Routine Management of Sickle Cell Anaemia

Date: 1\textsuperscript{st} March 2014

By

Prof. E. O. Temiye,
Department of Paediatrics,
College of Medicine University of Lagos

&

Consultant Paediatrician,
Lagos University Teaching Hospital
Learning Objectives

At the end of the session, the participants will be able to:

- Understand the basic pathophysiology of sickle cell disease
- Identify factors modulating severity of the disorder
- Describe the clinical manifestations of the disease described as crises
- General Management of sickle cell disease
- Management of the crises, especially painful crisis
- Describe the management of some sickle emergencies
Introduction

- Sickle-cell disease (also known as sickle-cell disorder) denotes all genotypes containing at least one sickle gene, in which HbS makes up at least half the haemoglobin present and presence of another abnormal haemoglobin.

- It is the most common single gene disorder in black Africans and results from the substitution of valine for glutamic acid at the 6th position in the \( \beta \)-globin gene.

- Sickle-cell anaemia is widespread globally; individuals of African descent exhibit the highest frequency of HBS.

- Individuals of Mediterranean, Carribbean, south and central American, Arab, and East Indian descent are also affected
The prevalence of the sickle-cell trait (healthy carriers who have inherited the mutant gene from only one parent) ranges between 10% and 40% across equatorial Africa and decreases to between 1% and 2% on the north African coast and <1% in South Africa.

This reflects the survival advantage sickle-cell trait confers against malaria and selection pressure due to the parasite resulting in high frequencies of the mutant gene, especially in areas of high malarial transmission.

In west African countries such as Ghana and Nigeria, the frequency of the trait is 15% to 30% whereas in Uganda it shows marked tribal variations, reaching 45% among the Baamba tribe in the west of the country.

Each year about 200 000 cases of sickle-cell anaemia are born in Africa.
Introduction

- Frequencies of the carrier state determine the prevalence of sickle-cell anaemia at birth.

- In some areas of sub-Saharan Africa, up to 2% of all children are born with the condition.

- In Nigeria, 25% of the population are carriers of the mutant gene and the prevalence of sickle-cell anaemia is about 20 per 1000 births.

- This means that in Nigeria alone, about 150 000 children are born annually with sickle-cell anaemia.

- The first description of sickle cell disease, published in 1910, has been followed by ten decades of genetic, haematologic, pathologic, clinical and molecular observations.
percent of population that has the sickle-cell allele (Hemoglobin S)

- **14+**
- **12-14**
- **10-12**
- **8-10**
- **6-8**
- **4-6**
- **2-4**
- **0-2**
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 becomes relatively insoluble and molecularly unstable under deoxy conditions forming a gel-like substance containing Hb crystals called tactoids.
- This lead to increased viscosity, and polymer formation.
Pathophysiology (cont)

- 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.

- If oxygen is present, the liquid state prevails, gelation of HbS occurs at concentrations >20.8 g/dL (the normal cellular Hb concentration is 30 g/dL).

- Repeated and prolonged sickling involves the membrane causing RBC to assume the characteristic sickled shape.
This eventually lead to membrane damage and the cells are no longer capable of resuming the biconcave shape upon reoxygenation.

Thus, they become irreversibly sickled cells (ISCs).
- About 5-50% of RBCs remain irreversibly sickled.

The presence of other haemoglobins such as normal adult haemoglobin (HbA) and fetal haemoglobin (HbF) have an inhibitory effect on gelation.

These and other Hb interactions affect the severity of clinical syndromes.
Pathophysiology (cont)

- Thus, HbSS produces a more severe disease than sickle cell HbC (HbSC), HbSD, HbSO Arab, and Hb with one normal and one sickle allele (HbSA).

- Cellular hydration, depends on the rate of potassium and water flux across the red cell membrane.

- The latter is mediated by the function of the:
  - Potassium/chloride co-transport, Mg++ activated pump, and the
  - Ca++ dependent potassium pump (Gardos channel)

- RBCs sickling, disrupts these pumps leading to gain in intracellular Na$^+$ and loss of intracellular K$^+$. 
Membrane permeability to Ca\(^{++}\) increases, possibly due, in part, to impairment in the Ca\(^{++}\) pump that depends on adenosine triphosphatase (ATPase). (the Gardos Channel)

The intracellular Ca\(^{++}\) concentration rises to 4 times the reference level. The membrane becomes more rigid, possibly due to changes in cytoskeletal protein interactions.

