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Editorial

Sickle cell disease (SCD) is a group of blood disorders typically inherited. The most common type is known as **sickle cell anaemia**. It results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells. This leads to a rigid, sickle-like shape under certain circumstances. Problems in sickle cell disease typically begin around 5 to 6 months of age. A number of health problems may develop, such as attacks of pain (known as a **sickle cell crisis**), anemia, swelling in the hands and feet, bacterial infections, and stroke. Long-term pain may develop as people get older. The average life expectancy in the developed world is 40 to 60 years.

Sickle cell disease occurs when a person inherits two abnormal copies of the β -globin gene (*HBB*) that makes haemoglobin, one from each parent. This gene occurs in chromosome 11. Several subtypes exist, depending on the exact mutation in each haemoglobin gene. An attack can be set off by temperature changes, stress, dehydration, and high altitude. A person with a single abnormal copy does not usually have symptoms and is said to have sickle cell trait. Such people are also referred to as carriers. Diagnosis is by a blood test, and some countries test all babies at birth for the disease. Diagnosis is also possible during pregnancy.

The care of people with sickle cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication. Other measures may include blood transfusion and the medication hydroxycarbamide (hydroxyurea). A small percentage of people can be cured by a transplant of bone marrow cells.

The “**DISEASE DIAGNOSIS**” segment of this issue outlines SICKLE CELL DISEASE for you in ample details yet in a simplified format.

“**INTERPRETATION**” interprets for you **HEMOGLOBIN PATTERNS IN COMMON HEMOGLOBINOPATHIES** in a tabular and descriptive form “**TROUBLE SHOOTING**” defines the term Hemoglobinopathy and enumerates the various types of Hemoglobins encountered in clinical practice alongwith features that one comes across in those anomalous Hemoglobins.

Nothing, yes nothing, has been omitted. Flip over to believe!.



DISEASE DIAGNOSIS

Sickle Cell Disease (SCD)

Background

Carriers of the sickle cell trait (ie, heterozygotes who carry one HbS allele and one normal adult hemoglobin [HbA] allele) have some resistance to the often-fatal malaria caused by *Plasmodium falciparum*. This property explains the distribution and persistence of this gene in the population in malaria-endemic areas. However, in areas such as the United States, where malaria is not a problem, the trait no longer provides a survival advantage. Instead, it poses the threat of SCD, which occurs in children of carriers who inherit the sickle cell gene from both parents (ie, HbSS). Although carriers of sickle cell trait do not suffer from SCD, individuals with one copy of HbS and one copy of a gene that codes for another abnormal variant of hemoglobin, such as HbC or Hb beta-thalassemia, have a less severe form of the disease.

Genetics

SCD denotes all genotypes containing at least one sickle gene, in which HbS makes up at least half the hemoglobin present. Major sickle genotypes described so far include the following:

- HbSS disease or sickle cell anemia (the most common form) - Homozygote for the S globin with usually a severe or moderately severe phenotype and with the shortest survival
- HbS/b-0 thalassemia - Double heterozygote for HbS and b-0 thalassemia; clinically indistinguishable from sickle cell anemia (SCA)
- HbS/b+ thalassemia - Mild-to-moderate severity with variability in different ethnicities
- HbSC disease - Double heterozygote for HbS and HbC characterized by moderate clinical severity
- HbS/hereditary persistence of fetal Hb (S/HPHP) - Very mild or asymptomatic phenotype
- HbS/HbE syndrome - Very rare with a phenotype usually similar to HbS/b+ thalassemia
- Rare combinations of HbS with other abnormal hemoglobins such as HbD Los Angeles, G-Philadelphia, HbO Arab, and others.

Sickle cell trait or the carrier state is the heterozygous form characterized by the presence of around 40% HbS, absence of anemia, inability to concentrate urine (isosthenuria), and hematuria. Under conditions leading to hypoxia, it may become a pathologic risk factor. SCD is the most severe and most common form. Affected individuals present with a wide range of clinical problems that result from vascular obstruction and ischemia. Although the disease can be diagnosed at birth, clinical abnormalities usually do not occur before age 6 months, when functional asplenia develops. Functional asplenia results in susceptibility to overwhelming infection with encapsulated bacteria. Subsequently, other organs are damaged. Typical manifestations include recurrent pain and progressive incremental infarction.

Pathophysiology

HbS arises from a mutation substituting thymine for adenine in the sixth codon of the beta-chain gene, GAG to GTG. This causes coding of valine instead of glutamate in position 6 of the Hb beta chain. The resulting Hb has the physical properties of forming polymers under deoxy conditions. It also exhibits changes in solubility and molecular stability. These properties are responsible for the profound clinical expressions of the

sickling syndromes. Under deoxy conditions, HbS undergoes marked decrease in solubility, increased viscosity, and polymer formation at concentrations exceeding 30 g/dL. It forms a gel-like substance containing Hb crystals called tactoids. The gel-like form of Hb is in equilibrium with its liquid-soluble form. A number of factors influence this equilibrium, including oxygen tension, concentration of Hb S, and the presence of other hemoglobins. Oxygen tension is a factor in that polymer formation occurs only in the deoxy state. If oxygen is present, the liquid state prevails. Concentration of Hb S is a factor in that gelation of HbS occurs at concentrations greater than 20.8 g/dL (the normal cellular Hb concentration is 30 g/dL). The presence of other hemoglobins is a factor in that normal adult hemoglobin (HbA) and fetal hemoglobin (HbF) have an inhibitory effect on gelation. These and other Hb interactions affect the severity of clinical syndromes. HbSS produces a more severe disease than sickle cell HbC (HbSC), HbSD, HbSO Arab, and Hb with one normal and one sickle allele (HbSA). When red blood cells (RBCs) containing homozygous HbS are exposed to deoxy conditions, the sickling process begins. A slow and gradual polymer formation ensues. Electron microscopy reveals a parallel array of filaments. Repeated and prolonged sickling involves the membrane; the RBC assumes the characteristic sickled shape. (See image below.)



Molecular and cellular changes of hemoglobin S.

After recurrent episodes of sickling, membrane damage occurs and the cells are no longer capable of resuming the biconcave shape upon reoxygenation. Thus, they become irreversibly sickled cells (ISCs). From 5-50% of RBCs permanently remain in the sickled shape. **When RBCs sickle, they gain Na and lose K.** Membrane permeability to Ca increases, possibly due, in part, to impairment in the Ca pump that depends on adenosine triphosphatase (ATPase). The intracellular Ca concentration rises to 4 times the reference level. The membrane becomes more rigid, possibly due to changes in cytoskeletal protein interactions; however, these changes are not found consistently. In addition, whether calcium is responsible for membrane rigidity is not clear. **Membrane vesicle formation occurs, and the lipid bilayer is perturbed.** The outer leaflet has increased amounts of phosphatidyl ethanolamine and contains phosphatidylserine. The latter may play a role as a contributor to thrombosis, acting as a catalyst for plasma clotting factors. Membrane rigidity can be reversed in vitro by replacing HbS with HbA, suggesting that HbS interacts with the cell membrane.

Interactions with vascular endothelium

Complex multifactorial mechanisms involving endothelial dysfunction underlie the acute and chronic manifestations of SCD. A current model proposes that vaso-occlusive crises in SCD result from adhesive interactions of sickle cell RBCs and leukocytes with the endothelium. **In this model, the endothelium becomes activated by sickle cell RBCs,** either directly, through adhesion molecules on the RBC surface, or indirectly through plasma proteins (eg, thrombospondin, von Willebrand factor) that act as a soluble bridge molecule. This leads, sequentially, to recruitment of adherent leukocytes, activation of recruited neutrophils and of other leukocytes (eg, monocytes or natural killer T cells), interactions of RBCs with adherent neutrophils, and clogging of the vessel by cell aggregates composed of RBCs, adherent leukocytes, and possibly platelets. **Sickle cells express very late antigen-4 (VLA-4) on the surface.** VLA-4 interacts with the endothelial cell adhesive molecule, vascular cell adhesive molecule-1 (VCAM-1). VCAM-1 is upregulated by hypoxia and inhibited by nitric oxide. **Hypoxia also decreases nitric oxide production,** thereby adding to the adhesion of sickle cells to the vascular endothelium. Nitric oxide is a vasodilator. Free Hb is an avid scavenger of nitric oxide. Because of the continuing active hemolysis, there is free Hb in the plasma, and it scavenges nitric oxide, thus contributing to vasoconstriction. **In addition to leukocyte recruitment, inflammatory activation of endothelium may** have an indispensable role in enhanced sickle RBC-endothelium interactions. Sick cell adhesion in postcapillary venules can cause increased microvascular transit times and initiate vaso-occlusion. **Several studies have shown involvement of an array of adhesion molecules** expressed on sickle RBCs, including CD36, α -4- β -1 integrin, intercellular cell adhesion molecule-4 (ICAM-4), and basal cell adhesion molecule (B-CAM). Adhesion molecules (ie, P-selectin, VCAM-1, α -V- β -3 integrin) are also expressed on activated endothelium. Finally, plasma factors and adhesive proteins (ie, thrombospondin [TSP], von Willebrand factor [vWf], laminin) play an important role in this interaction. **For example, the induction of VCAM-1 and P-selectin on activated endothelium** is known to enhance sickle RBC interactions. In addition, α -V- β -3 integrin is upregulated in activated endothelium in patients with sickle cell disease. α -V- β -3 integrin binds to several adhesive proteins (TSP, vWf, red-cell ICAM-4, and, possibly, soluble laminin) involved in sickle RBC adhesion, and antibodies to this integrin dramatically inhibit sickle RBC adhesion. **In addition, under inflammatory conditions, increased leukocyte recruitment** in combination with adhesion of sickle RBCs may further contribute to stasis. **Sickle RBCs adhere to endothelium because of**

increased stickiness. The endothelium participates in this process, as do neutrophils, which also express increased levels of adhesive molecules. **Deformable sickle cells express CD18 and adhere abnormally** to endothelium up to 10 times more than normal cells, while ISCs do not. As paradoxical as it might seem, individuals who produce large numbers of ISCs have fewer vaso-occlusive crises than those with more deformable RBCs.

