Thrombotic Complications in Sickle Cell Anemia

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Learning Outcomes

Introduction/Pathophysiology

Symptoms

Diagnosis/Treatment

Sickle Cell Crisis

Hypercoagulability

Factors that lead to Thrombosis

Impaired Fibrinolysis

Decreased levels of Natural Anticoagulants

Treatment Regimes

Introduction

Sickle Cell Anemia (SCA): Inherited, marked by abnormal hemoglobin

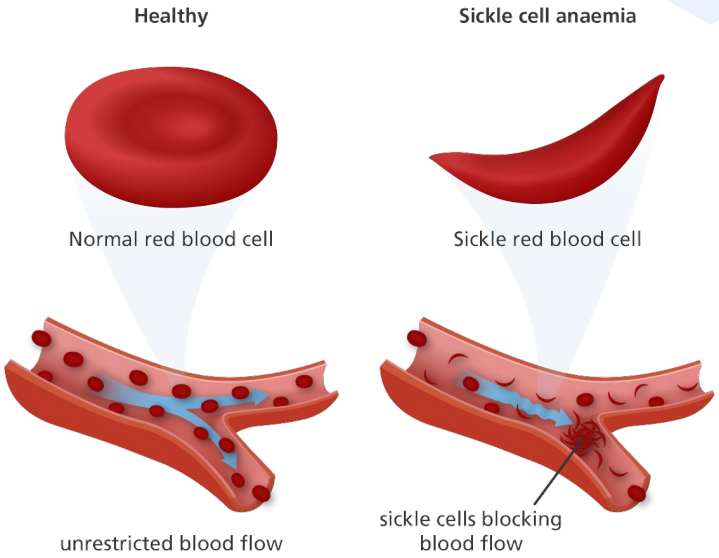
Sickle RBCs: Rigid, block blood flow; pain, organ damage

Lifespan: Normal RBCs: 120 days; sickle cells: 10–20 days

Anemia: Fewer RBCs; can lead to fatigue, complications

Trait: One sickle gene and one normal gene

VOC: Painful blockages



Pathophysiology

HBB Gene Mutation: Substitution (Glu → Val) at position 6 of β-globin; creates HbS

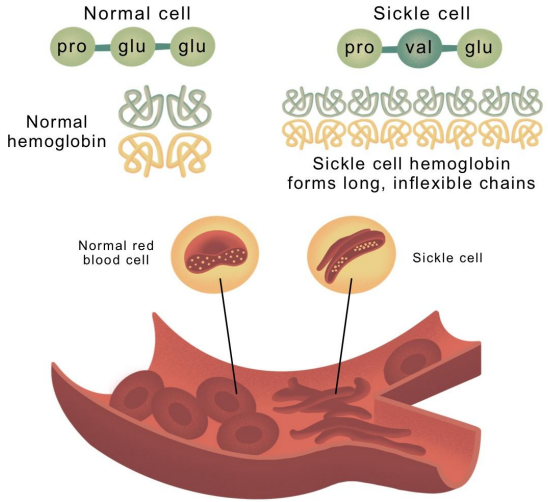
HbS Polymerization: Low O_2; HbS sticks together and RBCs sickle

