SICKLE CELL DISEASES

Definition

- Sickle cell disease (SCD) is the collective designation of a group of disorders characterized by the presence of >50% sickle hemoglobin (HbS) in the red cell and varying degrees of hemolytic anemia.
- Sickle cell trait: Sickle cell trait (Hb AS) is a benign carrier condition with no hematologic manifestations.
- Red cell morphology, red cell indices, and the reticulocyte count are normal, and irreversibly sickled cells (ISCs) are not found on the peripheral blood smear
- The prevalence of sickle cell trait is approximately 8 to 10 percent in African Americans and as high as 25 to 30 percent in certain areas of western Africa
- The usual partition of Hb A and Hb S in sickle cell trait is 60:40 because of a greater posttranslational affinity of alpha chains for beta A than for beta S chains
- Complications: Serious complications are rare in sickle cell trait, which should be considered a benign carrier condition in order to prevent employment and insurance discrimination

Epidemiology

- Sickle cell hemoglobinopathies occur worldwide, are not restricted to dark-skinned people, and are found in diverse populations including those of African, Mediterranean, Middle Eastern, and Asiatic Indian ethnicity.

Pathophysiology

- Hemoglobin S results from the substitution of a **valine** for **glutamic acid** as the sixth amino acid of the beta globin chain, which produces a hemoglobin tetramer (alpha2/beta S2) that is poorly soluble when deoxygenated
- This change endows Hb S when deoxygenated with a new property: the capacity to polymerize.
- **Polymerization:** A reaction in which a high molecular weight product is produced by successive additions to or condensations of a simpler compound
- This new property conspires against an indispensable feature of the red cell: its pliability in spite of a very high intra-erythrocytic concentration of hemoglobin (32 to 34 g/dL).
- Replacement of a hydrophilic glutamic acid by hydrophobic valine introduces an intermolecular contact point that results in **polymerization of deoxygenated HbS**.

- The polymerization of deoxy Hb S is the primary and indispensable event in the molecular pathogenesis of sickle cell disease
- The polymerization of deoxyhemoglobin (Hb) S is essential to vaso-occlusive phenomena
- The polymer assumes the form of an elongated rope-like fiber which usually aligns with other fibers, forming a fascicle, resulting in distortion of the affected red blood cell into the classic crescent or sickle shape and a marked decrease in red cell deformability
- Fibers of polymerized HbS make the red cells rigid and distort their round shape into characteristic sickle cells.
- Sickled red cells in the circulation and their increased adherence to the vascular endothelium are the ultimate causes of the many manifestations of SCD.
- In decreasing order of clinical severity, four common types of SCD are recognized: **HbSS, HbSβ^0**, **HbSC**, and **HbSβ^+ thalassemia**.
- Red blood cells that contain mostly HbS go through cycles of sickling and unsickling on oxygenation and deoxygenation as they pass through the circulation.
- The tendency of the individual RBC to sickle is influenced by several factors.
- These include the presence of other hemoglobins that may inhibit or enhance the polymerization of deoxy-HbS, the degree, to which the HbS is deoxygenated, and RBC deformability and hydration.
- When a solution of HbS is deoxygenated, there is a characteristic delay time during which no polymerization occurs, followed by a phase of rapid polymerization.
- A small percentage of RBC remains permanently sickled, even when fully oxygenated.
- Sickled red cells become dehydrated through loss of potassium and water, which enhances polymerization.
- Hemoglobins such as F and A within the red cell inhibit polymerization of HbS.
- Tissues with sluggish blood flow such as the spleen and bone marrow sinusoids, and areas with hypertonicity and high acidity such as the renal medulla, are especially susceptible to damage resulting from sickling.
- Hemolysis and vasoocclusion are the two major pathophysiological consequences of intravascular sickling.
- Intravascular hemolysis results from damage caused by repeated sickling and unsickling as well as by the microvascular trapping of rigid and stiff sickled RBC.
- These abnormal cells are more rapidly destroyed, and the mean RBC life span in HbSS disease is only 10 to 20 days compared with the 100 to 120 days of survival of normal red cells.
- Sickled RBC also adheres to and damage endothelial layers of small and large blood vessels.
- Microvascular occlusion leads to tissue ischemia and infarction and ultimately results in chronic organ failure.

