

# SICKLE CELL ANEMIA

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## Introduction: Hemoglobinopathies

Hemoglobinopathies are hereditary disorders caused by structural abnormalities in hemoglobin due to inherited mutations.

### Prototypic hemoglobinopathy: Sickle cell anemia

- Caused by mutation in  $\beta$ -globin gene
- Leads to formation of sickle hemoglobin (HbS)

✨ Numerous other hemoglobinopathies exist, but sickle cell anemia is the most common familial hemolytic anemia.

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## Epidemiology & Genetic Significance

- HbS provides protection against falciparum malaria

- Due to selective advantage, HbS allele is common in:
  - Equatorial Africa
  - Parts of India
  - Southern Europe
  - Middle East

### Statistics (High-Yield)

- ~8% of people of African descent → HbS heterozygous carriers
- ~1 in 600 → Sickle cell anemia (homozygous)

 Classic exam concept:

Malaria → natural selection → persistence of HbS allele

### NORMAL HEMOGLOBIN COMPOSITION

Hemoglobin	Structure	Percentage
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HbA	$\alpha_2 \beta_2$	~96%
HbA <sub>2</sub>	$\alpha_2 \delta_2$	~3%
HbF	$\alpha_2 \gamma_2$	~1%

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## GENETIC DEFECT IN SICKLE CELL ANEMIA

### Molecular Basis

- Single amino acid substitution in  $\beta$ -globin
- Position: 6th amino acid
- Change:
  - Glutamic acid (normal) → Valine (HbS)

 This small change has massive structural consequences.

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## PATHOGENESIS

## Core Mechanism Flowchart

- Deoxygenation of HbS → Conformational change in HbS → Self-association of HbS molecules → Polymer formation → Distortion of RBC membrane → Crescent / sickle-shaped RBC
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## Reversibility of Sickling

- Early sickling episodes:
    - Reversible on re-oxygenation
  - Repeated sickling:
    - Cumulative membrane damage
    - Becomes irreversible
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## Membrane Damage Cascade

- Repeated sickling → Membrane distortion → ↑ Calcium influx → Loss of potassium & water → RBC

dehydration → Damage to membrane skeleton →  
Irreversibly sickled cells → Hemolysis

 These irreversibly sickled cells are:


- Fragile
  - Short-lived
  - Prone to vascular obstruction
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## FACTORS AFFECTING HbS POLYMERIZATION

### I. Intracellular Hemoglobin Composition

HbA (Protective)

- Interacts weakly with deoxygenated HbS
- Retards polymerization

 Heterozygotes (HbAS):

- ~40% HbS
- ~60% HbA

- Minimal sickling in vivo

→ Sickle cell trait

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## HbF (Protective) 🧒

- Interacts weakly with HbS
- Delays disease onset

### 📌 Clinical correlation:

- Newborns with sickle cell anemia are asymptomatic
  - Symptoms appear when HbF falls  
→ Around 5-6 months of age
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## HbC (Another $\beta$ -globin mutation) 🔬

- Glutamic acid → Lysine at position 6
- Confers malaria protection
- Common in:
  - Sub-Saharan Africa
  - Parts of India

## Epidemiology:

- ~2.3% African-Americans → HbC carriers
  - ~1 in 1250 → HbC/HbS compound heterozygotes
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## 2. Intracellular Concentration of HbS

- Polymerization is concentration-dependent

### Promotes Sickling

- RBC dehydration → ↑ Hb concentration → ↑ HbS polymerization

### Reduces Sickling

- Coexisting  $\alpha$ -thalassemia → ↓ Hb concentration → ↓ polymerization
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## 3. Microvascular Transit Time

### Key concept:

Polymerization requires time.

- Normal capillary transit:
    - Too short for significant polymerization
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### Sites Most Vulnerable to Sickling

- Spleen
- Bone marrow

→ Blood flow is slow and sluggish

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### Role of Inflammation

- Inflammation causes:
    - ↑ Adhesion of RBCs & leukocytes to endothelium
    - ↑ Vascular permeability
    - Slowed blood flow
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## Adhesion Cascade Flowchart

- Repeated sickling → Membrane damage → RBCs become "sticky" → ↑ Adhesion to endothelium → Prolonged transit time → ↑ HbS polymerization → Vascular obstruction

 This is the basis of vaso-occlusive crises.

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## KEY TAKEAWAY SUMMARY

Feature	Sickle Cell Anemia
Defect	$\beta$ -globin mutation
Amino acid change	Glutamate → Valine
Hb involved	HbS
Shape	Sickle / crescent

Hemolysis	Both intra & extravascular
Protection	Against falciparum malaria
Onset in infants	After 5-6 months
Key pathology	HbS polymerization

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## Major Pathologic Consequences of Sickling ⚠️

Sickling of red cells leads to two major pathologic outcomes:

### I. Chronic Hemolytic Anemia

- Caused by repeated membrane damage
- Results in shortened RBC lifespan

 Key fact:


- Mean RBC lifespan  $\approx$  20 days  
(Normal  $\approx$  120 days)

 Severity correlates with:

- Fraction of irreversibly sickled cells
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## 2. Vascular Obstruction (Vaso-occlusion)

- Leads to:
  - Tissue ischemia
  - Infarction
  - Severe pain crises

 Important exam pearl:

Vaso-occlusion does NOT correlate with number of irreversibly sickled cells.