Rigid RBCs: Deformed cells block small vessels → vaso-occlusion

Hemolysis: Sickled RBCs rupture early → chronic anemia

Endothelial Damage: Free heme, inflammation → vessel wall activation

Prothrombotic State: ↑ Tissue Factor, platelets, microparticles → clots



Epidemiology

Prevalence: Common in African, Mediterranean, Middle Eastern, Indian populations

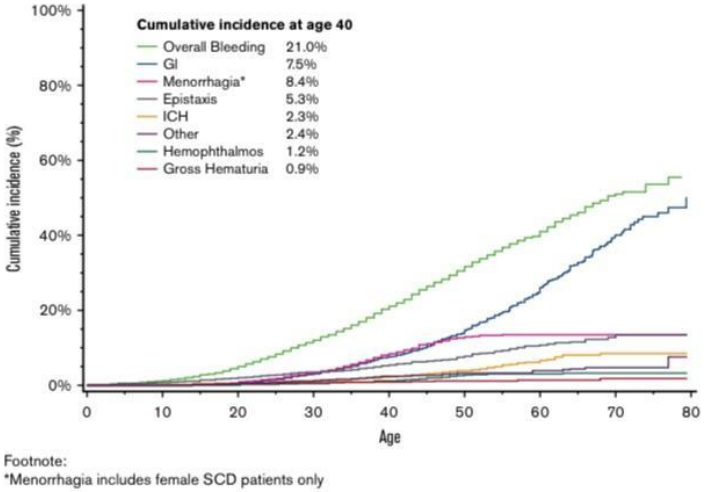
U.S. Statistics: 1 in 365 African American births have SCA

Trait: 1 in 13 African Americans carry sickle gene

Malaria Link: Sickle trait offers partial malaria protection

Incidence Rates

Summary: This study analyzed how often bleeding events occur in SCD patients, identify risk factors, and further examine how bleeding relates to mortality rates. They found that bleeding, specifically gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and hematuria was quite common and sometimes serious enough to require hospitalization.



Footnote:
*Menorrhagia includes female SCD patients only

Incidence Rates:

- 21% by age 40; 41% by age 60
- GI: 41.6% of cases were 4x higher than general population
- ICH: 178.9 per 100,000

Risk factors:

- VTE within 180 days before the bleed (HR 4.24).
- Frequent hospital stays (HR 2.16).

Bleeding in patients with sickle cell disease: a population-based study

Nisha Hariharan [1], Ann Brunson [2], Anjlee Mahajan [2], Theresa H M Keegan [2], Ted Wun [2,3],

Symptoms

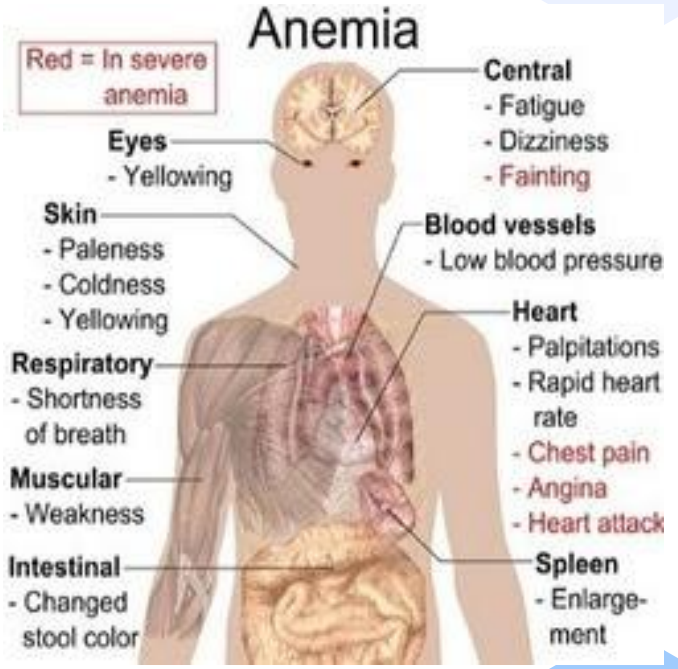
Acute Chest Syndrome: Chest pain, cough, fever, SOB; requires hospital care

Stroke: Sudden weakness, numbness, confusion, speech, vision issues

Avascular Necrosis: Blocked blood supply to bones; leads to tissue death and joint damage