Other properties of sickle cells

Sickle RBCs also adhere to macrophages. This property may contribute to erythrophagocytosis and the hemolytic process. **The microvascular perfusion at the level of the pre-arterioles** is influenced by RBCs containing Hb S polymers. This occurs at arterial oxygen saturation, before any morphologic change is apparent. **Hemolysis is a constant finding in sickle cell syndromes.** Approximately one third of RBCs undergo intravascular hemolysis, possibly due to loss of membrane filaments during oxygenation and deoxygenation. The remainder hemolyze by erythrophagocytosis by macrophages. This process can be partially modified by Fc (crystallizable fragment) blockade, suggesting that the process can be mediated by immune mechanisms. **Sickle RBCs have increased immunoglobulin G (IgG) on the cell surface.** Vaso-occlusive crisis is often triggered by infection. Levels of fibrinogen, fibronectin, and D-dimer are elevated in these patients. Plasma clotting factors likely participate in the microthrombi in the pre-arterioles.

Development of clinical disease

Although hematologic changes indicative of SCD are evident as early as the age of 10 weeks, symptoms usually do not develop until the age of 6-12 months because of high levels of circulating fetal hemoglobin. After infancy, erythrocytes of patients with sickle cell anemia contain approximately 90% hemoglobin S (HbS), 2-10% hemoglobin F (HbF), and a normal amount of minor fraction of adult hemoglobin (HbA2). Adult hemoglobin (HbA), which usually gains prominence at the age of 3 months, is absent.

The physiological changes in RBCs result in a disease with the following cardinal signs:

1. Hemolytic anemia
2. Painful vaso-occlusive crisis
3. Multiple organ damage from microinfarcts, including heart, spleen, and central nervous system

Silent cerebral infarcts are associated with cognitive impairment in SCD. These infarcts tend to be located in the deep white matter where cerebral blood flow is low. However, cognitive impairment, particularly slower processing speed, may occur independent of the presence of infarction and may worsen with age.

Musculoskeletal manifestations

The skeletal manifestations of sickle cell disease result from changes in bone and bone marrow caused by chronic tissue hypoxia, which is exacerbated by episodic occlusion of the microcirculation by the abnormal sickle cells. The main processes that lead to bone and joint destruction in sickle cell disease are as follows:

- Infarction of bone and bone marrow
- Compensatory bone marrow hyperplasia
- Secondary osteomyelitis
- Secondary growth defects

When the rigid erythrocytes jam in the arterial and venous sinusoids of skeletal tissue, the result is intravascular thrombosis, which leads to infarction of bone and bone marrow. Repeated episodes of these crises eventually lead to irreversible bone infarcts and osteonecrosis, especially in weight-bearing areas. These areas of osteonecrosis (avascular necrosis/aseptic necrosis) become radiographically visible

as sclerosis of bone with secondary reparative reaction and eventually result in degenerative bone and joint destruction. **Infarction tends to occur in the diaphyses of small tubular bones** in children and in the metaphyses and subchondrium of long bones in adults. Because of the anatomic distribution of the blood vessels supplying the vertebrae, infarction affecting the central part of the vertebrae (fed by a spinal artery branch) results in the characteristic *H* vertebrae of sickle cell disease. The outer portions of the plates are spared because of the numerous apophyseal arteries. **Osteonecrosis of the epiphysis of the femoral head** is often bilateral and eventually progresses to collapse of the femoral heads. This same phenomenon is also seen in the humeral head, distal femur, and tibial condyles.

Infarction of bone and bone marrow in patients with sickle cell disease can lead to the following changes (see images below):

- Osteolysis (in acute infarction)
- Osteonecrosis (avascular necrosis/aseptic necrosis)
- Articular disintegration
- Myelosclerosis
- Periosteal reaction (unusual in the adult)
- *H* vertebrae (steplike endplate depression; also known as the Reynold sign or codfish vertebrae)
- Dystrophic medullary calcification
- Bone-within-bone appearance



Skeletal sickle cell anemia. H vertebrae. Lateral view of the spine shows angular depression of the central portion of each upper and lower endplate.



Skeletal sickle cell anemia. Bone-within-bone appearance. Following multiple infarctions of the long bones, sclerosis may assume the appearance of a bone within a bone, reflecting the old cortex within the new cortex.

The shortened survival time of the erythrocytes in sickle cell anemia (10-20 days) leads to a compensatory marrow hyperplasia throughout the skeleton. The bone marrow hyperplasia has the resultant effect of weakening the skeletal tissue by widening the medullary cavities, replacing trabecular bone and thinning cortices.

Deossification due to marrow hyperplasia can bring about the following changes in bone:

- Decreased density of the skull
- Decreased thickness of outer table of skull due to widening of diploe
- Hair-on-end striations of the calvaria
- Osteoporosis sometimes leading to biconcave vertebrae, coarsening of trabeculae in long and flat bones, and pathologic fractures

Patients with sickle cell disease can have a variety of growth defects due to the abnormal maturation of bone. The following growth defects are often seen in sickle cell disease:

- Bone shortening (premature epiphyseal fusion)
- Epiphyseal deformity with cupped metaphysis
- Peg-in-hole defect of distal femur
- Decreased height of vertebrae (short stature and kyphoscoliosis)

Go to Skeletal Sickle Cell Anemia for complete information on this topic. SCD can result in significant skeletal muscle remodeling and reduced muscle functional capacities, which contribute to exercise intolerance and poor quality of life. In addition, changes in muscle and joints can result in altered posture and impaired balance control.

Renal manifestations

Renal manifestations of SCD range from various functional abnormalities to gross anatomic alterations of the kidneys.

Splenic manifestations

The spleen enlarges in the latter part of the first year of life in children with SCD. Occasionally, the spleen undergoes a sudden very painful enlargement due to pooling of large numbers of sickled cells. This phenomenon is known as splenic sequestration crisis. **The spleen undergoes repeated infarction**, aided by low pH and low oxygen tension in the sinusoids and splenic cords. Despite being enlarged, its function is impaired, as evidenced by its failure to take up technetium during nuclear scanning. **Over time, the spleen becomes fibrotic and shrinks.** This is, in fact, an autosplenectomy. The nonfunctional spleen is a major contributor to the immune deficiency that exists in these individuals. Failure of opsonization and an inability to deal with infective encapsulated microorganisms, particularly *Streptococcus pneumoniae*, ensue, leading to an increased risk of sepsis in the future.

Chronic hemolytic anemia

SCD is a form of hemolytic anemia, with red cell survival of around 10-20 days. Approximately one third of the hemolysis occurs intravascularly, releasing free hemoglobin (plasma free hemoglobin [PFH]) and arginase into plasma. PFH has been associated with endothelial injury including scavenging nitric oxide (NO), proinflammatory stress, and coagulopathy, resulting in vasomotor instability and proliferative vasculopathy. **A hallmark of this proliferative vasculopathy is the development of pulmonary hypertension in adulthood.** Plasma arginase degrades arginine, the substrate for NO synthesis, thereby limiting the expected compensatory increase in NO production and resulting in generation of oxygen radicals. Plasma arginase is also associated with pulmonary hypertension and risk of early mortality.

Infection

Life-threatening bacterial infections are a major cause of morbidity and mortality in patients with SCD. Recurrent vaso-occlusion induces splenic infarctions and consequent autosplenectomy, predisposing to

severe infections with encapsulated organisms (eg, *Haemophilus influenzae*, *Streptococcus pneumoniae*). Lower serum immunoglobulin M (IgM) levels, impaired opsonization, and sluggish alternative complement pathway activation further increase susceptibility to other common infectious agents, including *Mycoplasma pneumoniae*, *Salmonella typhimurium*, *Staphylococcus aureus*, and *Escherichia coli*. Common infections include pneumonia, bronchitis, cholecystitis, pyelonephritis, cystitis, osteomyelitis, meningitis, and sepsis. *Pneumococcal sepsis continues to be a major cause of death* in infants in some countries. Parvovirus B19 infection causes aplastic crises.

Etiology

SCD originated in West Africa, where it has the highest prevalence. It is also present to a lesser extent in India and the Mediterranean region. DNA polymorphism of the beta S gene suggests that it arose from five separate mutations: four in Africa and one in India and the Middle East. The most common of these is an allele found in Benin in West Africa. The other haplotypes are found in Senegal and Bantu, Africa, as well as in India and the Middle East. *The HbS gene, when present in homozygous form*, is an undesirable mutation, so a selective advantage in the heterozygous form must account for its high prevalence and persistence. Malaria is possibly the selecting agent because a concordance exists between the prevalence of malaria and Hb S. Sickling might protect a person from malaria by either (1) accelerating sickling so that parasitized cells are removed or (2) making it more difficult for the parasite to metabolize or to enter the sickled cell. While children with sickle cell trait Hb SA seem to have a milder form of falciparum malaria, those with homozygous Hb S have a severe form that is associated with a very high mortality rate. *The sickling process that prompts a crisis may be precipitated by multiple factors*. Local tissue hypoxia, dehydration secondary to a viral illness, or nausea and vomiting, all of which lead to hypertonicity of the plasma, may induce sickling. Any event that can lead to acidosis, such as infection or extreme dehydration, can cause sickling. More benign factors and environmental changes, such as fatigue, exposure to cold, and psychosocial stress, can elicit the sickling process. A specific cause is often not identified.

Vaso-occlusive crises are often precipitated by the following:

- Cold weather (due to vasospasm)
- Hypoxia (eg, flying in unpressurized aircraft)
- Infection
- Dehydration (especially from exertion or during warm weather)
- Acidosis
- Alcohol intoxication
- Emotional stress
- Pregnancy

Data also suggest a role for exertional stress, particularly when compounded with heat and hypovolemia.

Aplastic crises are often preceded by the following:

- Infection with parvovirus B19
- Folic acid deficiency
- Ingestion of bone marrow toxins (eg, phenylbutazone)

Acute chest syndrome has been linked to the following:

- Fat embolism
- Infections
- Pain episodes
- Asthma.

Epidemiology

SCD is present mostly in blacks. It also is found, with much less

frequency, in eastern Mediterranean and Middle East populations. Individuals of Central African Republic descent are at an increased risk for overt renal failure.

International statistics

In several sections of Africa, the prevalence of sickle cell trait (heterozygosity) is as high as 30%. Although the disease is most frequently found in sub-Saharan Africa, it is also found in some parts of Sicily, Greece, southern Turkey, and India, all of which have areas in which malaria is endemic. *The mutation that results in HbS is believed to have originated* in several locations in Africa and India. Its prevalence varies but is high in these countries because of the survival advantage to heterozygotes in regions of endemic malaria. As a result of migration, both forced and voluntary, it is now found worldwide.

Sex distribution

The male-to-female ratio is 1:1. No sex predilection exists, since sickle cell anemia is not an X-linked disease. *Although no particular gender predilection has been shown in most series*, analysis of the data from the US Renal Data System demonstrated marked male predominance of sickle cell nephropathy in affected patients.