- Vasoocclusion with ischemia and tissue damage are also the major causes of the episodic acute painful episodes that are the clinical hallmarks of SCD.

Clinical features

Acute episodes:

1. Infections:

- Infection is a major cause of morbidity and mortality in patients with SCD.
- Affected children are vulnerable to life-threatening infection as early as four months of age because of splenic dysfunction caused by sickling of the red cells within the spleen and the inability of the spleen to filter microorganisms from the blood stream.
- Splenic dysfunction is followed eventually by splenic infarction, usually by two to four years of age.
- *Streptococcus pneumoniae* sepsis causes death in 15 to 20% of children in the first 5 years of life.
- In the absence of normal splenic function, the patient is susceptible to overwhelming infection by encapsulated organisms, especially *Streptococcus pneumoniae* and *Haemophilus influenzae*.
- Dysfunctional IgG and IgM antibody responses, defects in alternative pathway fixation of complement, and opsonophagocytic dysfunction may also play a role in the predisposition to invasive infection
- The major factors contributing to this unusual vulnerability to severe pneumococcal sepsis are the early loss of splenic reticuloendothelial function (functional hyposplenia) combined with a lack of circulating antibodies against polysaccharide-encapsulated bacteria.
- The enlarged spleen gradually becomes small and fibrotic from autoinfarction and is rarely palpable after 6 years of age.
- The second reason for susceptibility to severe pneumococcal sepsis is the lack of circulating antibody directed against pneumococci.
- As a normal developmental phenomenon, young children cannot efficiently produce antibodies to polysaccharide antigens such as those present in the capsule of the pneumococcus.
- Intact pneumococci use phosphorylcholine to tether to the platelet activating factor (PAF) receptor, thereby inserting the bacteria into the PAF receptor uptake pathway and promoting cell entry
- A possible predisposing mechanism in SCD is the upregulation of PAF receptors on chronically activated endothelial cells.

- Haemophilus influenzae type b has been the second most common organism responsible for bacteremia in children with SCD, accounting for 10 to 25 percent of episodes
- There is an increased incidence of osteomyelitis in patients with sickle cell anemia resulting from infection of infarcted bone.
- The most common offending organisms are Salmonella species.

2. Acute painful episodes

- Episodes of acute pain, previously called sickle cell crisis, are the most common type of vasoocclusive event
- Acute pain is the first symptom of disease in more than 25 percent of patients and is the most frequent symptom after the age of two years
- The pain is thought to be a result of inflammation from tissue ischemia caused by acute vasoocclusion.
- The evolution of pain is also associated with changes in the levels of acute phase reactants (e.g. C-reactive protein, fibrinogen), serum lactate dehydrogenase, interleukin-1, tumor necrosis factor, and serum viscosity
- Pain may be precipitated by events such as weather conditions (e.g. high wind speed, low humidity, atmospheric pollutants), dehydration, infection, stress, menses, alcohol consumption, nocturnal hypoxemia, and rarely obstructive sleep apnea
- However, the majority of painful episodes have no identifiable cause.
- The episodes can affect any area of the body, with the back, chest, extremities, and abdomen being most commonly affected; the pain severity can range from trivial to excruciating.
- The earliest physical manifestation of HbSS is often the hand-foot syndrome or sickle cell dactylitis, a painful often.

3. Aplastic crisis

- The anemia of SCD is usually a chronic, reasonably well compensated hemolytic anemia with an appropriate reticulocytosis.
- Because of the very short, 10- to 20-day (mean life span of 17 days) RBC survival, patients with HbSS disease are able to maintain their low but steady hemoglobin levels by markedly increasing red blood cell production by the bone marrow.
- The usual cause of severe red cell aplasia is infection by parvovirus B19, a virus that destroys early red cell precursors in the bone marrow, causing an abrupt interruption of red cell production.
- A number of factors other than chronic hemolysis can contribute to the anemia.