Anemia: Dizziness, SOB

Jaundice: Yellow skin and eyes from rapid RBC breakdown



Diagnosis & Treatment

Tests: Blood test and genetic testing; detect HbS

Prenatal: Amniotic fluid or placental tissue sample

Newborn: Heel prick to collect blood on filter paper; lab analysis

Bone marrow transplant: Traditional curative option

Gene therapy: New FDA-approved treatments

Hydroxyurea: Oral medication — ↓ sickling, ↓ complications

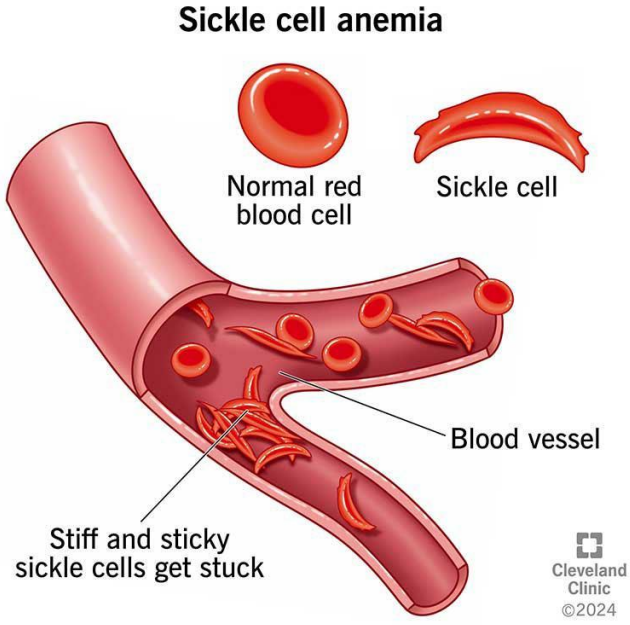
Sickle Cell Crisis

Cause: Blocked blood flow by misshapen, rigid sickle cells

Pain: Severe pain in chest, arms, and legs

Children: Swelling and pain in hands and/or feet

Impact: Organ damage, tissue death risk



Hypercoagulability in SCA Patients

A hypercoagulable state refers to an increased risk of forming blood clots caused by one or more underlying factors that can either be inherited or acquired.

- **Elevated Tissue Factor (TF) Expression:** Endothelial cells, monocytes and microparticles express ↑ TF; produce constant thrombin
- **Thrombin Overproduction:** Excess thrombin (↑ prothrombin fragment 1.2, TAT complexes)
- **Platelet Activation:** Chronic inflammation and sickled cells; ↑ platelet activation
- **Phosphatidylserine (PS) Exposure on Red Blood Cells (RBCs):** Sickled RBCs expose PS; promotes clotting
- **Chronic Inflammation and Hemolysis:** Hemolysis releases free heme and hemoglobin, forages for nitric oxide, drives endothelial activation and inflammation; ↑ clotting

Factors that lead to Thrombosis in SCA Patients

- **Chronic hemolysis:** Red blood cells (RBCs) hemolyze; releasing free hemoglobin and trigger clot risk.
- **Endothelial dysfunction:** Impaired vessel lining; ↑ clotting
- **Hypercoagulability:** Driven by ↑ TF, ↓ anticoagulants, ↑ platelets
    - **Elevated TF levels:** Hemolyzed endothelial cells and monocytes release more TF
    - **Decreased levels of natural anticoagulants:** ↓ protein C, S, antithrombin
    - **Increased platelet activation:** Sickled cells and chronic inflammation damage healthy tissue and activate platelets
- **Slow blood flow:** Enables clotting factors to build up
- **High white blood cell and hemoglobin levels:** Signal chronic inflammation; activates the clotting system
- **Low fetal hemoglobin (HbF%):** More severe sickling, resulting in more blockages and blood clot formation

Factors that lead to Thrombosis in SCA Patients (cont.)

- **Renal dysfunction:** Kidney damage results in fluid imbalance and inflammation
  - **Chronic inflammation:** Release of pro-inflammatory cytokines from immune cells; clot risk
- **Central venous catheters and hospitalization:** Central lines can irritate vessel walls and provide sites for clot formation
  - **Virchow's Triad:** Describes the three primary factors that increase the risk factor of developing DVT
    - **Venous Stasis:** Slow blood flow caused by low mobility
    - **Endothelial Injury:** Damage to the blood vessel lining from trauma, inflammation, or surgery
    - **Hypercoagulability:** "Thick blood" is more prone to clotting
- **Hydroxyurea use:** ↑ HbF but severe cases require frequent hospitalization and catheters
- **Pregnancy and estrogen therapy:** ↑ clotting factors; higher clot risk
- **Obesity and splenectomy:** Slow blood flow and inflammation; high clot risk
- **Genetic mutations:** Improper spleen function; abnormal cells stay longer