Clinical characteristics at different ages

Although hematologic changes indicative of the disorder are evident as early as the age of 10 weeks, clinical characteristics of SCD generally do not appear until the second half of the first year of life, when fetal Hb levels decline sufficiently for abnormalities caused by HbS to manifest. SCD then persists for the entire lifespan. After age 10 years, rates of painful crises decrease, but rates of complications increase. *The median age at the time of renal failure in patients* with SCD is 23.1 years, the median survival time after the diagnosis of ESRD is about 4 years, and the median age of death is 27 years, despite dialysis treatment.

Prognosis

Because SCD is a lifelong disease, prognosis is guarded. The goal is to achieve a normal life span with minimal morbidity. As therapy improves, the prognosis also improves. Morbidity is highly variable in patients with SCD, partly depending on the level of HbF. Nearly all individuals with the condition are affected to some degree and experience multiple organ system involvement. Patients with Hb SA are heterozygous carriers and essentially are asymptomatic. *Vaso-occlusive crisis and chronic pain are associated with considerable economic loss and disability*. Repeated infarction of joints, bones, and growth plates leads to aseptic necrosis, especially in weightbearing areas such as the femur. This complication is associated with chronic pain and disability and may require changes in employment and lifestyle.

Prognostic factors in SCD

The following prognostic factors have been identified as predictors of an adverse outcome:

- Hand-foot syndrome (dactylitis) in infants younger than 1 year
- Hb level of less than 7 g/dL
- Leukocytosis in the absence of infection

Hand-foot syndrome, which affects children younger than 5 years, has proved a strong predictor of overall severity (ie, death, risk of stroke, high pain rate, recurrent acute chest syndrome). Those that have an episode before age 1 year are at high risk of a severe clinical course. The risk is further increased if the child's baseline hemoglobin level is less than 7 g/dL or the baseline WBC count is elevated.

Pregnancy in SCD

Pregnancy represents a special area of concern. The high rate of fetal loss is due to spontaneous abortion. Placenta previa and abruption are common due to hypoxia and placental infarction. At birth, the infant often

is premature or has low birth weight.

Mortality in SCD

Mortality is high, especially in the early childhood years. Since the introduction of widespread penicillin prophylaxis and pneumococcal vaccination, a marked reduction has been observed in childhood deaths. The leading cause of death is acute chest syndrome. Children have a higher incidence of acute chest syndrome but a lower mortality rate than adults; the overall death rate from acute chest syndrome is 1.8% and 4 times higher in adults than in children. Causes of death are pulmonary embolism and infection. [In the Dallas newborn cohort, estimated survival at 18 years was 94%.](#) In a recent neonatal United Kingdom cohort followed in a hospital and community-based program including modern therapy with transcranial Doppler ultrasonography (TCD) screening, the estimated survival of HbSS children at 16 years was 99%. Data from the 1995 cooperative study of SCD (CSSCD) suggested that the median survival for individuals with SCD was 48 years for women and 42 years for men. This life expectancy was considerably lower than that for African Americans who do not have SCD. [In Africa, available mortality data are sporadic and incomplete.](#) Many children are not diagnosed, especially in rural areas, and death is often attributed to malaria or other comorbid conditions. [Data from Quinn et al in 2004 suggest that mortality from SCD has improved over the past 30 years.](#) In earlier reports, approximately 50% of patients did not survive beyond age 20 years, and most did not survive to age 50 years. [In one study, the median survival time in patients with SCD after the diagnosis of ESRD was about 4 years,](#) and the median age of death after diagnosis was 27 years, despite dialysis treatment. [The cooperative study of SCD \(CSSCD\) estimated that the median survival for individuals with SS was 48 years for women and 42 years for men.](#) In the Dallas newborn cohort, estimated survival at 18 years was 94%. In a recent neonatal United Kingdom cohort followed in a hospital and community-based program including modern therapy with TCD screening, the estimated survival of HbSS children at 16 years was 99%. [This significant increase in life expectancy and survival of patients with SCD has been achieved thanks to early detection and introduction of disease-modifying therapies.](#) Neonatal screening, penicillin prophylaxis for children, pneumococcal immunization, red cell transfusion for selected patients and chelation therapy, hydroxyurea therapy, parental and patient education and, above all, treatment in comprehensive centers have all likely contributed to this effect on longevity. [However, as the population of patients with SCD grows older,](#) new chronic complications are appearing. Pulmonary hypertension is emerging as a relatively common complication and is one of the leading causes of morbidity and mortality in adults with SCD. [A study of 398 outpatients with SCD in France found that the prevalence of pulmonary hypertension confirmed by right heart catheterization was 6%;](#) echocardiography alone had a low positive predictive value for pulmonary hypertension.

Patient Education

Patients must be educated about the nature of their disease. They must be able to recognize the earliest signs of a vaso-occlusive crisis and seek help, treat all febrile illness promptly, and identify environmental hazards that may precipitate a crisis. Reinforcement should occur incrementally during the course of ongoing care. [Patients or parents should be instructed on how to palpate the abdomen](#) to detect splenic enlargement, and the importance of observation for pallor, jaundice, and fever. Teach patients to seek medical care in certain situations, including the following:

- Persistent fever ($>38.3^{\circ}\text{C}$)

- Chest pain, shortness of breath, nausea, and vomiting
- Abdominal pain with nausea and vomiting
- Persistent headache not experienced previously

Patients should avoid the following:

- Alcohol
- Nonprescribed prescription drugs
- Cigarettes, marijuana, and cocaine
- Seeking care in multiple institutions

Families should be educated on the importance of hydration, diet, outpatient medications, and immunization protocol. Emphasize the importance of prophylactic penicillin. Patients on hydroxyurea must be educated on the importance of regular follow-up with blood counts. [Patients \(including asymptomatic heterozygous carriers\)](#) should understand the genetic basis of the disease, be educated about prenatal diagnosis, and know that genetic counseling is available. Genetic testing can identify parents at risk for having a child with sickle cell disease. [If both parents have the sickle cell trait,](#) the chance that a child will have sickle cell disease is 25%. If one parent is carrying the trait and the other actually has disease, the odds increase to 50% that their child will inherit the disease. Screening and genetic counseling theoretically have the potential to drastically reduce the prevalence of SCD. This promise has not been realized. Some authors have recommended emergency department screening or referral for patients unaware of their status as a possible heterozygote. [Families should be encouraged to contact community sickle cell agencies](#) for follow-up information, new drug protocols, and psychosocial support. Families should also follow the advances of gene therapy, bone marrow transplantation, and the usage of cord blood stem cells.

Clinical Presentation

History

Sickle cell disease (SCD) usually manifests early in childhood. For the first 6 months of life, infants are protected largely by elevated levels of Hb F; soon thereafter, the condition becomes evident. [The most common clinical manifestation of SCD is vaso-occlusive crisis.](#) A vaso-occlusive crisis occurs when the microcirculation is obstructed by sickled RBCs, causing ischemic injury to the organ supplied and resultant pain. Pain crises constitute the most distinguishing clinical feature of sickle cell disease and are the leading cause of emergency department visits and hospitalizations for affected patients. [Approximately half the individuals with homozygous Hb S disease](#) experience vaso-occlusive crisis. The frequency of crisis is extremely variable. Some have as many as 6 or more episodes annually, whereas others may have episodes only at great intervals or none at all. Each individual typically has a consistent pattern for crisis frequency. [Pain crises begin suddenly.](#) The crisis may last several hours to several days and terminate as abruptly as it began. [The pain can affect any body part.](#) It often involves the abdomen, bones, joints, and soft tissue, and it may present as dactylitis (bilateral painful and swollen hands and/or feet in children), acute joint necrosis or avascular necrosis, or acute abdomen. With repeated episodes in the spleen, infarctions and autosplenectomy predisposing to life-threatening infection are usual. The liver also may infarct and progress to failure with time. Papillary necrosis is a common renal manifestation of vaso-occlusion, leading to isosthenuria (ie, inability to concentrate urine). [Severe deep pain is present in the extremities, involving long bones.](#) Abdominal pain can be severe, resembling acute abdomen; it may result from referred pain from other sites or intra-abdominal solid organ or soft tissue infarction. Reactive ileus leads to intestinal distention and pain. [The face also may be involved.](#) Pain may be accompanied by

fever, malaise, and leukocytosis. **Bone pain is often due to bone marrow infarction.** Certain patterns are predictable, since pain tends to involve bones with the most bone marrow activity and because marrow activity changes with age. During the first 18 months of life, the metatarsals and metacarpals can be involved, presenting as dactylitis or hand-foot syndrome. **As the child grows older, pain often involves** the long bones of the extremities, sites that retain marrow activity during childhood. Proximity to the joints and occasional sympathetic effusions lead to the belief that the pain involves the joints. As marrow activity recedes further during adolescence, pain involves the vertebral bodies, especially in the lumbar region. **Although the above patterns describe** commonly encountered presentations, any area with blood supply and sensory nerves can be affected.

Triggers of vaso-occlusive crisis

Often, no precipitating cause can be identified. However, because deoxygenated hemoglobin S (HbS) becomes semisolid, the most likely physiologic trigger of vaso-occlusive crises is hypoxemia. This may be due to acute chest syndrome or accompany respiratory complications. **Dehydration can precipitate pain,** since acidosis results in a shift of the oxygen dissociation curve (Bohr effect), causing hemoglobin to desaturate more readily. Hemoconcentration also is a common mechanism. **Another common trigger is changes in body temperature**—whether an increase due to fever or a decrease due to environmental temperature change. Lowered body temperature likely leads to crises as the result of peripheral vasoconstriction. Patients should wear proper clothing and avoid exposure to ensure normal core temperature.

Chronic pain in SCD

Many individuals with SCD experience chronic low-level pain, mainly in bones and joints. Intermittent vaso-occlusive crises may be superimposed, or chronic low-level pain may be the only expression of the disease.

Anemia

Anemia is universally present. It is chronic and hemolytic in nature and usually very well tolerated. While patients with an Hb level of 6-7 g/dL who are able to participate in the activities of daily life in a normal fashion are not uncommon, their tolerance for exercise and exertion tends to be very limited. **Anemia may be complicated with megaloblastic changes** secondary to folate deficiency. These result from increased RBC turnover and folate utilization. Periodic bouts of hyperhemolysis may occur. **Children exhibit few manifestations of anemia** because they readily adjust by increasing heart rate and stroke volume; however, they have decreased stamina, which may be noted on the playground or when participating in physical education class.