Membrane vesicle formation occurs, and the lipid bilayer is perturbed. The outer leaflet has increased amounts of phosphatidyl ethanolamine and contains phosphatidylserine.

These changes contribute to thrombosis, acting as a catalyst for plasma clotting factors.
Ion Transport Pathways involved in Sickle Cell

**Figure 1:** Schematic diagram of the ion transport pathways involved in sickle cell dehydration and action sites of potential therapeutic blockers: Ca2+-activated K+ channel (Gardos channel, KCNN4): Clotrimazole (CLT) and ICA-17043; K-Cl cotransport (KCC1/3/4): Magnesium (Mg) Pidolate; Deoxygenation-induced pathway: Dipyridamole; Anion conductive pathway: NS3623. Deoxygenation induces Hb S polymerization and sickling, with associated increased membrane permeability and abnormal function of different ion transport pathways, resulting in K+, Cl- and water loss and red cell dehydration (modified from De Franceschi L et al. Haematologica 89: 348, 2004).
Interactions with vascular endothelium

- 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.

- 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. Nitric oxide (NO) is a vasodilator.

- Hypoxia also decreases NO production, thereby adding to the adhesion of sickle cells to vascular endothelium.
Interactions with vascular endothelium

- Free Hb is an avid scavenger of nitric oxide. Continuing active hemolysis, provides free Hb in the plasma, and it scavenges nitric oxide, contributing to vasoconstriction.

- In addition, under inflammatory conditions, increased leukocyte recruitment in combination with adhesion of sickle RBCs further contribute to stasis.

- The substantially larger and less deformable granulocytes adhere to activated endothelium (inflammation) and cause flow retardation, which favours adhesion.

- Activated monocytes cause further activation of the endothelial cells by releasing TNF
Interactions with vascular endothelium

- Sickle RBC adhesion in post-capillary venules causes increased microvascular transit times and initiate vaso-occlusion.

- Other adhesion molecules expressed on sickle RBCs, that are involved in vaso occlusion include:
  - CD36, expressed on the surface of immature erythroid cells, and less on the surface of normal reticulocytes.
  - Integrins α4β1 (VLA 4) and α5β1, also expressed on the surface of immature erythroid cells.
  - Intercellular cell adhesion molecule-4 (ICAM-4), and
  - Basal cell adhesion molecule (B-CAM).

- Adhesion molecules (i.e, P-selectin, VCAM-1, α-V-β-3 integrin) are also expressed on activated endothelium.

- Finally, plasma factors and adhesive proteins (i.e, thrombospondin [TSP], von Willebrand factor [vWF], laminin) play an important role in this interaction.
Interactions with vascular endothelium

- Induction of VCAM-1 and P-selectin on activated endothelium enhances sickle RBC interactions.

- In addition, α-V-β-3 integrin is upregulated in activated endothelium in patients with sickle cell disease which binds to several adhesive proteins (TSP, vWF, red-cell ICAM-4, and, possibly, soluble laminin) involved in sickle RBC adhesion.

- 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 haemolyze by erythrophagocytosis by macrophages.
Other properties of sickle cells

- This process can be partially modified by Fc (crystallizable fragment) blockade, suggesting that the process is mediated by immune mechanisms.

- Sickle RBCs have increased immunoglobulin G (IgG) on the cell surface.

- Vaso-occlusive crisis is often triggered by infection and levels of fibrinogen, fibronectin, and D-dimer are elevated in these patients.

- Plasma clotting factors are likely participate in the microthrombi in the pre-arterioles.
Interactions with vascular endothelium

Blood Flow

Increased Erythropoiesis

Oxidation and Dehydration

Aged RBC

Endothelial Cells

Reversal of membrane phospholipids; Appearance of phosphatidyl-serine promoting coagulation

Activation of Endothelial Cells

Stress Reticulocyte

GP1b/2b3a-like

HMW vWF

CD36

Thrombospondin

GP1b-like

BCAM/Lu

Laminin

IgG

FcR

Platelets

VLA4

VCAM1
Vasopathology of Sickle Cell Disease

- Sickle-RBC Adhesion
- Abnormal Shear
- ↑ Inflammation
- Oxidative endothelial cell damage (ROS)
- ↑ serum free hemoglobin (Hb)
- Dysregulation of nitric oxide pathway (NO/NOS)