Impaired Fibrinolysis in SCA Patients

- **Study:** Examined how blood clotting and fibrinolysis are affected in patients with SCD; compared during baseline, crises, and infections
- **Results:** During infections, patients had a much lower ability to break down clots
- **Evidence:** Longer euglobulin lysis times, smaller lysis zones
- **Cause:** Vessel damage lowers body's production of plasminogen activator; less clot breakdown

Impaired fibrinolysis in sickle cell disease. Relation to crisis and infection

D Green et al. Thromb Diath Haemorrh. 1970.

Decreased Levels of Natural Anticoagulants

Summary:

- Researchers investigated whether children with SCA have decreased levels of natural anticoagulants
- Specifically Protein C, Protein S, and Antithrombin III (AT III)

Results:

- **Antithrombin III:** Significantly lower in SCA patients ($p<0.001$)
- **Protein C levels:** Significantly lower in SCA patients compared to healthy children ($p<0.001$)
- **Protein S levels:** Slightly lower in SCA patients than healthy children, but the difference was not statistically significant ($p>0.05$)

Conclusion:

- SCA kids show ↓ natural anticoagulants even when stable
- Confirms chronic hypercoagulable state
- Low anticoagulants may contribute to the increased risk of thrombosis and vaso-occlusion; stroke risk

Natural coagulation inhibitors (protein C, protein S, antithrombin) in patients with sickle cell anemia in a steady state

A K Bayazit et al. Pediatr Int. 2001 Dec.

Changes in Platelets, Endothelial Cells, and Microparticles in SCA

Platelets:

- **Hyperactivation and increased count:** ↑ count & activation (P-selectin); promote aggregation and adhesion
- **Endothelial stimulation:** Activated platelets trigger endothelial inflammatory/adhesion molecule expression (ICAM-1, VCAM-1, E-selectin) via NF-kB

Endothelial Cells:

- **Chronic activation:** ↑ TF & adhesion molecules due to heme/TNF-alpha and platelet/monocyte interactions
- **Inflammatory cross-talk:** Monocyte-derived TNF alpha activates endothelium

Microparticles:

- **Elevated levels:** RBCs, platelets, ECs, monocytes; carry TF, PS, and heme
- **Pro-thrombotic and inflammatory:** Promote coagulation, inflammation, and vaso-occlusion

TNF Alpha in Sickle Cell Disease

Summary:

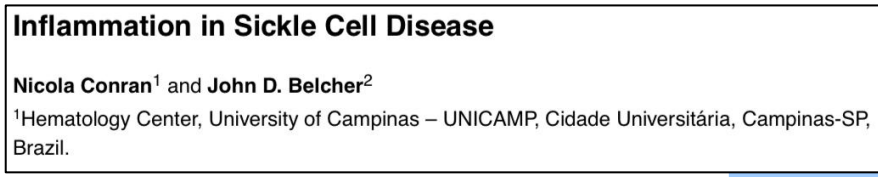
- Researchers investigated whether TNF-alpha contributes directly to endothelial cell activation and the inflammatory state in SCD, and whether blocking TNF-alpha can reduce this activation in a mouse model

Results:

- Sickle mice showed increased TNF-alpha levels and higher endothelial adhesion molecular expression compared to controls
- TNF-alpha directly unregulated VCAM-1 and ICAM-1 on ECs
- TNF-alpha inhibition with etanercept greatly reduced endothelial activation and lowered leukocyte adhesion in these mice

Conclusion:

- TNF-alpha drives endothelial cell activation; ↑ VCAM-1, ICAM-1
- "Stickier" vessels: binds sickled RBCs, platelets, leukocytes
- Promotes vaso-occlusion; local thrombin and microparticles released



Inflammation in Sickle Cell Disease

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Management of Thrombosis in SCD