Aplastic crisis

A serious complication is the aplastic crisis. This is caused by infection with Parvovirus B-19 (B19V). This virus causes fifth disease, a normally benign childhood disorder associated with fever, malaise, and a mild rash. This virus infects RBC progenitors in bone marrow, resulting in impaired cell division for a few days. Healthy people experience, at most, a slight drop in hematocrit, since the half-life of normal erythrocytes in the circulation is 40-60 days. In people with SCD, however, the RBC lifespan is greatly shortened (usually 10-20 days), and a very rapid drop in Hb occurs. The condition is self-limited, with bone marrow recovery occurring in 7-10 days, followed by brisk reticulocytosis.

Splenic sequestration

Splenic sequestration occurs with highest frequency during the first 5 years of life in children with sickle cell anemia. Splenic sequestration can occur at any age in individuals with other sickle syndromes. This

complication is characterized by the onset of life-threatening anemia with rapid enlargement of the spleen and high reticulocyte count. **Splenic sequestration is a medical emergency that demands prompt and appropriate treatment.** Parents should be familiar with the signs and symptoms of splenic sequestration crises. Children should be seen as rapidly as possible in the emergency room. Treatment of the acute episode requires early recognition, careful monitoring, and aggressive transfusion support. Because these episodes tend to recur, many advocate long-term transfusion in young children and splenectomy in older children.

Infection

As HbS replaces HbF in the early months of life, problems associated with sickling and red cell membrane damage begin. The resulting rigid cells progressively obstruct and damage the spleen, which leads to functional asplenia. This, along with other abnormalities, results in extreme susceptibility to infection. **Organisms that pose the greatest danger include encapsulated respiratory bacteria,** particularly *Streptococcus pneumoniae*. The mortality rate of such infections has been reported to be as high as 10-30%. Consider osteomyelitis when dealing with a combination of persistent pain and fever. Bone that is involved with infarct-related vaso-occlusive pain is prone to infection. *Staphylococcus* and *Salmonella* are the 2 most likely organisms responsible for osteomyelitis. **During adult life, infections with gram-negative organisms,** especially *Salmonella*, predominate. Of special concern is the frequent occurrence of *Salmonella* osteomyelitis in areas of bone weakened by infarction.

Effects on growth and maturation

During childhood and adolescence, SCD is associated with growth retardation, delayed sexual maturation, and being underweight. Rhodes et al demonstrated that growth delays during puberty in adolescents with SCD is independently associated with decreased Hb concentration and increased total energy expenditure. **Rhodes et al found that children with SCD** progressed more slowly through puberty than healthy control children. Affected pubertal males were shorter and had significantly slower height growth than their unaffected counterparts, with a decline in height over time; however, their annual weight increases did not differ. In addition, the mean fat free mass increments in affected males and females were significantly less than those of the control children.

Hand-foot syndrome

Infants with SCD may develop hand-foot syndrome, a dactylitis presenting as exquisite pain and soft tissue swelling of the dorsum of the hands and feet. The syndrome develops suddenly and lasts 1-2 weeks. Hand-foot syndrome occurs between age 6 months and 3 years; it is not seen after age 5 years because hematopoiesis in the small bones of the hands and feet ceases at this age. Osteomyelitis is the major differential diagnosis. **Cortical thinning and destruction of the metacarpal and metatarsal bones** appear on radiographs 3-5 weeks after the swelling begins. Leukocytosis or erythema does not accompany the swelling.

Acute chest syndrome

In young children, the acute chest syndrome consists of chest pain, fever, cough, tachypnea, leukocytosis, and pulmonary infiltrates in the upper lobes. Adults are usually afebrile and dyspneic with severe chest pain and multilobar and lower lobe disease. **Acute chest syndrome is a medical emergency and must be treated immediately.** Patients are otherwise at risk for developing acute respiratory distress syndrome. **Acute chest syndrome probably begins with infarction of ribs,** leading to chest splinting and atelectasis. Because the appearance of radiographic changes may be delayed, the diagnosis may not be recognized immediately. **In children, acute chest syndrome is usually due to**

infection. Other etiologies include pulmonary infarction and fat embolism resulting from bone marrow infarction. Recognition of the specific cause is less critical than the ability to assess the management and pace of the lung injury.

Central nervous system involvement

Central nervous system involvement is one of the most devastating aspects of SCD. It is most prevalent in childhood and adolescence. The most severe manifestation is stroke, resulting in varying degrees of neurological deficit. Stroke affects 30% of children and 11% of patients by 20 years. It is usually ischemic in children and hemorrhagic in adults. **Hemiparesis is the usual presentation.** Other deficits may be found, depending on the location of the infarct. **Convulsions are frequently associated with stroke.** Convulsions occur as an isolated event but also appear in the setting of evolving acute chest syndrome, pain crisis, aplastic crisis, and priapism. Rapid and excessive blood transfusion to a hemoglobin level of greater than 12 g/dL increases blood viscosity and can lead to stroke. **Children with sickle cell disease may have various anatomic and physiologic abnormalities** that involve the CNS even if they appear to be neurologically healthy. These silent brain infarcts occur in 17% of patients and may be associated with deterioration in cognitive function, with effects on learning and behavior; these infarcts may increase the potential risk for clinical and subclinical damage to the CNS. **Hemorrhagic stroke is often caused by rupture of aneurysms** that might be a result of vascular injury and tend to occur later in life. Moya moya, a proliferation of small fragile vessels found in patients with stenotic lesions, can also lead to cerebral hemorrhage. Hemorrhagic stroke is associated with a mortality rate of more than 29%.

Cardiac involvement

The heart is involved due to chronic anemia and microinfarcts. Hemolysis and blood transfusion lead to hemosiderin deposition in the myocardium. Both ventricles and the left atrium are all dilated. **A study by Nicholson et al also indicated that coronary artery dilation** is common in children with SCD. The prevalence of coronary artery ectasia in patients with SCD was 17.7%, compared with 2.3% for the general population. Furthermore, a systolic murmur is usually present, with wide radiation over the precordium.

Cholelithiasis

Cholelithiasis is common in children with SCD, as chronic hemolysis with hyperbilirubinemia is associated with the formation of bile stones. Cholelithiasis may be asymptomatic or result in acute cholecystitis, requiring surgical intervention. The liver may also become involved. Cholecystitis or common bile duct obstruction can occur. **Consider cholecystitis in a child who presents with right upper quadrant pain,** especially if associated with fatty food. Consider common bile duct blockage when a child presents with right upper quadrant pain and dramatically elevated conjugated hyperbilirubinemia.

Renal involvement

The kidneys lose concentrating capacity. Isosthenuria results in a large loss of water, further contributing to dehydration in these patients. Kidney failure may ensue, usually preceded by proteinuria. Nephrotic syndrome is uncommon but may occur.

Eye involvement

Paraorbital facial infarction may result in ptosis. Retinal vascular changes also occur. A proliferative retinitis is common in Hb SC disease and may lead to loss of vision. See Ophthalmic Manifestations of Sickle Cell Anemia for a complete discussion of this topic.

Leg ulcers

Leg ulcers are a chronic painful problem. They result from minor injury to the area around the malleoli. Because of relatively poor circulation,

compounded by sickling and microinfarcts, healing is delayed and infection becomes established.

Priapism

Priapism, defined as a sustained, painful, and unwanted erection, is a well-recognized complication of SCD. Priapism tends to occur repeatedly. When it is prolonged, it may lead to impotence. **According to one study, the mean age at which priapism occurs is 12 years,** and, by age 20 years, as many as 89% of males with sickle cell disease have experienced one or more episodes of priapism. Priapism can be classified as prolonged if it lasts for more than 3 hours or as stuttering if it lasts for more than a few minutes but less than 3 hours and resolves spontaneously. Stuttering episodes may recur or develop into more prolonged events. **Prolonged priapism is an emergency** that requires urologic consultation. Recurrent episodes of priapism can result in fibrosis and impotence, even when adequate treatment is attempted.

Avascular necrosis

Vascular occlusion can result in avascular necrosis (AVN) of the femoral or humeral head and subsequent infarction and collapse at either site. AVN of the femoral head presents a greater problem because of weight bearing. Patients with high baseline hemoglobin levels are at increased risk. Approximately 30% of all patients with SCD have hip pathology by age 30 years. **The natural history of symptomatic hip disease in patients with sickle cell disease** who are treated conservatively varies with the patient's age. In skeletally immature patients aged 12 years or younger, treatment with analgesics, NSAIDs, and protected weight bearing usually results in healing and remodeling of the involved capital epiphysis, similar to that observed in Legg-Calve-Perthes disease. This approach results in preservation of the joint despite the persistence of deformity, such as coxa magna and coxa plana. **In contrast, conservative management of osteonecrosis** usually fails in older adolescents and adults. Progressive flattening and collapse of the femoral head results in painful secondary degenerative arthritis.

Pulmonary hypertension

Blood in the pulmonary circulation is deoxygenated, resulting in a high degree of polymer formation. The lungs develop areas of microinfarction and microthrombi that hinder the flow of blood. The resulting areas that lack oxygenation aggravate the sickling process. Pulmonary hypertension may develop. This may be due in part to the depletion of nitric oxide. Various studies have found that more than 40% of adults with SCD have pulmonary hypertension that worsens with age. **This is increasingly recognized as a serious complication of sickle cell disease,** with an incidence as high as 31.8%. Familial clustering has also been recognized. Hemolysis, chronic hypoxia caused by sickle cell disease, and pulmonary disease (eg, recurrent acute chest syndrome, asthma, obstructive sleep apnea) are contributing factors. **Pulmonary hypertension is characterized by a regurgitant pulmonary (tricuspid) jet** velocity of more than 2.5 m/s by echocardiography. Recently, there has been a lot of debate about the positive predictive value of measuring tricuspid regurgitant jet velocity. A recent study found that in a population of sickle cell patients, 25% had a tricuspid regurgitant jet of more than 2.5 m/s, but only 6% had actual pulmonary hypertension on right-sided heart catheterization. It is associated with a high mortality rate in adult patients. Children with pulmonary hypertension have lower mortality, but the disease is associated with high morbidity.