- ↑ Cell adhesion molecule (CAM) and tissue factor (TF) expression
- Loss of vasoregulation
- Intimal hyperplasia
- Platelet and leukocyte adhesion
- Propagation of fibrin clot
- Entrapment of rigid sickle RBCs
Genetics

- 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/β⁰ thalassemia - Double heterozygote for HbS and β⁰ thalassemia; clinically indistinguishable from sickle cell anemia (SCA)
  - HbS/ β⁺ thalassemia - Mild-to-moderate severity with variability in different ethnicities
  - HbSC disease - Double heterozygote for HbS and HbC characterized by moderate clinical severity
Genetics

- 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/ $\beta^+$ thalassemia
- Rare combinations of HbS with other abnormal haemoglobins such as HbD Los Angeles, G-Philadelphia, HbO Arab, and others
Sickle-cell disease is inherited in the autosomal recessive pattern.
Modulators of disease severity

- Some factors have been identified to affect severity of SCD.
- Genotype is the most important risk factor for disease severity.
- Individuals with Hb SS are most severely affected, followed by those with HB Sβ⁰-thalassemia.
- Those with HB SC and HB Sβ⁺-thalassemia tend to have a more benign course of the disease.
- However, individuals with HB SC have increased risk of thromboembolic complications, retinopathy, and renal papillary necrosis when compared with individuals with Hb SS.
### Incidence of complications sickle Cell Disease in the United States, by genotype

<table>
<thead>
<tr>
<th>Complication</th>
<th>Gene variant</th>
<th>Hb SS</th>
<th>HB SC</th>
<th>Hb Sβ⁺-thalassemia</th>
<th>Hb Sβ⁻-thalassemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Chest syndrome (per 100 patient-years)</strong></td>
<td>Hb SS</td>
<td>12.8</td>
<td>5.2</td>
<td>9.4</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>HB SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁻-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁺-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cerebrovascular accidents (per 100 patient-years)</strong></td>
<td>Hb SS</td>
<td>0.6</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>HB SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁻-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁺-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain crises (per patient-year)</strong></td>
<td>Hb SS</td>
<td>0.8</td>
<td>0.04</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>HB SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁻-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb Sβ⁺-thalassemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modulators of disease severity

- Other factors associated with disease severity include β-globin haplotype.
- Among the most common haplotypes in sickle cell disease the:
  - Senegalese haplotype is associated with the most benign form, followed by:
  - Benin haplotype,
  - Bantu haplotype is associated with the most severe form
- The Bantu haplotype have a two-fold increased risk of complications and early mortality when compared with the other haplotypes.
Modulators of disease severity

Alpha-thalassemia

- Co-inheritance with α-thalassemia, and sickle cell anemia have been found to be protective against some sickle cell complications, e.g.,
  - Acute Chest Syndrome (ACS),
  - Anaemia (because of decreased rate of haemolysis), and
  - Cerebrovascular accidents (CVA)

- However, it increases susceptibility to other sickle cell complications, such as pain crises.
Modulators of disease severity

Fetal Haemoglobin

- An important factor known to ameliorate severity of sickle cell disease is the persistence of high level of haemoglobin F (Hb F) in the erythrocytes (hereditary persistence of foetal haemoglobin).

- However, this condition is rare, and is found in only 1:188,000 individuals with SCD.

- In these individuals, Hb F comprises > 20% of the haemoglobin in the erythrocytes.