- These include: Inappropriately low serum erythropoietin (EPO) concentrations, which may result in deficient compensation for hemolysis
- Folate and/or iron deficiency resulting from increased utilization of folate and enhanced urinary losses of iron.
- The net effect is that iron deficiency is present in approximately 20 percent of patients with sickle cell disease
- Acute severe anemia: There are three settings in which an acute fall in hemoglobin concentration may be superimposed upon the chronic anemia: splenic sequestration crisis; aplastic crisis; and hyperhemolytic crisis
- An aplastic crisis is characterized by the transient arrest of erythropoiesis, leading to abrupt reductions in hemoglobin concentration and red cell precursors in the bone marrow, and a markedly reduced number of reticulocytes in the peripheral blood (i.e., reticulocytes <1.0 percent and an absolute reticulocyte count <10,000 per microL,
- Impaired erythropoiesis can be associated with a variety of infections.
- Most cases in children follow infection with human parvovirus B19, which specifically invades proliferating erythroid progenitors
- Other reported causes of transient aplasia are infections by Streptococcus pneumoniae, salmonella, streptococci, and Epstein-Barr virus
- Affected patients require acute transfusion therapy.

4. Cerebrovascular accidents

- Neurologic complications, including transient ischemic attacks, infarctive stroke, intracerebral hemorrhage, spinal cord infarction or compression, vestibular dysfunction, and sensory hearing loss, occur in 25 percent of patients with sickle cell anemia.
- Cognitive impairment may occur as a consequence of vascular disease and/or silent cerebral infarcts.
- There are three clinical presentations of stroke: cerebral infarcts and hemorrhage, which result in weakness and paralysis, aphasia, and seizures, and transient ischemic attacks (TIA).
- TIA is likely to be missed in young children.

5. Splenic sequestration:

- With splenic sequestration crisis, vaso-occlusion within the spleen and splenic pooling of red cells produce a marked fall in hemoglobin concentration accompanied by persistent reticulocytosis and a rapidly enlarging spleen
- Although primarily associated with aplastic crisis, parvovirus B19 infection may also be a risk factor for splenic sequestration

- Splenic infarction can develop at high altitude
- In young children in whom autoinfarction has not as yet occurred, the spleen may become acutely enlarged and engorged with blood sequestered from the systemic circulation, with resultant hypovolemia, severe anemia, and massive splenic enlargement.

6. Acute chest syndrome:

- The usual etiology is thought to be vaso-occlusion but infarction, embolism, and infrequently bacterial pneumonia are precipitating causes.
- The development of new pulmonary infiltrate, often accompanied by fever, chest pain, tachypnea, and hypoxia, defines the acute chest syndrome.
- This may be a result of pulmonary infarction, infection, atelectasis, or fat embolism secondary to bone marrow infarction.
- Recurrent microvascular obstruction resulting in the development of pulmonary hypertension, endothelial dysfunction, and parenchymal fibrosis is probably the primary mechanism

7. Priapism:

- Priapism is a prolonged painful erection that occurs in about 10% of boys with HbSS.
- Priapism is defined as an unwanted painful erection that occurs in 6 to 42 percent of males with SCD
- The onset of priapism can be acute, recurrent, acute on chronic, or stuttering
- It appears to be associated with signs of increased hemolysis, decreasing the availability of nitric oxide, which plays an important role in erectile function
- The engorgement in priapism affects the corpora cavernosa and usually spares the glans penis and corpus spongiosum.
- In a minority of patients, usually postpubertal, the engorgement also affects the corpus spongiosum and glans

8. Bone complications

- The skeletal system is frequently involved in sickle cell disease due accelerated hematopoiesis and/or bone infarction.
- The extended hematopoietic marrow resulting from the chronic hemolysis can lead to chronic tower skull, bossing of the forehead, and fish-mouth deformity of vertebrae.
- These effects cause widening of the medullary space, thinning of the trabeculae and cortices and osteoporosis.

- Bone complications in sickle cell disease include the following: Bone infarction and necrosis
- Osteonecrosis (also called avascular, ischemic, or aseptic necrosis) results from infarction of bone trabeculae and marrow cells and occurs in all sickle cell disease genotypes.

