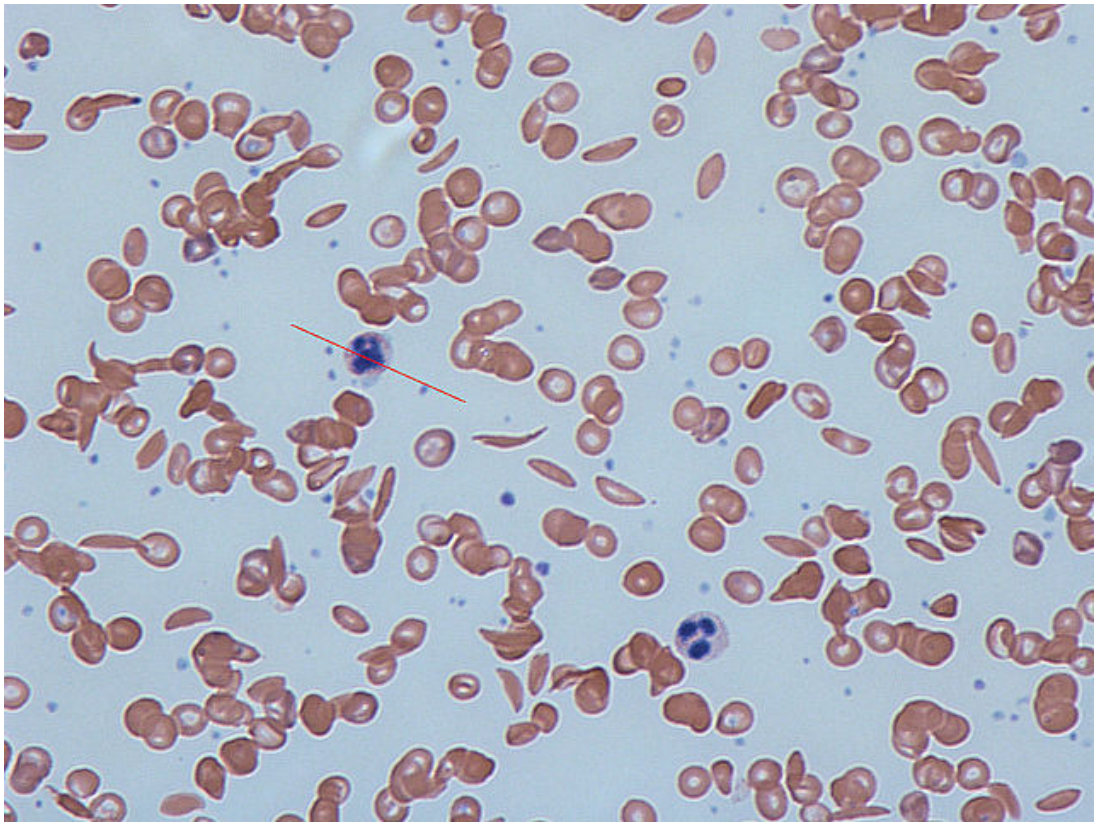
Normocytic Anemia: Sickle Cell Anemia (Sickle Cell Disease)

See online here

Sickle cell anemia leads to the sickling of erythrocytes during hypoxic conditions. This can occlude blood vessels and may manifest as other clinical presentations. Transfusion of red blood cell concentrates and treatment with hydroxyurea are viable options to manage this condition.



Definition of Sickle Cell Anemia

Sickle cell anemia is an inherited variant of hemolytic anemia based on a point mutation. Erythrocytes contain sickle cell hemoglobin (Hb-S) instead of normal hemoglobin.

Epidemiology of Sickle Cell Anemia

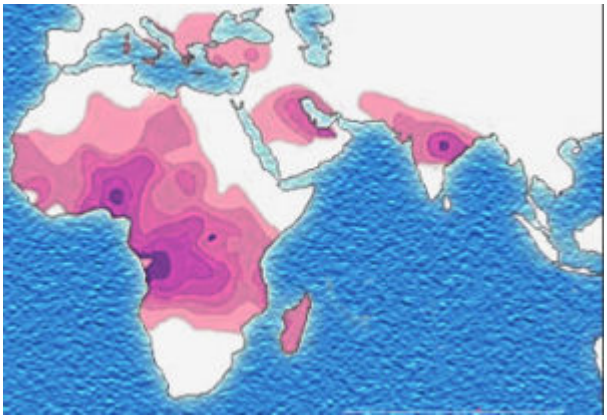


Image: “Distribution of the Sickle-cell Trait Shown in Pink and Purple,” by Muntuwandi. License: CC BY-SA 3.0

Sickle cell anemia is a condition exclusively found in African Americans and dark-skinned individuals.