- Hydroxyurea, act by raising foetal haemoglobin levels.
<table>
<thead>
<tr>
<th>Disease variant</th>
<th>β genotype</th>
<th>Hb electrophoresis</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell trait</td>
<td>βA/βS</td>
<td>HbS 35-45%</td>
<td>Heterozygous &quot;sickle cell trait&quot; • Clinically asymptomatic</td>
</tr>
<tr>
<td>(HbAS)</td>
<td></td>
<td>HbA 55-60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 &lt;3.5%</td>
<td></td>
</tr>
<tr>
<td>SCD (HbSS)</td>
<td>βS/βS</td>
<td>HbS 80-96%</td>
<td>Homozygous condition • Most severe form</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbF 2-20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 &lt;3.5%</td>
<td></td>
</tr>
<tr>
<td>SCD (HbSC)</td>
<td>βS/βC</td>
<td>HbS 50-55%</td>
<td>Heterozygous for HbS and HbC • Mild to moderate severity • Retinopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbC 45-50%</td>
<td>more common than in HbSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 &lt;3.5%</td>
<td></td>
</tr>
<tr>
<td>SCD (S/β°-thalassemia)</td>
<td>βS/β°</td>
<td>HbA 0%</td>
<td>Heterozygous for HbS and thalassemia • As severe as HbSS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 4-6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbS 50-85%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbF 2-30%</td>
<td></td>
</tr>
<tr>
<td>SCD (βS/+ -thalassemia)</td>
<td>βS/β+</td>
<td>HbA 10-30%</td>
<td>Mild-to-moderate severity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 4-6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbF 0-20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbS 50-80%</td>
<td></td>
</tr>
<tr>
<td>SCD (HPFH)</td>
<td>βS/HPFH</td>
<td>HbS 60-80%</td>
<td>Often asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA 0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA2 &lt;3.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbF 15-35%</td>
<td></td>
</tr>
</tbody>
</table>
Modulators of disease severity

- Homozygous sickle cell disease and sickle β0-thalassemia have a comparable spectrum of severity.

- If the child inherits an S gene from one parent and another abnormal haemoglobin, such as D, G or O, from the other parent, other rarer variants result.

- Persons with sickle cell trait (the carrier form of this recessive condition) have more than 50 percent normal hemoglobin.

- They are essentially asymptomatic, except under unusual circumstances.
Development of clinical disease

- Haematologic changes indicative of SCD are evident as early as 10 weeks of fetal life, symptoms usually do not develop until the age of 6-12 months because of high levels of circulating fetal haemoglobin.

- After infancy, erythrocytes of patients with sickle cell anemia contain approx 90% HbS, 2-10% HbF, and normal amount of minor fraction of HbA2.

- Adult haemoglobin (HbA), which usually becomes predominant at the age of 3 months, is absent.

- This physiological changes in RBCs result in a disease with the following cardinal signs:
  1. hemolytic anemia;
  2. painful vaso-occlusive crisis; and
  3. multiple organ damage from microinfarcts, including heart, skeleton, spleen, and central nervous system.
Distribution of Normal Haemoglobins in the foetus and after birth
Clinical manifestations

- Sickle-cell anaemia covers a wide spectrum of illnesses.
- Most of the clinical problems associated with sickle cell disease are described as crises.
- Four major types of crises are associated with sickle cell anaemia.

These are:
- Vaso-occlusive crisis
- Splenic/hepatic sequestration crisis
- Erythroblastopenic (aplastic) crisis
- Hyperhaemolytic crisis
Clinical manifestations (cont)

- Known and unknown environmental factors can precipitate sickle cell crises; some of which are:
  - Dehydration
  - Infection
  - Fever
  - Hypoxia (decrease in oxygen to body tissue)
  - Bleeding
  - Cold exposure
  - Drug and alcohol use
  - Pregnancy and stress

- It is pertinent to know that sickle cell disease affects almost all organs in the body.
Early Symptoms and Complications

- Typically appear during infant's first year
  - 1st symptom: dactylitis and fever (6 mo-2 yrs)
  - Pain in the chest, abdomen, limbs and joints
  - Enlargement of the heart, liver and spleen, epistasis
  - Frequent upper respiratory infections
  - Chronic anemia as children grow older

- Over time Sickle Cell sufferers can experience damage to organs such as liver, kidney, lungs, heart and spleen

- Can result in death
Presentation of Sickle Cell Disorder

abnormal hemoglobin → sickling of red blood cells → rapid destruction of sickled cells → anemia → overactivity of bone marrow → weakness and fatigue → skull deformation

abnormal hemoglobin → sickling of red blood cells → clumping of cells and interference with blood circulation → heart damage (local failures in blood supply) → lung damage → pneumonia → heart failure

abnormal hemoglobin → sickling of red blood cells → collection of sickle cells in the spleen → gastrointestinal tract damage → brain damage → paralysis → abdominal pain

abnormal hemoglobin → sickling of red blood cells → collection of sickle cells in the spleen → kidney damage → enlargement, then fibrosis of spleen

increase in amount of bone marrow → dilatation of heart → poor physical development → impaired mental function

increase in amount of bone marrow → overactivity of bone marrow → kidney failure
Medical Complications