Physical Examination

Physical findings are not specific. Scleral icterus is present, and, upon ophthalmoscopic examination of the conjunctiva with the +40 lens, abnormal or corkscrew-shaped blood vessels may be seen. The mucous membranes are pale. A systolic murmur may be heard over the entire

precordium. **Hypotension and tachycardia may be signs of septic shock or splenic sequestration crisis.** With the severe anemia that accompanies aplastic crisis, patients may exhibit signs of high-output heart failure. **Orthostasis suggests hypovolemia.** Tachypnea suggests pneumonia, heart failure, or acute chest syndrome. Dyspnea suggests acute chest syndrome, pulmonary hypertension, and/or heart failure. **Fever suggests infection in children;** however, it is less significant in adults unless it is a high-grade fever. Examine the head and neck for meningeal signs or possible source of infection (eg, otitis, sinusitis). **Auscultate the heart to search for signs of congestive heart failure.** Auscultate the lungs for signs of pneumonia, heart failure, or acute chest syndrome (similar to pulmonary embolism). Palpate for tenderness (abdomen, extremities, back, chest, femoral head) and hepatosplenomegaly. **In childhood, splenomegaly may be present,** although this is not present in adults due to autosplenectomy. Spleen size should be measured, and parents should be made aware of it. A tongue blade may be used as a "spleen stick" in a small child, with the upper end of the blade corresponding to the nipple in the midclavicular line and a marking made on the stick corresponding to the edge of the spleen. **Growth parameters show patients** falling below the growth isobars. This usually occurs around the prepubertal age because of delayed puberty. **Observe for pallor, icterus, and erythema or edema** of the extremities or joints. In adults, leg ulcers may be found over the malleoli. Perform a neurological examination to search for focal neurological deficits.

Ocular manifestations

Sickle cell vasoocclusive events can affect every vascular bed in the eye, often with visually devastating consequences in advanced stages of the disease.

Anterior segment abnormalities include the following:

- Segmentation "corkscrew" conjunctival vessel, more commonly seen in the inferior bulbar conjunctiva
- Iris infarct and atrophy
- Cataracts
- Phthisis bulbi
- Hyphema

The abnormalities of the posterior segment can be divided into 6 categories, as follows :

- Optic disc changes
- Posterior retinal and macular vascular occlusion Chronic macular changes (sickling maculopathy)
- Choroidal vascular occlusions
- Nonproliferative retinal changes
- Proliferative retinal changes

Optic disc changes

Intravascular occlusions on the surface of the optic disc appear ophthalmoscopically as dark-red intravascular spots. These occlusions are transient and do not produce any clinical impairment. These changes are most common in hemoglobin SS disease but can also occur in patients with hemoglobin SC and hemoglobin S.

Posterior retinal and macular vascular occlusions

Retinal artery occlusions are either central or branch. Peripapillary or macular arteriolar occlusions are rare. Retinal vein occlusions also are rare with SCD.

Chronic macular changes

Chronic macular vascular occlusions occur in SCD. These are manifested by microaneurysms resembling dots, hairpin-shaped vascular loops, and abnormal foveal avascular zone (FAZ).

Choroidal vascular occlusions

This is an extremely rare manifestation of SCD. Only 3 cases have been reported thus far in the literature.

Nonproliferative retinal changes

Nonproliferative or background sickle retinopathy includes the following manifestations:

- Venous tortuosity
- Salmon-patch hemorrhage
- Schisis cavity
- The black sunburst

Venous tortuosity probably is due to arteriovenous shunting from the retinal periphery. It can occur in many patients with hemoglobin SS and hemoglobin SC disease. **Salmon-patch hemorrhages are superficial intraretinal hemorrhages.** They are usually seen in the mid periphery of the retina adjacent to a retinal arteriole. **The schisis cavity is a space caused by the disappearance** of the intraretinal hemorrhage. Nonproliferative sickle retinopathy features iridescent spots and glistening refractive bodies in the schisis cavity. **The black sunburst consists of round chorioretinal scars** usually located in the equatorial fundus. These lesions result from pigment accumulated around the vessels. They do not cause any visual symptoms.

Proliferative sickle retinopathy

Proliferative sickle retinopathy (PSR) is the most severe ocular change in SCD. This is a peripheral retinal change most frequent in patients with hemoglobin SC but also can be present in patients with hemoglobin S–thalassemia disease, homozygous hemoglobin SS, and hemoglobin AS and hemoglobin AC disease. **PSR is progressive.** A desirable objective is to treat the neovascular tissue before a vitreous hemorrhage occurs.

Goldberg classified PSR into the following 5 stages:

1. Peripheral arteriolar occlusions
2. Arteriolar-venular anastomosis
3. Neovascular proliferation
4. Vitreous hemorrhage
5. Retinal detachment

In stage I, the peripheral arteriolar vessels occlude, with anteriorly located avascular vessels evident. Early in the process, the occluded arterioles are dark-red lines, but eventually they turn into silver-wire–appearing vessels.

In stage II, peripheral arteriolar-venular anastomosis occurs as the eye adjusts to peripheral arteriolar occlusion, and blood is diverted from the occluded arterioles into the adjacent venules. Peripheral to these anastomoses, no perfusion is present.

In stage III, new vessel formation occurs at the junction of the vascular and avascular retina. These neovascular tufts resemble sea fans. Initially, the sea fans can be fed by a single arteriole and draining vessel. Later, as the sea fan grows in size, it is difficult to distinguish the major feeding and draining vessels. The sea fans may acquire a glial and fibrotic tissue envelope. This envelope may pull on the vitreous. A full-thickness retinal break, which may lead to total rhegmatogenous retinal detachment, may occur. **For more information,** see Ophthalmologic Manifestations of Sickle Cell Disease (SCD).

Meningitis

Meningitis is 200 times more common in children with HbSS. Consider lumbar puncture in children with fever who appear toxic and in those with neurologic findings such as neck stiffness, positive Brudzinski or Kernig signs, or focal deficits. Meningeal signs are not reliable if the children are irritable and inconsolable.

Skeletal manifestations

The characteristic appearance in children with sickle cell disease includes frontal and parietal bossing and prominent maxilla due to marrow hyperplasia expanding the bone. The extremities may appear proportionately longer than normal because there is often flattening of the vertebrae. Bone marrow expansion often causes maxillary hypertrophy with overbite; orthodontics consultations are recommended to prevent or correct this problem. The physical findings of acute infarction include local effects from swelling of the affected bone, such as proptosis or ophthalmoplegia from orbital bone infarction. Also present is pain, swelling, and warmth of the involved extremity, such on the dorsa of the hands and feet in patients with dactylitis. Sequelae of chronic infarction include structural and functional orthopedic abnormalities. Examples include an immobile or nonfunctional shoulder joint, abnormal hip growth and deformity, secondary osteoarthritis, shortened fingers and toes, and kyphoscoliosis.

Hand-foot syndrome

Hand-foot syndrome, or aseptic dactylitis, is a common presentation of sickle cell disease. This condition is caused by infarction of bone marrow and cortical bone in the metacarpals, metatarsals, and proximal phalanges. Hand-foot syndrome is usually one of the earliest manifestations of the disease.

Acute bone pain crisis

Acute bone pain crisis is caused by bone marrow ischemia or infarction. These crises usually start after age 2-3 years and occur as gnawing, progressive pain, most commonly in the humerus, tibia, and femur and less commonly in the facial bones. Periarticular pain and joint effusion, often associated with a sickle cell crisis, are considered a result of ischemia and infarction of the synovium and adjacent bone and bone marrow. Patients with acute bone pain crisis usually present with fever, leukocytosis, and warmth and tenderness around the affected joints. This process tends to affect the knees and elbows, mimicking rheumatic fever and septic arthritis.

Osteonecrosis

In adolescence and adulthood, the most prominent complication is osteonecrosis of 1 or more epiphyses, usually of the femoral or humeral heads. Chronic pain is often associated with later stages of osteonecrosis, particularly in the femoral head. Pain due to avascular necrosis is most notable with weight bearing on the joint. Patients often have pain associated with functional limitation of the affected joint.

Osteomyelitis

Patients with sickle cell disease are prone to infection of the bone and bone marrow in areas of infarction and necrosis. Although *Staphylococcus aureus* is the most common cause of osteomyelitis in the general population, studies have shown that in patients with sickle cell disease, the relative incidence of *Salmonella* osteomyelitis is twice that of staphylococcal infection.

Differential Diagnoses

Diagnostic Considerations

SCD is suggested by the typical clinical picture of chronic hemolytic anemia and vaso-occlusive crisis. The diagnosis is confirmed when electrophoresis demonstrates the presence of homozygous HbS. In addition to HbSS, this test may also document other hemoglobinopathies (eg, HbSC, HbS-beta⁺ thalassemia). Sickling variants and sickle trait must be distinguished from HbS disease. HbS exists in combination with other hemoglobins in a double heterozygous state. The clinically important diseases involved, observed in patients in the United States, are HbSC and Hb-beta thalassemia. HbSC disease is

a milder sickling disorder. It is present in 1 in 1100 African Americans. In the HbC mutation, lysine replaces glutamic acid in position 6 on the beta chain. HbA is not present. The RBCs contain 50% HbS and 50% HbC. Anemia is much milder, with Hb levels of 11 g/dL or higher. Symptoms of HbSC disease are similar to SCD but less frequent and less severe. Splenomegaly often persists well into adult life. Aseptic necrosis of the femoral head is not more common than in SCD. A proliferative retinopathy may lead to progressive loss of vision. The diagnosis of HbSC disease is made with Hb electrophoresis. The peripheral blood smear may have some sickled cells and a high proportion of target cells. In addition, microcytic, dehydrated, dense RBCs are seen. These may contain crystal-like condensations. Treatment and management strategies are similar to those employed in HbS disease. In HbS-beta⁰ thalassemia, only HbS is found on electrophoresis. HbA₂ is elevated and splenomegaly usually is present. The clinical picture is similar to SCD but is slightly less severe. Management is similar to that for SCD. In HbS-beta⁺ thalassemia, Hb A is present, usually between 10% and 30%. The spleen is usually enlarged. This disease is otherwise similar to SCD but is milder. Sickle cell trait is the heterozygous carrier state of HbS. These individuals have approximately 40% HbS and 60% HbA, less so with coexisting alpha-thalassemia trait.

People with sickle trait generally are well and have the following characteristics:

- Normal life expectancy
- Not at excessive risk for infection
- Not subject to painful crisis under normal circumstances
- No anemia

Nevertheless, providing genetic counseling to prospective parents with sickle cell trait is important. Reports exist of excessive deaths under extreme conditions, such as military basic training involving strenuous exertion; however, this is very uncommon. Similarly, isolated reports exist of organ infarction and crisis under unusual circumstances. Many of these patients lose urine-concentrating capacity. Painless hematuria may be present. HbS variants may occur as double heterozygotes with other Hb variants. These include HbD, HbE, and HbO Arab. These are observed very infrequently in the United States, and information about them can be found in hematology texts.

