ Tachycardia ◦ Growth Retardation • Splenomegaly (child) • Cholelithiasis

Vaso-occlusive crisis (infarction)	Fever plus any of the following: • CNS: ischemic stroke • Eyes: retinopathy, blindness • Lung: cor pulmonale • Heart: silent myocardial infarction • Spleen: autosplenectomy (adults) • Kidney: glomerulonephritis, proteinuria, hematuria, renal papillary necrosis • GI: acute abdomen • Liver: RUQ syndrome (RUQ pain and jaundice) • Penis: painful priapism • Bones: osteomyelitis, septic arthritis • Skin: ulceration
Acute pain crisis	• Splenic sequestration: ◦ In children ◦ Spleen pools blood → shock (low Hb) • Acute chest syndrome: ◦ Fever ◦ Hypoxia ◦ Chest pain: ■ Myocardial infarction ■ Pneumonia ■ Pulmonary fat embolism • Infections/bacteremia: ◦ Auto-splenectomy → encapsulated organisms ◦ *Streptococcus pneumoniae* ◦ *Haemophilus influenzae* ◦ *Neisseria meningitidis* ◦ Osteomyelitis (salmonella, *Staph. Aureus*) • Aplastic crisis: ◦ Transient bone marrow suppression secondary to parvovirus B19

Video Gallery

Sickle Cell Anemia: Vaso-occlusive Crisis by Carlo Raj, MD

Diagnostics

- **CBC**
  - ↓↓ Hb (Hb <6)
  - Normal MCV
  - ↑↑ retic
  - ↓ Hct
  - ↓ ESR
  - ↑ WBC
  - ↑ bilirubin
  - ↑ BUN, ↑ creatinine
  - LFT -↑ AST/ALT
- **Sickle Smear Prep:** expose smear to sodium metabisulfite → low oxygen tension
  - Best initial test
  - Sickle cell
  - Howell-Jolly bodies (patients with autosplenectomy)
  - Cannot differentiate between HbAS and HbSS
- Hb electrophoresis
  - Most accurate test

        - No HbA
        - HbS band (90%)
        - HbA2 normal
        - ↑↑ HbF (8%)
        - In sickle cell trait: HbA is present, HbS is 45%
    - Genetic screening

Diagnostic tests useful in complications		
Complication	**Test**	**Findings**
Acute chest syndrome	ECG	Myocardial infarction (STEMI/NSTEMI changes)
	CXR	Pneumonia: consolidation
Vaso-occlusive crisis	X-ray	Avascular necrosis (MRI most accurate)
Septic arthritis	Joint aspiration	Increased leukocyte Salmonella-growth
Kidney	Urine-analysis	Hematuria Proteinuria Casts
CNS	CT/MRI	Stroke (ischemic)
Cardiac	ECHO	Pulmonary hypertension Systolic dysfunction

Video Gallery

Sickle Cell Anemia: Hemoglobin Electrophoresis by Carlo Raj, MD

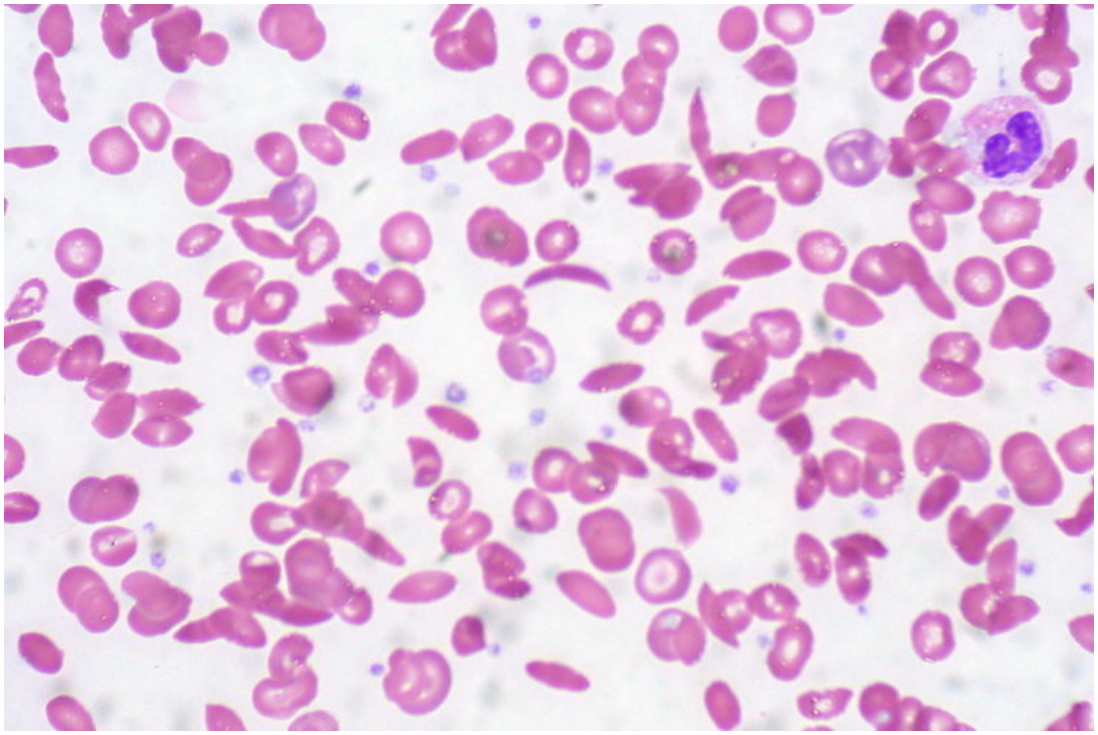


Image: “Sickle Cell Anemia” Peripheral blood smear by Ed Uthman. License: CC BY 2.0

Treatment

- Genetic counseling
- HbAS: no treatment needed
- HbSS:
    - Folic acid to compensate for high turn-over and folate deficiency
    - Hydroxyurea:
        - Enhances differentiation of stem cells to HbF
        - Reduces polymerization
    - Treating vaso-occlusive crisis
    - Screening for complications
    - Prevention of crisis: preventing infection, hypoxia, acidosis

Management of HbSS	
Symptom	**Management**
Acute pain crisis	• Oxygen • Hydration • Analgesics/opioids • Exchange transfusion ◦ Hb <6 ◦ ACS ◦ Aplastic crisis ◦ Splenic sequestration ◦ Stroke
Acute splenic sequestration	• Exchange transfusion • Splenectomy (delay until the age of 3–5 years)
Infections	Prevention: • Immunization: pneumococcus, meningococcal, and Hib • Prophylactic penicillin for children <5 years
Priapism	• Hydration • Analgesics

Aplastic Anemia	• IVIG (intravenous immunoglobin)
Screening	• Stroke: transcranial doppler; annually (age 2–16 years) • Retinopathy: retinal exam; annually (beginning at 10 years) • ECHO: pulmonary hypertension (childhood/early adulthood) • Urinalysis: annually for proteinuria/casts
Refractory	Hematopoietic stem cell transplant (HSCT) for: • Refractory to hydroxyurea • End organ damage • Child (age < 18)

Differential Diagnoses

- **Hemolytic Anemia**: encompasses anemia due to a shortened RBC half-life. Sickle cell disease is a form of hemolytic anemia. Other causes of hemolytic anemia must be considered as differential diagnoses.
- **Thalassemia:** An inherited deficiency in either the alpha (α) or beta (β) globin chain, resulting in hypochromic anemia. The presentation is mainly due to severe anemia, and the patient is transfusion dependent.

Notes