1. pain episodes
2. strokes
3. increased infections
4. leg ulcers
5. bone damage
6. yellow eyes or jaundice
7. early gallstones
8. lung blockage
9. kidney damage and loss of body water in urine
10. painful erections in men (priapism)
11. blood blockage in the spleen or liver (sequestration)
12. eye damage
13. low red blood cell counts (anaemia)
14. delayed growth
Serious Complications

- **Infectious complications**
  - Prominent early in life
  - Leading cause of morbidity and mortality
  - Great improvement in the prognosis related to newborn screening for sickle cell disease, vaccination for childhood illnesses, the use of prophylactic antibiotics, and aggressive diagnosis and treatment of febrile events

- **Acute splenic sequestration**
  - Episodes of rapid increase in splenic size and decrease in hemoglobin
  - Potential source of morbidity and mortality early in life for children with sickle cell anemia and at any age for those with Hb SC disease and sickle thalassemia
Serious Complications

- **Strokes**
  - Up to 15% of children may have overt or silent strokes during childhood
  - Chronic transfusion therapy reduces the recurrence rate of overt stroke which may approach 75% without intervention

- **Bone disease**
  - Early risk is primarily from osteomyelitis
    - Infectious usually painful inflammatory disease of bone often of bacterial origin and may result in bone tissue death
  - Avascular necrosis of the femur and humerus
    - Death of bone tissue due to disrupted blood supply
    - Marked by severe pain in the affected region and by weakened bone that may flatten and collapse
Serious Complications

- **Leg ulcers**
  - Seen in patients older than 10 years of age
  - Resistant to therapy and cause significant morbidity

- **Ophthalmic complications**
  - Proliferative retinopathy, vitreous hemorrhage, & retinal detachment

- **Priapism**
  - Distressing complication that occurs at all ages
  - Difficult to treat
  - Causes a high incidence of impotence

- **Chronic Anemia**
  - Associated with fatigue, irritability, jaundice, pain, delayed puberty, leg sores, eye problems, gum disease
Serious Complications: PAIN

Recurrent Pain Episodes or Sickling Crises

- Occur at any age but appear to be particularly frequent during late adolescence and early adult life:
  - Unpredictable
  - Red Blood Cells get stuck in the small veins and prevent normal blood flow
  - Characterized by severe pain in the back, chest, abdomen, extremities, and head
  - Highly disruptive to life
  - Most common reasons for individuals to seek health care
## Symptomatology and Clinical Manifestations of Vaso-occlusive Crisis

<table>
<thead>
<tr>
<th>Symptomatology</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot syndrome (dactylitis)</td>
<td>Under 5 years of age; painful swelling of the hands and feet</td>
</tr>
<tr>
<td>Bone pain crisis</td>
<td>Painful bone crises usually beginning at age 3 years; must be distinguished from osteomyelitis</td>
</tr>
<tr>
<td>Abdominal crises (sickle cell girdle syndrome)</td>
<td>Related to sickle cell vaso-occlusion of mesenteric blood supply and infarction in the liver, spleen, or lymph nodes that results in capsular stretching; must be distinguished from acute abdomen</td>
</tr>
<tr>
<td>CNS crises</td>
<td>May include convulsions, meningeal signs, blindness, radiculopathy, vertigo and acute mental syndrome, cerebral infarction. Incidence: 7-29%; mean age of onset 7.7 years and increased incidence of subarachnoid haemorrhage</td>
</tr>
<tr>
<td>Symptomatology</td>
<td>Manifestations</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pulmonary crises (acute chest syndrome)</td>
<td>Presents with chest pain that may be pleuritic, unexplained dyspnoea, and fever; differential diagnosis from pneumonia may be difficult; it may be associated with full-blown sickle cell girdle syndrome.</td>
</tr>
<tr>
<td>Priapism</td>
<td>Predisposing factors: sexual intercourse, masturbation, infection, and local trauma; impotence in many cases</td>
</tr>
<tr>
<td>Haematuria</td>
<td>Painless and usually mild; defect is papillary necrosis</td>
</tr>
<tr>
<td>Intrahepatic vaso-occlusive crisis (hepatic sequestration)</td>
<td>Sudden, painful enlargement of liver; massive rise in bilirubin (mostly direct) and liver enzymes; it may occur at any age once the spleen has atrophied and fibrosed.</td>
</tr>
</tbody>
</table>
Danger Signs of a Crisis