Other problems to be considered

Gaucher disease also expands the marrow cavity and causes bone marrow infarction. Unlike sickle cell disease, which causes splenic infarction, Gaucher disease causes splenomegaly.

Depending on the clinical presentation, the differential diagnosis may also include the following:

- Valvular heart disease
- Septic arthritis
- Sepsis
- Upper respiratory tract infection
- Aortic arch syndrome
- Facioscapulohumeral muscular dystrophy
- Incontinentia pigmenti
- Familial exudative vitreoretinopathy
- Lupus erythematosus
- Macroglobulinemia
- Polycythemia vera
- Talc and cornstarch emboli
- Uveitis, including pars planitis

Differential Diagnoses

- Acute Anemia
- Carotid-Cavernous Fistula (CCF)

- Hemoglobin C Disease
- Hemolytic Anemia
- Legg-Calve-Perthes Disease Imaging
- Ophthalmologic Manifestations of Leukemias
- Osteomyelitis in Emergency Medicine
- Pulmonary Embolism (PE)
- Rheumatoid Arthritis Hand Imaging
- Septic Arthritis

Workup

Approach Considerations

Screening for hemoglobin S (HbS) at birth is currently mandatory in the United States. This method of case finding allows institution of early treatment and control. [Prenatal diagnosis is also available](#). The laboratory procedures employed in prenatal testing are sensitive and rapid. Prenatal testing must be accompanied with genetic and psychological counseling. Chorionic villus sampling can be performed at 8-12 weeks' gestation to obtain DNA. This low-risk procedure is safe. DNA from amniotic fluid cells can be examined at 16 weeks' gestation. Investigational attempts are ongoing to isolate fetal cells from maternal blood for DNA assay. [Children with sickle cell disease \(SCD\)](#) frequently have abnormal pulmonary function test (PFT) results. PFTs should be performed regularly in children with a history of recurrent acute chest episodes or low oxygen saturation. Because lung function declines with age, it is important to identify those who require close monitoring and treatment. [Newer techniques for noninvasive assessment of the brain](#) have also been used to identify children with asymptomatic brain disease. Transcranial near-infrared spectroscopy or cerebral oximetry is increasingly being used as a screening tool for low cerebral venous oxygen saturation in children with sickle cell disease. [Measurement of blood flow velocity by transcranial Doppler ultrasound \(TCD\)](#) has proved a good predictor of stroke risk. Although overall, children with SCD have a stroke risk of 1% per year, those with high cerebral blood flow velocities (time-averaged mean velocity >200 cm/s) have stroke rates of greater than 10% a year. TCD surveillance remains the gold standard for stroke risk prediction in children with TCD; annual TCD screening from 2 to 16 years of age has been recommended. [Consider lumbar puncture to exclude meningitis](#) if there is altered mental status, meningeal signs, or fever. When focal neurologic signs are present or intracranial hemorrhage is suspected, consider CT prior to lumbar puncture. Consider lumbar puncture if a subarachnoid hemorrhage is suspected and head CT is unrevealing. [Meningitis in children with SCD requires early recognition](#); aggressive diagnostic evaluation including CBC count, urinalysis, chest radiographs, and blood cultures; prompt administration of intravenous antibiotics active against *S pneumoniae*; and close observation. [Children younger than 12 months](#) with a temperature of higher than 39°C who appear toxic, with an infiltrate on chest radiograph and an elevated WBC count, should be admitted to the hospital. Consider only outpatient treatment if no high-risk features appear on history, physical examination, or laboratory evaluation; if the child is older than 12 months; and if outpatient follow-up care can be ensured. [According to the 2003 BCSH guidelines](#), a full blood count is required for all patients who are admitted to the hospital, with other investigations performed as necessitated by the clinical situation. Intravenous fluids are not routinely indicated, but should be given if the patient is unable to drink, has diarrhea or is vomiting. Nasogastric fluids are an appropriate alternative to IV fluids. [In acute chest syndrome, arterial blood oxygen saturation](#) commonly falls to a greater degree than that seen in simple pneumonia of the same magnitude. Patients with

acute chest syndrome often have progressive pulmonary infiltrates despite treatment with antibiotics. Infection may set off a wave of local ischemia that produces focal sickling, deoxygenation, and additional sickling. [The 2003 BCSH guidelines](#) strongly advocate the use of incentive spirometry for patients with chest or back pain.

Newborn hemoglobinopathy screening

The introduction of newborn screening has been one of the greatest advances in the management of sickle cell disease. Currently, 50 states and the District of Columbia have mandatory universal programs for newborn screening for hemoglobin disorders. Guidelines for screening for sickle cell disease in newborns have been established. If results are positive, a repeat hemoglobin electrophoresis should be performed for confirmation. [Fetal hemoglobin is predominant in young infants](#). If results show only hemoglobin (Hb) F and S, the child has either sickle cell anemia or HbS- β -0 thalassemia. If results show HbF, S, and C, the child has HbSC disease. If results show HbF, S, and A, determine whether the child has received a transfusion. [If the child has not received a transfusion and S is greater than A](#), HbS-beta+ thalassemia is most likely the diagnosis. If A is greater than S, the child is presumed to have the sickle trait. If A and S concentrations are close, conduct a study of the parents to determine if one of them has the thalassemia trait. Repeat Hb electrophoresis on the child after several months.

Hemoglobin electrophoresis

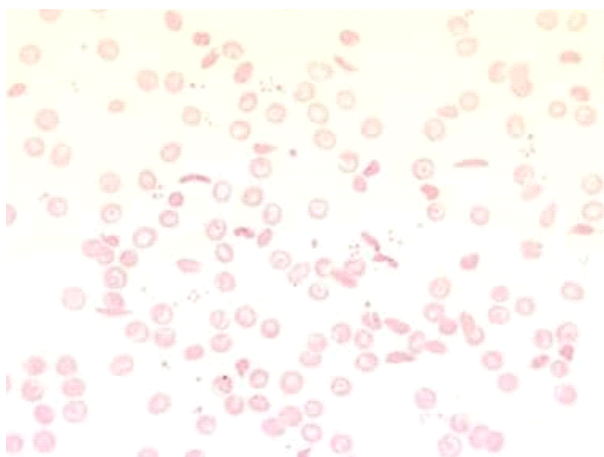
Hemoglobin electrophoresis differentiates individuals who are homozygous for HbS from those who are heterozygous. It establishes the diagnosis of SCD by demonstrating a single band of HbS (in HbSS) or HbS with another mutant hemoglobin in compound heterozygotes. [In children with normocytic hemolytic anemia](#), if results of electrophoresis show only HbS with an HbF concentration of less than 30%, the diagnosis is sickle cell anemia. If HbS and HbC are present in roughly equal amounts, the diagnosis is HbSC disease. [In children with microcytic hemolytic anemia](#), order quantitative Hb A₂ in addition to electrophoresis. If HbS is predominant, Hb F is less than 30% and Hb A₂ is elevated, a diagnosis of HbS-beta-0 thalassemia can be inferred. If possible, perform a study of the parents. If the HbA₂ level is normal, consider the possibility of concomitant HbSS and iron deficiency. If HbS is greater than A and HbA₂ is elevated, a diagnosis of HbS-beta+ thalassemia can be inferred. If HbS and HbC are present in equal amounts, the diagnosis is HbSC disease. [A homozygous patient will have hemoglobin SS](#) (HbSS, 80-90%), hemoglobin F (HbF, 2-20%), and hemoglobin A₂ (HbA₂, 2-4%). A carrier patient will have HbSS (35-40%) and hemoglobin A (HbA, 60-65%). The test is not accurate in a patient who has recently received blood transfusions.

Baseline Blood Study Abnormalities

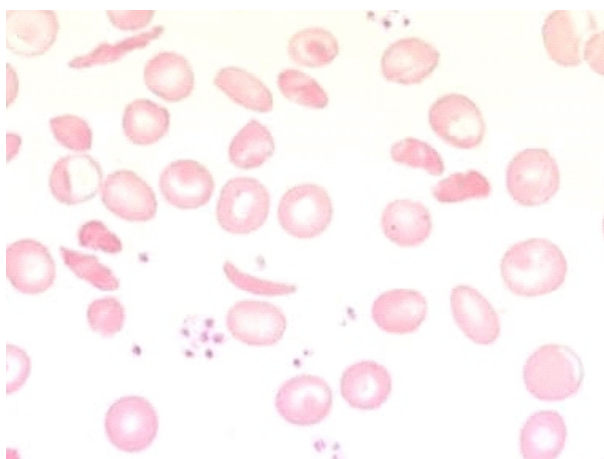
Typical baseline abnormalities in the patient with SCD are as follows:

- Hemoglobin level is 5-9 g/dL
- Hematocrit is decreased to 17-29%
- Total leukocyte count is elevated to 12,000-20,000 cells/mm³ (12-20 X 10³ /L), with a predominance of neutrophils
- Platelet count is increased
- Erythrocyte sedimentation rate is low
- The reticulocyte count is usually elevated, but it may vary depending on the extent of baseline hemolysis
- Peripheral blood smears demonstrate target cells, elongated cells, and characteristic sickle erythrocytes
- Presence of RBCs containing nuclear remnants (Howell-Jolly bodies) indicates that the patient is asplenic
- Results of hemoglobin solubility testing are positive, but they do not distinguish between sickle cell disease and sickle cell trait.

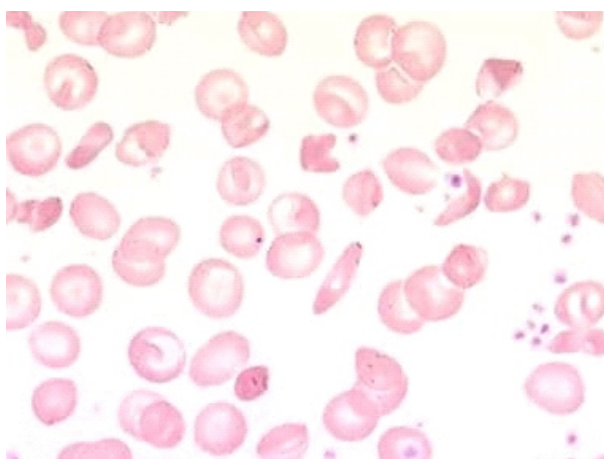
Findings on peripheral blood smears are shown in the images below.



Peripheral blood with sickled cells at 400X magnification.



Peripheral blood smear with sickled cells at 1000X magnification.



Peripheral blood smear with Howell-Jolly body, indicating functional asplenia.