Chronic organ damage

- In addition to splenic dysfunction, progressive functional abnormalities occur with increasing age in the kidneys, eyes, lungs, heart, and liver.
- Renal complications include hyposthenuria, papillary necrosis and hematuria, nephrosis, nephritis, and renal failure.
- Occlusion of retinal vessels may lead to proliferative retinopathy, retinal detachment, and loss of vision.
- Progressive pulmonary infarction may lead to pulmonary hypertension and hypoxemia and right-sided heart failure.
- High-output left-sided heart failure may occur in patients with more severe degrees of anemia
- Liver enlargement and failure may occur as a result of infarction, bile stasis, or infection.
- Cholelithiasis secondary to chronic hemolysis can occur as early as 3 to 4 years of age, and more than half of adults with HbSS have gallstones.
- Growth retardation is commonly observed during childhood, but normal adult height is almost always eventually achieved.
- The onset of puberty and development of secondary sex characteristics are usually delayed by 2 to 3 years.

Diagnostic testing

- The goals and methods of diagnosis of SCD vary with the age of the patient.
- DNA based testing is used for prenatal diagnosis.
- The diagnostic methods used after birth are those that separate hemoglobin species according to amino acid composition (hemoglobin electrophoresis or thin layer isoelectric focusing), solubility testing, and examination of the peripheral blood smear.
- Characterization of adult hemoglobins in the fetal and newborn periods can be difficult because of the predominance of Hb F, which confounds detection of Hb S by solubility testing
- Clinical manifestations of SCD are not present at birth, and usually begin to become apparent after the first few months of life as the concentration of Hb S rises and Hb F declines.
- Sickled cells can be seen in the peripheral blood of children with SCD at three months of age and moderately severe hemolytic anemia is apparent by four months of age

Treatment:

- There are two major components to the management of SCD:
  - Treatment and prevention of the acute manifestations of sickle cell disease (e.g. infection prevention and control, pain control)
  - The use of hydroxyurea to interfere with the sickle hemoglobin polymerization process by increasing the production of fetal hemoglobin, reducing the incidence of subsequent painful episodes, hospitalization, and death

General principles

Infection control and prophylaxis

- Parents of small children should be instructed regarding early recognition of infection and the palpation of enlarging spleens to permit early detection of potentially fatal splenic sequestration crisis
- Children with SCD should be immunized against Streptococcus pneumoniae, Haemophilus influenzae type B, hepatitis B virus, and influenza
- Prophylactic penicillin should be given as 125 mg penicillin V orally twice daily until two to three years of age and 250 mg twice daily thereafter until the age of five

Routine treatments and evaluations

- Folic acid is given orally in a dose of 1 mg/day
- Cerebral blood flow should be evaluated by transcranial Doppler (TCD) since children at risk for cerebrovascular accidents can be identified with this technique and the incidence of stroke reduced by chronic transfusion therapy
- Retinal evaluation is begun at school age and continued routinely to detect early proliferative sickle retinopathy.
- Sexually active women should have routine pelvic examinations and birth control.

Hydroxyurea

- The use of hydroxyurea is a mainstay in the overall management of the patient with sickle cell disease, and has been shown to reduce the incidence of acute painful episodes and hospitalization rates, and to prolong survival.

Pain management

Overview

- The acute painful episode is the most frequent cause for patients with sickle cell disease to seek medical attention
- The approach to the patient presenting with pain consists of exclusion of causes other than vasoocclusion (e.g. infection), optimal hydration by oral or intravenous fluid resuscitation (particularly in children); and aggressive pain relief using opiates, other analgesics, or other modalities

Opiates

- Hospitalization and intravenous administration of fluid and opiates are often required for the treatment of severe painful episodes of SCD. There are a number of analgesic agents that can be used in such patients
- We recommend an aggressive approach using intravenous morphine, followed by varying combinations of rescue or maintenance analgesia, continuous infusion, and patient-controlled analgesia.
- The suggested initial dose of morphine for most opioid-naive adults with a severe painful episode due to sickle cell disease that is not responding to oral analgesic agents is in the range of 0.10 to 0.15 mg/kg IV, with monitoring for respiratory depression and reevaluation of pain status within 15 to 30 minutes after the first morphine injection
- Individualization of the dose is highly recommended, as "real world" safe and effective initial doses have ranged from 0.05 to >2.0 mg/kg.
- Fentanyl, a synthetic derivative of morphine, is approximately 100 times more potent. It is also more lipid-soluble than morphine, which results in a more rapid onset of action, due to improved penetration of the blood-brain barrier, and a shorter half-life of two to three hours. Fentanyl usually is administered as a continuous intravenous infusion
- Hydromorphone (Dilaudid) is a semisynthetic opiate agonist which, like fentanyl, has a more rapid onset of analgesia (within 30 minutes) and a shorter half-life (2.4 hours) than morphine.
- Because it is available in a highly concentrated preparation (10 mg/mL), it may be beneficial in fluid-restricted patients who require large doses of opiates.
- Meperidine is not recommended for the treatment of painful episodes of SCD, since it is less effective than morphine and has a higher incidence of side effects