1. Fever
2. Chest pain
3. Shortness of Breath
4. Increasing tiredness
5. Abdominal swelling
6. Unusual headache
7. Any sudden weakness or loss of feeling
8. Pain that will not go away with home treatment
9. Priapism (painful erection that will not go down)
10. Sudden vision change

SEEK URGENT HOSPITAL TREATMENT IF IN CRISIS
Diagnosis

Prenatal Testing:

- Accurate diagnosis can be made by restriction endonuclease analysis of DNA prepared from foetal fibroblasts (obtained by amniocentesis), or

  - Amniocentesis
    - 16 and 18 weeks of the pregnancy
    - small risk of causing a miscarriage (1 in 100)

  - Chorionic villus sampling (CVS)
    - 9th or 10th week of pregnancy
    - very small amount of material from the developing placenta
    - slightly higher chance of miscarriage
Diagnosis

During newborn period:
- High-performance liquid chromatography (most commonly used)
- Citrate agar with pH of 6.2, a system that provides distinct separation of haemoglobin S, A, and F.
- Acid and alkaline electrophoresis
- PCR amplification of DNA.

These tests can be performed on cord blood or on dried blood specimen blotted on filter paper.

In older children:
- Alkaline electrophoresis
Laboratory Diagnosis

- Solubility testing methods (Sickledex, Sicklequik) and sickle cell preparations are inappropriate diagnostic techniques.
  - Although solubility testing identify sickle haemoglobin, they miss haemoglobin C and other genetic variants.
  - Solubility testing is inaccurate in the newborn, in whom fetal haemoglobin is overwhelmingly predominant.
  - Solubility testing methods also fail to detect sickle hemoglobin in persons with severe anemia.
  - Although haemolysis is a feature of all forms of sickle cell disease, patients with haemoglobin SC disease or sickle β+-thalassemia may not have significant anemia.

- Thalassemia is suspected if microcytosis or hypochromia is present in the absence of iron deficiency.

- DNA analysis provides the most accurate diagnosis in patients of any age, but it is still relatively expensive.
MANAGEMENT

Comprehensive care:
- Prevention of complications is as important as treatment – which is best provided in a comprehensive setting.
  - Infections should be prevented through immunization and malaria prophylaxis as soon as diagnosis is made
  - Folate therapy prevents anaemic crisis
  - Regular clinic follow-ups even when there are no problems.

Early diagnosis of infection requires:
- Education of the family to identify a child with fever and prompt presentation to the physician
- The child should be seen immediately by a physician
Health Maintenance

- Frequent visits: every 3 to 6 months
- Immunizations
  - Routine immunizations, including Hib
  - 7 valent Pneumovax at infancy
- Penicillin prophylaxis beginning not later than two months
- Nutrition and fluids
Health Maintenance

- Physical exam with attention to:
  - Growth and development, jaundice, liver/spleen size, heart murmur of anemia, malocclusion from increased bone marrow activity, delayed puberty

- Lab evaluations:
  - CBC with differential and reticulocyte count, urinalysis, renal & liver function
Routine health maintenance-related laboratory and special studies in patients with sickle cell disorder.

<table>
<thead>
<tr>
<th></th>
<th>Starting age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td>At diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Red cell antigen typing</td>
<td>At diagnosis</td>
<td>--</td>
</tr>
<tr>
<td>Liver and renal functions</td>
<td>At diagnosis</td>
<td>Yearly</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>1 year</td>
<td>Yearly</td>
</tr>
<tr>
<td><strong>Special studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>5 years</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>5 years</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Eye examinations</td>
<td>5 years</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>Transcranial Doppler</td>
<td>2 years</td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Current Recommendations - penicillin prophylaxis

- **Penicillin Prophylaxis: SS, Sβ° Thalassemia**
  - 2 months to 3 years: 125 mg PO BID
  - Over 3 years: 250 mg PO BID
    - When to discontinue is controversial