Etiology and Pathogenesis of Sickle Cell Anemia

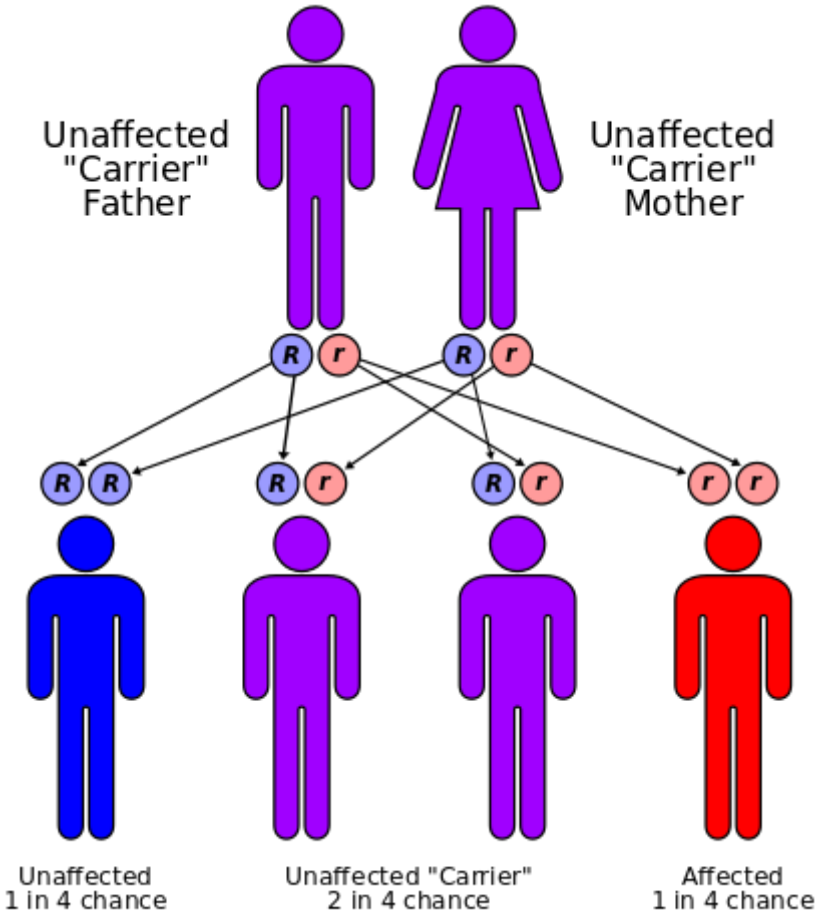


Image: “Sickle Cell Disease is Inherited in an Autosomal Recessive Pattern,” by C Burnett. License: CC BY-SA 3.0

Sickle cell anemia results from a base mutation in the DNA (thymine, instead of adenine), which is characterized by the exchange of an amino acid at position 6 of the ß-chain of hemoglobin. Genetically, this is a point mutation that results in the crystallization of the altered hemoglobin in the erythrocytes. When the partial pressure of oxygen decreases,

the erythrocytes assume a characteristic sickle shape, leading to micro-embolism and infarction.

The severity of the disease depends on the level of Hb-S in the erythrocytes, which is determined by hereditary disposition and the inheritance model. While heterozygosity leads to **Hb-S levels** of < 50%, homozygosity results in Hb-S values of approximately 70–99%.

Since crystallization of Hb-S depends on the partial pressure of oxygen, symptoms of sickle cell anemia mainly manifest in situations leading to hypoxia. Excessive physical exertion, infections, living at higher altitudes, increased exposure to cold weather, as well as surgeries can lead to hemolytic crises.