Suggested Routine Clinical Laboratory Evaluations

Obtaining a series of baseline values on each patient to compare with those at times of acute illness is useful. The table below shows a typical schedule of routine clinical laboratory evaluations.

Table. Schedule of Laboratory Tests for Patients with Sickle Cell Disease

Tests	Age	Frequency
CBC count with WBC differential,	3-24 mo	every 3 mo
reticulocyte count	>24 mo	every 6 mo
Percent Hb F	6-24 mo >24 mo	every 6 mo annually
Renal function (creatinine, BUN, urinalysis)	≥ 12 mo	annually
Hepatobiliary function (ALT, fractionated bilirubin)	≥ 12 mo	annually
Pulmonary function (transcutaneous O ₂ saturation)	≥ 12 mo	every 6 mo

Laboratory Studies in the Ill Child

Standard laboratory tests cannot be used to distinguish pain crisis from the baseline condition. If laboratory tests are obtained, they should be interpreted in light of baseline values. **There is a near ubiquitous recommendation to obtain "routine" CBC and reticulocyte counts** in all sickle cell patients with an acute illness, including those presenting with apparently uncomplicated painful crisis. However, a meta-analysis found that "the routine use of complete blood count and reticulocyte count in sickle cell patients presenting with painful crisis does not alter management decisions. Selective use of these tests can be based on patient age, reported symptoms, vital signs, physical examination, and clinical judgment." **Febrile children with SCD, especially those younger than 5 years,** should have an aggressive investigation. The following are usually indicated:

- CBC with differential and reticulocyte count
- Liver function tests (LFTs)
- Urinalysis
- Blood cultures

Additional studies may be indicated, depending on the clinical presentation. Type and crossmatch blood in case transfusion is necessary. **On the CBC, anemia is often identified;** however, a major drop in hemoglobin (ie, more than 2 g/dL) from previously recorded values indicates a hematologic crisis. Leukocytosis is expected in all patients with sickle cell anemia, but a major elevation in the WBC count (ie, >20,000/mm) with a left shift raises suspicion for infection. Leukopenia is suggestive of parvovirus infection. The platelet count is typically elevated. If it is low, consider hypersplenism. **The reticulocyte percentage documents the briskness of the marrow response.** If the reticulocyte count is normal, splenic sequestration is the probable cause. If the reticulocyte count is low, an aplastic crisis is the probable cause. If the reticulocyte count is high, hyperhemolytic crisis is the probable cause.

Additional Tests

Measurement of blood urea nitrogen (BUN), serum creatinine, and serum electrolytes can be useful. Assays of lactic dehydrogenase and haptoglobin are useful but not required. Elevated levels of lactic dehydrogenase support the diagnosis of hemolysis being released from destroyed RBCs. Decreased levels of haptoglobin confirm the presence of hemolysis.

Arterial blood gases

Arterial blood gas measurements (ABGs) may be obtained in patients who are in respiratory distress, to supplement information provided by

oxygen saturation monitoring. This will reflect the severity of pulmonary crisis. Serial ABGs are necessary to follow the response in pulmonary crisis.

Urinalysis

Perform urinalysis if the patient has fever or signs of urinary tract infection (UTI). Patients with sickle cell anemia often have hematuria and isosthenuria. If signs of UTI are present, obtain a urine Gram stain and culture.

Sickling test

Because of mandated newborn screening for sickle hemoglobinopathies, the diagnosis of SCD is already established in most patients with the disease who present for emergency care. If the diagnosis of sickle cell anemia is uncertain, a sickling test will establish the presence of HbS gene. It will not, however, differentiate between individuals who are homozygous and those who are heterozygous.

Secretory phospholipase A2

Secretory phospholipase A2 (sPLA2), an enzyme that cleaves fatty acids from triglycerides, is an accurate marker for identifying present or incipient acute chest syndrome in young patients with sickle cell pain crisis. Its serum concentration increases before acute chest syndrome becomes clinically apparent, peaks at the clinical onset of acute chest syndrome, and declines during its resolution.

Imaging studies

Imaging studies that aid in the diagnosis of sickle cell anemia in patients in whom the disease is suggested clinically include the following:

- **Radiography:** Chest x-rays should be performed in patients with respiratory symptoms
- **MRI:** Useful for early detection of bone marrow changes due to acute and chronic bone marrow infarction, marrow hyperplasia, osteomyelitis, and osteonecrosis
- **CT scanning:** May demonstrate subtle regions of osteonecrosis not apparent on plain radiographs in patients who are unable to have an MRI and to exclude renal medullary carcinoma in patients presenting with hematuria
- **Nuclear medicine scanning:** Tc bone scanning detects early stages of osteonecrosis; In WBC scanning is used for diagnosing osteomyelitis
- **Transcranial Doppler ultrasonography:** Can identify children with SCD at high risk for stroke
- **Abdominal ultrasonography:** May be used to rule out cholecystitis, cholelithiasis, or an ectopic pregnancy and to measure spleen and liver size
- **Echocardiography:** Identifies patients with pulmonary hypertension
- **Transcranial near-infrared spectroscopy or cerebral oximetry:** Can be used as a screening tool for low cerebral venous oxygen saturation in children with SCD.

Management

The goals of treatment in SCD are symptom control and management of disease complications. Treatment strategies include the following 7 goals:

- Management of vaso-occlusive crisis
- Management of chronic pain syndromes
- Management of chronic hemolytic anemia
- Prevention and treatment of infections
- Management of the complications and the various organ damage syndromes associated with the disease
- Prevention of stroke
- Detection and treatment of pulmonary hypertension

Pharmacotherapy

SCD may be treated with the following medications:

- Antimetabolites: Hydroxyurea
- Hemoglobin oxygen-affinity modulators (eg, voxelotor)
- P-selectin inhibitors (eg, crizanlizumab)
- Opioid analgesics (eg, oxycodone/aspirin, methadone, morphine sulfate, oxycodone/acetaminophen, fentanyl, nalbuphine, codeine, acetaminophen/codeine)
- Nonsteroidal analgesics (eg, ketorolac, aspirin, acetaminophen, ibuprofen)
- Tricyclic antidepressants (eg, amitriptyline)
- Antibiotics (eg, cefuroxime, amoxicillin/clavulanate, penicillin VK, ceftriaxone, azithromycin, cefaclor)
- Vaccines (eg, pneumococcal, meningococcal, influenza, and recommended scheduled childhood/adult vaccinations)
- Endothelin-1 receptor antagonists (eg, bosentan)
- Phosphodiesterase inhibitors (eg, sildenafil, tadalafil)
- Vitamins (eg, folic acid)
- L-glutamine
- Antiemetics (eg, promethazine)

Non-pharmacologic therapy

Other approaches to managing SCD include the following:

- Stem cell transplantation: Can be curative
- Transfusions: For sudden, severe anemia due to acute splenic sequestration, parvovirus B19 infection, or hyperhemolytic crises
- Wound debridement
- Physical therapy
- Heat and cold application
- Acupuncture and acupressure
- Transcutaneous electric nerve stimulation (TENS)

Combination pharmacotherapy and non-pharmacotherapy

- Vigorous hydration (plus analgesics): For vaso-occlusive crisis
- Oxygen, antibiotics, analgesics, incentive spirometry, simple transfusion, and bronchodilators: For treatment of acute chest syndrome.

INTERPRETATION

HEMOGLOBIN PATTERNS IN COMMON HEMOGLOBINOPATHIES

Condition	Genotype	Neonatal screening*	By age 6 weeks	Older children (≥5 years), adolescents, and adults				
				Hb A (%)	Hb A ₂ (%)	Hb F (%)	Hb S (%)	Hb C (%)
Normal	AA	FA	FA or AF	95 to 98	2 to 3	<2	0	0
Beta thalassemia trait	A/(β ⁰ or β ⁺)	FA	FA	90 to 95	>3.5 (unless due to δβ; can be normal or lower)	1 to 3 (significantly higher if due to δβ deletion)	0	0
Sickle cell trait	AS	FAS	FAS	50 to 60	<3.5	<2	35 to 45; may be lower if concomitant alpha thalassemia	0
Homozygous sickle cell (Hb SS) disease	SS	FS	FS	0	<3.5 but may be increased with concomitant α-thalassemia. May be falsely elevated when measured by HPLC	5 to 15; may be higher in rare cases	85 to 95	0
Sickle-β ⁰ thalassemia	Sβ ⁰	FS	FS	0	>3.5 but may be falsely elevated when measured by HPLC	2 to 15	80 to 92	0
Sickle-β ⁺ thalassemia	Sβ ⁺	FSA or FS [†]	FSA	3 to 30	>3.5 but may be falsely elevated when measured by HPLC	2 to 10	65 to 90	0
Hb SC disease	SC	FSC	FSC	0	<3.5	1 to 5; may be higher in rare cases	45 to 50	45 to 50
Hb CC disease ^Δ	CC	FC	FC	0	<3.5	<2	0	95
Hb C trait ^Δ	AC	FAC	FAC	50 to 60	<3.5	<2	0	40 to 50

Hemoglobin may be analyzed by one or more of several separation techniques including HPLC, capillary electrophoresis, isoelectric focusing, or gel electrophoresis. Numbers are approximate and may vary depending on the laboratory method used. Transfusions will affect the percentages measured. Levels of Hb A₂ can be affected by thalassemia, iron deficiency, and various other conditions and cannot be used to make a diagnosis of Hb S-beta thalassemia. In selected cases, DNA analysis may be helpful. Refer to UpToDate for discussions of hemoglobin analysis and diagnosis of specific syndromes.

Hb: hemoglobin; Hb A: adult hemoglobin; Hb F: fetal hemoglobin; δβ: delta-beta; HPLC: high-performance liquid chromatography; DNA: deoxyribonucleic acid.

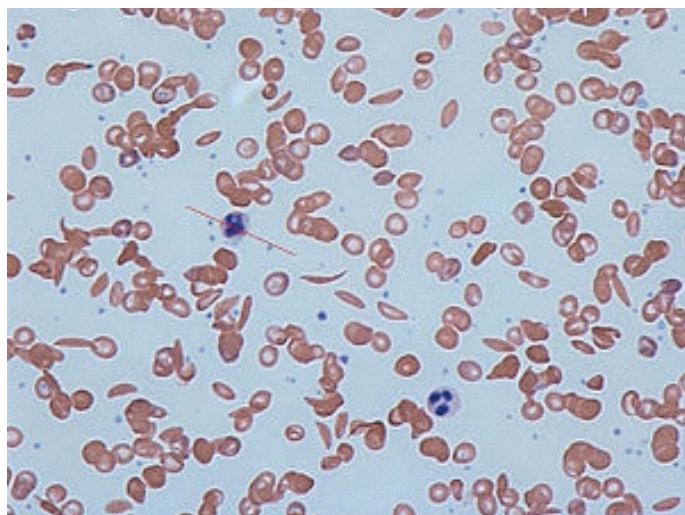
* The neonatal screening patterns list the different hemoglobins in order of abundance. As an example, the FAS pattern has the greatest amount of Hb F, followed by Hb A, followed by Hb S.