- **General principles:** SCD is prothrombotic — ↑ thrombin, fibrin, TF
- **Antiplatelet therapy:** Aspirin, P2Y12 inhibitors — mixed results
- **Anticoagulation:** Heparins, LMWH, and DOACs — case-specific
- **TNF alpha inhibitors:** Experimental —↓ endothelial & TF activation
- **Hydroxyurea:** ↓ WBC & monocytes — ↓ TF & activation
- **Emerging targets:** Anti-P selectin — ↓ VOC, possible ↓ thrombosis

Treatment Regimes

- **Hydroxyurea:** ↑ HbF, ↓ WBC, TF, monocytes
- **Antiplatelet agents:** Block platelet activation
- **Anticoagulants:** Inhibit coagulation cascade
- **Crizanlizumab (anti-P selectin)**: Blocks P-selectin (adhesion, inflammation)
- **TNF alpha inhibitors:** ↓ Monocyte and endothelial activation
- **Complement inhibitors:** Limit hemolysis damage
- **Transfusion:** Lowers HbS levels
- **Curative (gene therapy):** Stops defective RBC production

Conclusion

Complications

- SCA is caused by a mutation in the HBB gene, producing HbS
- Sickled cells block vessels; anemia, pain and tissue damage
- Triggers chronic inflammation and endothelial dysfunction
- Leads to serious symptoms

Diagnosis and Treatment

- Genetic and blood tests
- Hydroxyurea, blood transfusions, anticoagulants
- Gene defects, P-selectin, and TNF-alpha

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References

Bayazit, A.K., and Y. Kilinç. "Natural Coagulation Inhibitors (Protein C, Protein S, Antithrombin) in Patients with Sickle Cell Anemia in a Steady State." *Pediatric International,* vol. 43, no. 6, Dec. 2001, pp. 592-596. *PubMed,* doi:10.1046/j.1442-200x.2001.01476.x. Accessed 5 July 2025.

Belcher JD et al. "TNF-alpha is a mediator of inflammation in sickle cell disease." Blood. 2003;101(10):3943–3948. PMID: 12531797

Clopton, Jennifer. "Sickle Cell Crisis." *WebMD,* medically reviewed by Melinda Ratini, MS, DO, 29 Oct. 2024, https://www.webmd.com/a-to-z-guides/sickle-cell-crisis. Accessed 24 June 2025.

Green, D., H. C. Kwaan, and G. Ruiz. *Impaired Fibrinolysis in Sickle Cell Disease: Relation to Crisis and Infection*. Northwestern Division of Medicine and the Hektoen Institute for Medical Research, Cook County Hospital, and the Veterans Administration Research Hospital, Chicago, Illinois 60611.

Hariharan, Nisha, et al. "Bleeding in Patients with Sickle Cell Disease: A Population-Based Study." *Blood Advances,* vol. 4, no. 5, 10 Mar. 2020, pp. 793-802. American Society of Hematology, doi:10.1182/bloodadvances.2019000940.

References

Hernández Castillo, Anna. *Hypercoagulable State: What Is It, Causes, Pregnancy, Diagnosis, Treatment, and More*. Edited by Antonella Melani and Ian Mannarino, illustrated by Abbey Richard, Osmosis, 4 Mar. 2025, https://www.osmosis.org/answers/hypercoagulable-state. Accessed 30 June 2025.

Lizarralde-Iragorri, Maria Alejandra, and Anita Shet. *"Sickle Cell Disease: A Paradigm for Venous Thrombosis Pathophysiology." International Journal of Molecular Science,* vol. 21, no. 15, 2020, p. 5279. MDPI, doi:10.3390/ijms21155279

"Sickle Cell Disease." *National Heart, Lung, and Blood Institute,* U.S. Dept. of Health and Human Services, 30 Sept. 2024, www.nhlbi.nih.gov/health/sickle-cell-disease. Accessed 17 June 2025.

Srisuwananukorn, Anant, et al. *"Clinical, Laboratory, and Genetic Risk Factors for Thrombosis in Sickle Cell Disease." Blood Advances,* vol. 4, no. 23, 2020, pp. 5823-5832. American Society of Hematology, doi:10.1182/bloodadvances.2020001989