The diagrammatic representation above indicates the following:

- Point mutation in the ß-globin gene causing glutamate-valine substitution at amino acid 6 (Hb-S)
- Autosomal recessive inheritance

Clinical Presentation of Sickle Cell Anemia

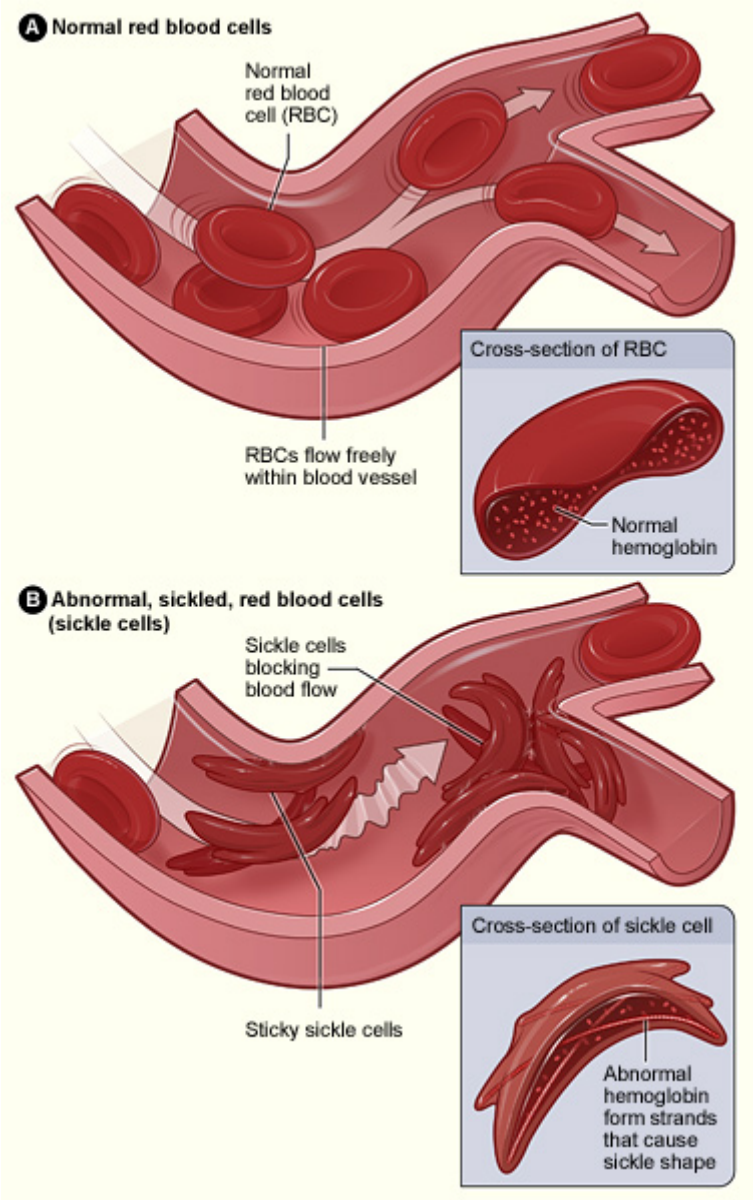


Figure A: Normal Red Blood Cells (RBCs) Flowing Freely in a Blood Vessel. Inset: Cross-section of a Normal RBC With Normal Hemoglobin. Figure B: Abnormal, Sickled RBCs Blocking Blood Flow in a Blood Vessel. Inset: Cross-section of a Sickle Cell with Abnormal (Sickle) Hemoglobin Forming Abnormal Strands.

Patients with sickle cell anemia show typical symptoms of chronic hemolytic anemia. Additionally, they suffer from abdominal colic; bone and joint pain have also been reported by some patients. Owing to the pathogenesis, infarcts are frequently observed in the kidneys, spleen, lung, liver, and bone tissue. In children, the earliest clinical sign is the conspicuous shortening of extremities (**hand-foot syndrome**).

Deoxyhemoglobin S has a tendency to polymerize, which causes sickling of the erythrocytes when oxygen levels are low. This phenomenon can result in the following outcomes:

- Infection
- Dehydration
- Hypoxia

Sickle cells are cleared in the spleen, which results in hemolytic anemia. Consequently, they occlude the splenic microvasculature, causing vaso-occlusive crises.