In sickle-β⁺ thalassemia, the quantity of Hb A at birth may be insufficient for detection.

Δ In Hb C trait, concomitant alpha thalassemia variants lower the percentage of Hb C, and Hb C levels <40% after iron deficiency is excluded or corrected may indicate a two-gene deletion at the alpha locus. Hb C trait plus a beta thalassemia variant could be misdiagnosed as Hb CC disease.

TROUBLESHOOTING

Hemoglobinopathy



Red blood cells from a person with sickle cell trait

Hemoglobinopathy is the medical term for a group of inherited blood disorders and diseases that primarily affect red blood cells. They are single-gene disorders and, in most cases, they are inherited as autosomal co-dominant traits. **There are two main groups:** abnormal structural hemoglobin variants caused by mutations in the hemoglobin genes, and the thalassemias, which are caused by an underproduction of otherwise normal hemoglobin molecules. The main structural hemoglobin variants are HbS, HbE and HbC. The main types of thalassemia are alpha-thalassemia and beta thalassemia. **The two conditions may overlap** because some conditions which cause abnormalities in hemoglobin proteins also affect their production. Some hemoglobin variants do not cause pathology or anemia, and thus are often not classed as hemoglobinopathies.

Hemoglobin structural biology

Normal human hemoglobins are tetrameric proteins composed of two pairs of globin chains, each of which contains one alpha-like (α -like) chain and one beta-like (β -like) chain. Each globin chain is associated with an iron-containing heme moiety. Throughout life, the synthesis of the alpha-like and the beta-like (also called non-alpha-like) chains is balanced so that their ratio is relatively constant and there is no excess of either type.

The specific alpha and beta-like chains that are incorporated into Hb are highly regulated during development:

- Embryonic Hbs are expressed as early as four to six weeks of embryogenesis and disappear around the eighth week of gestation as they are replaced by fetal Hb. Embryonic Hbs include:
 - ❖ Hb Gower-1, composed of two ζ globins (zeta globins) and two ϵ globins (epsilon globins) ($\zeta_2\epsilon_2$)
 - ❖ Hb Gower-2, composed of two alpha globins and two epsilon globins ($\alpha_2\epsilon_2$)
 - ❖ Hb Portland, composed of two zeta globins and two gamma globins ($\zeta_2\gamma_2$)

- Fetal Hb (Hb F) is produced from approximately eight weeks of gestation through birth and constitutes approximately 80 percent of Hb in the full-term neonate. It declines during the first few months of life and, in the normal state, constitutes <1 percent of total Hb by early childhood. Hb F is composed of two alpha globins and two gamma globins ($\alpha_2\gamma_2$).
- Adult Hb (Hb A) is the predominant Hb in children by six months of age and onward; it constitutes 96-97% of total Hb in individuals without a hemoglobinopathy. It is composed of two alpha globins and two beta globins ($\alpha_2\beta_2$).
- Hb A2 is a minor adult Hb that normally accounts for approximately 2.5-3.5% of total Hb from six months of age onward. It is composed of two alpha globins and two delta globins ($\alpha_2\delta_2$).

Classification of hemoglobinopathies

A) Qualitative

Structural abnormalities

Hb variants: Hb structural variants are qualitative defects that cause a change in the structure (primary, secondary, tertiary, and/or quaternary) of the Hb molecule. The majority of Hb variants do not cause disease and are most commonly discovered either incidentally or through newborn screening. A subset of Hb variants can cause severe disease when inherited in the homozygous or compound heterozygous state in combination with another structural variant or a thalassemia mutation. When clinical consequences occur, they may include anemia due to hemolysis or polycythemia due to alterations in the oxygen affinity of the abnormal Hb. Common examples of hemoglobin variants associated with hemolysis include sickle Hb (Hb S) and Hb C. Hb variants can usually be detected by protein-based assay methods; however, DNA-based methods may be required for variants with ambiguous or unusual results from protein analysis.

The major functional consequences of Hb structural variants can be classified as follows:

- Change in physical properties (solubility): Common beta globin mutations can alter the solubility of the Hb molecule: Hb S polymerizes when deoxygenated and Hb C crystallizes.
- Reduced protein stability (instability): Unstable Hb variants are mutations that cause the Hb molecule to precipitate, spontaneously or upon oxidative stress, resulting in hemolytic anemia. Precipitated, denatured Hb can attach to the inner layer of the plasma membrane of the red blood cell (RBC) and form Heinz bodies.
- Change in oxygen affinity: High or low oxygen affinity Hb molecules are more likely than normal to adopt the relaxed (R, oxy) state or the tense (T, deoxy) state, respectively. High oxygen affinity variants (R state) cause polycythemia (e.g., Hb Chesapeake, Hb Montefiore). Low oxygen affinity variants can cause cyanosis (e.g., Hb Kansas, Hb Beth Israel).
- Oxidation of heme iron: Mutations of the heme binding site, particularly those affecting the conserved proximal or distal histidine residues, can produce M-hemoglobin, in which the iron atom in heme is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, with resultant methemoglobinemia.

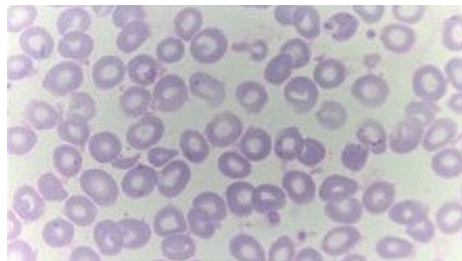
Chemical abnormalities

- Methemoglobinemia:
 - ❖ a condition caused by elevated levels of methemoglobin in the blood. Methaemoglobin is a form of Hb that contains the ferric [Fe^{3+}] form of iron. The affinity for oxygen of ferric iron is impaired. The binding of oxygen to methaemoglobin results in an *increased* affinity for oxygen

in the remaining heme sites that are in ferrous state within the same tetrameric haemoglobin unit.

B) Quantitative

Production abnormalities



Red blood cells from a person with beta thalassemia

Copy number variation (e.g., deletion, duplication, insertion) is also a common genetic cause of Hb disorders, and complex rearrangements and globin gene fusions can also occur.

- **Thalassemias:** Thalassemias are quantitative defects that lead to reduced levels of one type of globin chain, creating an imbalance in the ratio of alpha-like chains to beta-like chains. As noted above, this ratio is normally tightly regulated to prevent excess globin chains of one type from accumulating. The excess chains that fail to incorporate into Hb form non-functional aggregates that precipitate within the RBC. This can lead to premature RBC destruction in the bone marrow (beta thalassemia) and/or in the peripheral blood (alpha thalassemia). Types:

- ❖ Alpha
- ❖ Beta (Major)
- ❖ Beta (Minor)

Hemoglobin variants

Haemoglobin variant are not necessarily pathological. For example, haemoglobin Valletta and haemoglobin Marseille are two haemoglobin variants which are non-pathological.

- HbS
- HbC
- HbE
- Hb Bart's
- Hb D-Punjab
- HbO (Hb O-Arab)
- Hb G-Philadelphia
- Hb H
- Hb Constant Spring
- Hb Hasharon
- Hemoglobin Kenya
- Hb Korle-Bu
- Hb Lepore
- Hb M
- Hb Kansas
- Hb J
- Hb N-Baltimore
- Hb Hope
- Hb Pisa

Electrophoretic migration patterns

Hemoglobin variants can be detected by gel electrophoresis.

Alkaline electrophoresis

In general on alkaline electrophoresis in order of increasing mobility are hemoglobins A₂, E=O=C, G=D=S=Lepore, F, A, K, J, Bart's, N, I, and H.

In general a sickling test is performed on abnormal hemoglobins migrating in the S location to see if the hemoglobin precipitates in solution of sodium bisulfite.

Acid electrophoresis

In general on acid electrophoresis in order of increasing mobility are hemoglobins F, A=D=G=E=O=Lepore, S, and C.

This is how abnormal hemoglobin variants are isolated and identified using these two methods. For example, a Hgb G-Philadelphia would migrate with S on alkaline electrophoresis and would migrate with A on acid electrophoresis, respectively.

BOUQUET

You have *succeeded in life* when all you really want is only what you really need.

✕

Perfection is not attainable. But if we *chase* perfection we can *catch* excellence.

✕

Wisdom Whispers

If you change the way you *look* at things, the things you *look* at change.

✕

live out of your *imagination*, not your history.

✕

In Lighter Vein



INTELLIGENCE IS LIKE UNDERWEAR: IT IS IMPORTANT TO HAVE IT, BUT NOT NECESSARY THAT YOU SHOW IT OFF...

MY TEACHER POINTED ME WITH HIS RULER AND SAID: "AT THE END OF THIS RULER THERE'S AN IDIOT!"



I GOT DETENTION AFTER ASKING WHICH END.

My brain is like The Bermuda Triangle...

Information goes in and then it's never found again.



Brain Teasers

- What is the name of abnormal sites for development of blood cells?
 - Extramedullary hemopoiesis
 - Bone marrow
 - Spleen
 - Liver
- The volume of red cells expressed as a percentage of the volume of whole blood in sample is known as:
 - Hematocrit
 - Erythrocytosis
 - Hemoglobin
 - All.
- Reduction in the concentration of hemoglobin in the peripheral blood below normal for age and sex known as:
 - Anemia
 - Hematuria
 - Polycythemia
 - Methemoglobinemia.
- EDTA preserves cellular morphology for:
 - 2–3 hours
 - 5–10 hours
 - 10 days
 - 5 days.

ANSWER: 1: A, 2: A, 3: A, 4: A

Sickle Cell Anaemia Diagnosis

Through an Innovative Point-of-Care Test from Tulip...

SICKLECHECK™

Point-of-care Rapid Test for the detection of Sickle Cell Disease and Trait

Facilitates classification of sickle cell trait, disease
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Reliable results

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Storage at 4°C- 40°C
Suitable for most climatic conditions

Evaluated by ICMR Centre
Credible test results



Easy Result Interpretation



Normal



Sickle Cell Disease



Sickle Cell Trait



Other Hemoglobinopathies

Comparable with HPLC.... a Simple, Rapid Test!

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