Newer approaches

- Newer approaches to the management of acute pain include the use of potent nonsteroidal antiinflammatory drugs, opioid receptor-binding agents, surfactants that inhibit cell adherence and aggregation, inhaled nitric oxide, anticoagulants, glucocorticoids, and epidural anesthesia.
    - Ketorolac
    - Tramadol
    - Inhaled nitric oxide
    - Epidural analgesia
    - Methylprednisolone

Chronic pain

- In rare patients, sickle cell pain is a chronic syndrome.
- Therapy in this situation is similar to that used for the management of the pain of terminal cancer, and includes such agents as long-acting morphine and fentanyl patches

Management of infection

- Infection is a frequent complication of SCD and is particularly serious when accompanied by bacteremia.
- Results of the complete blood count are compared to baseline values.
- A "left shift" (i.e. the presence of increased band forms and/or metamyelocytes in the white blood cell differential count) suggests bacterial infection.

Febrile episodes

- Febrile episodes without localized symptoms are treated according to estimated risk.
- High risk: Patients with sickle cell anemia or sickle cell-beta (0) thalassemia who appear toxic, have temperatures >40ºC, or are not receiving prophylactic penicillin should be hospitalized for administration of ceftriaxone (75 mg/kg IV).

Specific infections

- Therapy of specific infections varies with the clinical setting:
- Bacteremia: Several days of parenteral penicillin or ceftriaxone therapy followed by oral antibiotics is appropriate therapy for documented S. pneumoniae bacteremia.
- Meningitis: Therapy for meningitis should provide coverage for S. pneumoniae and H. influenzae type b and should be continued for at least two weeks

- Acute chest syndrome: Antibiotics should provide coverage for S. pneumoniae, H. influenzae type b, Mycoplasma pneumoniae, and Chlamydia pneumoniae
- We recommend the combination of cefuroxime and erythromycin, unless there is an appreciable incidence of high-grade penicillin-resistant pneumococcal infection in the area.
- Osteomyelitis: The diagnosis of osteomyelitis should be confirmed by culture of blood or infected bone.

Transfusion therapy

- Chronic red cell transfusion lowers the percent of sickle hemoglobin (HbS) in subjects with sickle cell disease by three mechanisms: dilution; suppression of erythropoietin release secondary to the rise in hematocrit, thereby reducing the production of new sickle erythrocytes; as well as via the longer circulating lifespan of normal compared to sickle erythrocytes.
- Patients with sickle cell disease receive blood transfusions in three situations:
- To improve oxygen carrying capacity and as blood volume replacement during an aplastic or splenic sequestration crisis
- To provide protection from imminent danger during acute chest syndrome or septicemia
- To improve rheologic properties of blood and prevent initial or recurrent cerebral thrombosis, to prevent recurrent priapism, and to reduce perioperative complications
- *Transfusion volume:* The general rule for normal size adults is that each unit of red cells infused will increase the hemoglobin concentration by approximately 1 g/dL or three percentage points in the hematocrit.

New therapies

- Some progress has been made in the development of new therapies for the management of SCD.
- Hydroxyurea, a cytotoxic agent that increases levels of HbF, decreases the WBC, reduces the frequency of painful crises, acute chest syndrome, and transfusions about 50% in adults and in initial studies in children.
- Other agents that can increase fetal hemoglobin include butyrate analogues, and other short-chain fatty acids are being investigated.
- Bone marrow transplantation (BMT) from an HLA-matched sibling is the only curative therapy