Vaso-occlusion can lead to the following conditions:

- Pain: Microvascular ischemia causing severe pain (almost all patients with sickle cell anemia are eventually addicted to opiates)
- Acute chest syndrome: Hypoxemia caused by microvascular disease of the lungs
- Stroke
- Autosplenectomy: Involution of the spleen causing susceptibility to infections by encapsulated bacteria (almost all patients are auto-splenectomized by adulthood)
- Painful priapism

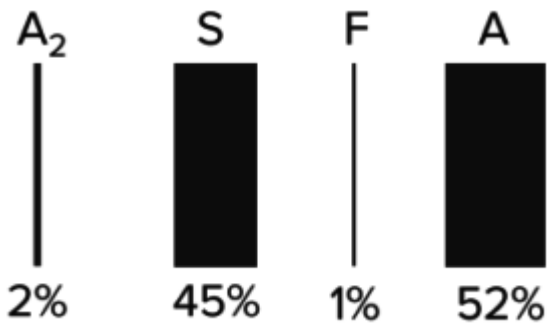
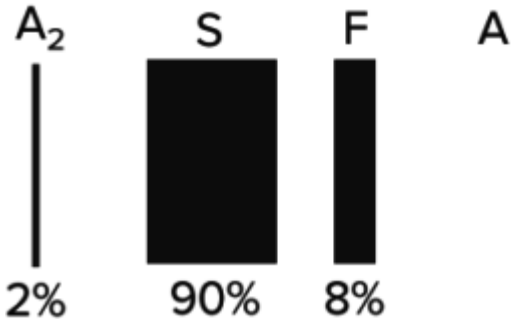
Patients are also susceptible to the following conditions:

- Aplastic crisis with parvovirus B-19 infection
- *Salmonella* osteomyelitis
- Sequelae of chronic hemolytic anemia

Diagnosis of Sickle Cell Anemia

- Newborn screening: Genetic test for *E6V* mutation
- Sickle prep: Peripheral blood smear shows sickled cells after treatment with sodium metabisulfite
- Hemoglobin electrophoresis

Hemoglobin electrophoresis

	**No anemia**	**Sickle cell trait** Note that there is inadequate Hb-S to cause spontaneous sickling in the peripheral blood.
	**Normocytic**	**Sickle cell disease** Note that there is no Hb-A; however, there is adequate Hb-S to cause spontaneous sickling.

Therapy of Sickle Cell Anemia

The **minor form** usually does not require treatment. The **major form** often leads to death in childhood, if untreated. Thus, allogeneic **HLA-identical bone marrow transplantation** should be attempted if the affected individual has siblings as a donor. Otherwise, therapy for the major form is symptomatic and limited to avoiding situations

of oxygen deficiency. Repletion of folate and transfusion of red blood cell concentrates constitute viable options. Additionally, the following interventions may be considered:

- Hydroxyurea (to increase the production of fetal hemoglobin over Hb-S)
- Bone marrow transplantation
- Fluid-replacement therapy
- Use of analgesics

Course and Prognosis of Sickle Cell Anemia

Owing to Hb-S values between 25 and 50%, the heterozygous form of this disorder rarely shows symptoms; thus, for practical purposes, it is not considered a disease. A state of hypoxia, e.g., after severe exertion or due to prior infectious diseases, can trigger hemolytic crises; however, life expectancy is not significantly affected. In addition, individuals with sickle cell anemia exhibit resistance against **malaria tropica** owing to the point mutation and the resulting morphological changes of the erythrocytes.

Patients with homozygous sickle cell anemia tend to be severely ill as their Hb-S values are between 70 and 99%. If untreated, homozygous and double heterozygous patients die during their childhood.

References

Baldwin, C. (2003). *Sickle cell disease*. Chicago, IL: Heinemann Library.

Gold, S. D. (2001). *Sickle cell disease*. Berkeley Heights, NJ: Enslow.

Peterson, J. M. (2009). *Sickle cell anemia*. New York: Rosen Pub.

Sills, R. H. (2003). *Practical algorithms in pediatric hematology and oncology*. Basel: Karger.

Notes