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## Triggers of Vaso-occlusive Crises

- Infection

- Inflammation
- Dehydration
- Acidosis

### Trigger Mechanism Flowchart

- Superimposed stress (infection / dehydration / acidosis) → Slowed microvascular flow → Prolonged RBC transit time → Deoxygenation of HbS → Sickling within microvasculature → Vaso-occlusion & ischemia

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## MORPHOLOGY

### Basis of Morphologic Changes


Abnormalities arise due to:

1. Chronic hemolytic anemia
2. Increased bilirubin from heme breakdown
3. Microvascular obstruction → ischemia & infarction

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## Peripheral Blood Smear

- Irreversibly sickled cells
  - Elongated
  - Spindled
  - Boat-shaped

 Diagnostic clue in homozygous disease

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## Bone Marrow

- Compensatory erythroid hyperplasia
- ↑ Reticulocyte production

## Skeletal Changes (Chronic Hemolysis)

- Marrow hyperplasia
  - Bone resorption
  - Secondary new bone formation

 Results in:

- Prominent cheekbones
  - "Crew-cut" skull appearance on X-ray
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## Extramedullary Hematopoiesis

- Liver
- Spleen

Seen in response to chronic anemia

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## Spleen Changes

### In Childhood

- Moderate splenomegaly  
(Weight up to 500 g)
- Due to congestion by trapped sickled RBCs

### Progression Over Time

- Chronic red cell stasis → Hypoxia → Repeated infarctions → Fibrosis

 End result:

- Autosplenectomy
  - Spleen reduced to a small fibrotic “nubbin” by adulthood
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Other Organ Involvement   

Vascular congestion, thrombosis & infarction can affect:

- Bones (most common)
- Liver
- Kidney
- Retina
- Brain
- Lung
- Skin

 Bone marrow vulnerability:

- Sluggish blood flow
- High metabolic demand

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## Priapism ⚠️

- Due to vaso-occlusion in penile vasculature
- May cause:
  - Penile fibrosis
  - Erectile dysfunction

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## Gallbladder 🟡

- Pigment gallstones
- Due to chronic hemolysis

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## CLINICAL FEATURES 🩺

### Age of Onset 🧒

- Usually asymptomatic until 6 months
- Symptoms begin after:
  - HbF → HbS transition

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## Anemia

- Moderate to severe
- Hematocrit: 18-30%  
(Normal: 38-48%)

## Associated findings:

- Hyperbilirubinemia
- Reticulocytosis

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## VASO-OCCLUSIVE CRISES

### General Characteristics

- Severe pain
- Recurrent
- Major cause of morbidity & mortality

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### Major Types of Crises

## 1. Hand-Foot Syndrome (Dactylitis) 🖐️🦶

- Infarction of bones of hands & feet
  - Most common presenting symptom in young children
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## 2. Acute Chest Syndrome 🫁⚠️

- Triggered by:
  - Pneumonia
  - Fat emboli from infarcted bone

### Pathogenesis Flowchart 🔄

- Lung inflammation → Sluggish pulmonary blood flow  
→ Sickling in hypoxemic lung beds → Worsening hypoxia → More sickling → Vicious cycle of vaso-occlusion

📌 One of the leading causes of death

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## 3. Stroke 🧠

- Often associated with acute chest syndrome
  - Major cause of ischemia-related mortality
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#### 4. Proliferative Retinopathy

- Due to retinal vaso-occlusion
  - Can cause:
    - Visual loss
    - Blindness
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### APLASTIC CRISIS

- Sudden ↓ RBC production
- Usually caused by Parvovirus B19

#### Mechanism Flowchart

- Parvovirus B19 infection → Infection of erythroblasts → Temporary marrow suppression → Rapid worsening of anemia

 Severe but self-limited

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## INFECTIONS IN SICKLE CELL DISEASE

Why Infection Risk Is High

- Functional asplenia:
    - Children: congested spleen
    - Adults: autosplenectomy
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Common Pathogens

- Encapsulated bacteria
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
- Osteomyelitis pathogens
  - *Salmonella*
  - *E. coli*

 Osteomyelitis often follows bone infarction

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## DIAGNOSIS

### Peripheral Smear

- Homozygous disease:
  - Irreversibly sickled cells seen routinely
- Sickle cell trait:
  - Sickling induced in vitro by hypoxia

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### Screening & Genetic Diagnosis

- Newborn screening (mandated in USA)
  - Heel-stick blood
  - Hb electrophoresis
- Prenatal diagnosis
  - Amniocentesis
  - Chorionic villus sampling
  - Fetal DNA analysis

# TREATMENT & PROGNOSIS

## Supportive Care

- Vaccination
- Prophylactic penicillin (especially <5 years)

 Has significantly improved survival

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## Hydroxyurea

A mainstay of therapy

## Mechanisms

- ↑ HbF production
- ↓ WBC count → anti-inflammatory
- ↑ RBC size → ↓ Hb concentration
- Metabolized to NO
  - Vasodilation
  - ↓ Platelet aggregation

 Results:

- ↓ Pain crises
  - ↓ Severity of anemia
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## Curative Therapies (Emerging) 🌱

- Allogeneic bone marrow transplantation
- Corrective gene therapy

📌 Both are potentially curative

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## PROGNOSIS 📈

- Highly variable
  - With modern care:
    - ~50% survive beyond 50 years
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## Concept 🏆

Sickle cell anemia causes chronic hemolytic anemia and episodic vaso-occlusive crises due to HbS

polymerization, leading to multisystem ischemic injury.

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-> The End <-