- **Penicillin Prophylaxis: SC and Sβ⁺ Thalassemia**
  - SC warrants penicillin prophylaxis similar to SS
  - Sβ⁺ Thalassemia: penicillin prophylaxis can be safely discontinued at 5 years
    - Routine use in infants and children is controversial

- **Special Circumstances**
  - History of repeated sepsis, surgical splenectomy
Eye Examination

- Retinal vessel disease
  - Incidence 33% in hemoglobin SC
  - Incidence 3% in SS
- Annual evaluation after age 10 years by ophthalmologist
  - Laser photocoagulation for vessel disease
Emergencies

- Fever/infection
- Acute chest syndrome
- Eye trauma (hyphema)
- Priapism
- Stroke
- Splenic sequestration
- Severe pain
Fever and Infection

- Fever > 38.5°C (101°F) is an **EMERGENCY**
- Basic laboratory evaluation:
  - CBC with differential and reticulocyte count, blood, urine, and throat cultures, urinalysis, chest x-ray

- Indications for hospitalization & IV antibiotics:
  - Child appears ill
  - Any temperature > 40°C
  - Abnormal laboratory values

- Start IV antibiotics **IMMEDIATELY** if child appears ill or temperature > 40°C (DO NOT WAIT FOR LABS)
Acute Chest Syndrome

A leading cause of death in sickle cell disease

Clinically:

- Acute onset of fever, respiratory symptoms, new infiltrate on chest x-ray

Causes

- Infection
- Fat emboli
- Lung infarct

Treatment:

- Antibiotic therapy - should consist of a cephalosporin with macrolides - Mycoplasma infection.
- Oxygen,
- Blood transfusion
Eye Trauma

Eye trauma is an emergency in ALL sickle conditions (including sickle trait)

- Get sickle prep -rapid test- if sickle status unknown
- Complications if untreated:
  - glaucoma,
  - optic nerve atrophy,
  - retinal artery blockage
Priapism

Commonly occurs in children and adolescents with SS or SC

Treatment is difficult
- Opioid pain medication
- Intravenous fluids
- Aspiration and irrigation of the corpus cavernosum
- Surgery
- Blood Transfusions

Impotence with severe disease or recurrent episodes
Splenic Sequestration

- Sudden trapping of blood within the spleen
- Usually occurs in infants under 2 years of age with SS
- Spleen enlarged on physical exam, may not be associated with fever, pain, respiratory, or other symptoms
- Circulatory collapse and death can occur in less than thirty minutes

Recurrence very common (50%) Associated with high mortality (20%)
Splenic Sequestration

- **Hemoglobin SS**
  - Incidence increased: 6 and 36 months
  - Overall incidence about 15%

- **Hemoglobin SC**
  - Incidence increased: 2 and 17 years
    - Mean age 8.9 years
    - Can occur in adolescence and adulthood
    - Incidence about 5%
Treatments For Splenic Sequestration

- Intravenous fluids
  - Maintain vascular volume
- Cautious blood transfusion
  - Treat anemia, sequestered blood can be released from spleen
- Spleen removal or splenectomy
  - If indicated
Pain Management

Acute pain

- Hand-foot syndrome (dactylitis)
- Painful episodes: vasoocclusion
- Splenic sequestration
- Acute chest syndrome
- Cholelithiasis
- Priapism
- Avascular necrosis
- Right upper quadrant syndrome
Pain Management

**Pain is an emergency**

Hospital evaluation:

- Hydration: 1.5 times maintenance unless acute chest syndrome suspected
- Assess pain level and treat
  - Do not withhold opioids
  - Frequently reassess pain control
- Assess for cause of pain/complications
Pain Management

Mild-moderate pain

- **Acetaminophen**
  - Hepatotoxic

- **Non-steroidal anti-inflammatory agents (NSAIDs)**
  - Contraindicated in patients with gastritis/ulcers and renal failure
  - Monitor renal function if used chronically
Pain Management

- Moderate-severe pain
  - Opioids are first-line treatment
  - Morphine sulfate or hydromorphone
  - Meperidine NOT recommended
    - (Metabolite causes seizures & renal toxicity)

- Moderate or less severe pain
  - Acetaminophen or NSAID's in combination with opioids
  - Other adjuvant medications (sedatives, anxiolytics)
    - May increase efficacy of analgesics
## Recommended initial Dose and Interval of Analgesics in Children

<p>|                  | Dose (mg)                          | Route   | Interval | Comment                                                        |
|------------------|------------------------------------|---------|----------|                                                               |
| <strong>Severe pain</strong>  |                                    |         |          |                                                               |
| Morphine         | 0.15 mg/kg/dose (max 10 mg)        | S.C, I.M| q3h      | Drug of choice                                                |
| Meperidine       | 1.5 mg/kg/dose (max 100 mg)        | I.M     | q3h      | Increased incidence of seizures; avoid in patients with renal or neurologic disease |
| <strong>Moderate pain</strong>|                                    |         |          |                                                               |
| Oxycodone        | 0.1-0.2 mg/kg/dose                 | PO      | q4h      | Patient over 5 yr                                            |
| Methadone        | 0.15 mg/kg/dose                    | PO      | q6h      | Effective in patients usually requiring parenteral narcotics; NOT FOR ROUTINE USE |
| Meperidine       | 1.5 mg/kg/dose (max 100mg/dose)    | PO      | q3½h     |                                                               |</p>
<table>
<thead>
<tr>
<th>Mild pain</th>
<th>Dose (mg)</th>
<th>Route</th>
<th>Interval</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.5-1.0 mg/kg/dose</td>
<td>PO</td>
<td>q4h</td>
<td>May be effective up to 6 hours</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10-15 mg/kg/dose (max 80 mg/kg/day)</td>
<td>PO</td>
<td>q4h</td>
<td>May be given with a narcotic for added analgesia</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>10-15 mg/kg/dose (max 90 mg/kg/day)</td>
<td>PO</td>
<td>q4h</td>
<td>May be given with a narcotic for added analgesia</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>5-10 mg (max 40 mg/kg/day)</td>
<td>PO</td>
<td>q6h</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>5-6 mg mg/kg/dose (max 24 mg/kg/day)</td>
<td>PO</td>
<td>q12h</td>
<td></td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.25-0.5 mg/kg/dose (max 2 mg/kg/day)</td>
<td>IV</td>
<td>q6h</td>
<td></td>
</tr>
</tbody>
</table>
Chronic Pain

- Pain lasting >3 to 6 months
- Patients should receive comprehensive psychologic and clinical assessment

Treatment
- Analgesics
- Hydroxyurea
- TENS units
- Relaxation techniques
- Physical and occupational therapy
**Stroke**

Any acute neurologic symptom other than mild headache, even if transient, requires urgent evaluation.

- Historically 8 to 10% of children with SS usually infarctive stroke
- “Silent Stroke” in 22% of children with hemoglobin SS
- Intracranial hemorrhage
  - More common in adults

Treatment: Chronic transfusion therapy to maintain sickle hemoglobin at or below 30%
Stroke - Prevention

- Transcranial Doppler (TCD) ultrasonography is a sensitive, noninvasive method for assessing blood flow velocities in the large intracranial vessels of the circle of Willis.
- This method has been used to determine risk of developing stroke in children with sickle cell disease.
TCD Screening

All children 2–18 years of age with SCD-SS or SCD-S beta thalassemia should have at a minimum 1 TCD study per year.

Mean TCD velocities in the ICA or MCA is interpreted as follows:

- < 170 cm/sec = low risk ("normal")
- 170–200 cm/sec = intermediate risk abnormal ("conditional")
- > 200 cm/sec = high risk ("abnormal")

Note: In normal children 5–15 years old, mean TCD velocity in MCA is 79 ± 13.
Recommendations for clinical management of patients with abnormal TCD

- All abnormal TCD results in asymptomatic patients must be repeated.
- Intermediate risk abnormal results, repeat TCD within 16 weeks of the abnormal study, and every 26 weeks thereafter if results are still in the same range.
- Children with high-risk abnormal results, repeat TCD and MRI/MRA within 4 weeks.
- If high-risk abnormal results are confirmed, offer chronic transfusion therapy.
- *There is no proven alternate method of management for these patients.*
- If transfusion therapy is refused, clearly document the refusal in the patient’s medical record.
### Summary of Action on TCD Result

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; TCD Study</th>
<th>Action</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; TCD Study</th>
<th>Follow-up Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 170 cm/sec</td>
<td>Next TCD in 1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>170–199 cm/sec</td>
<td>Next TCD in 16 weeks</td>
<td>170–199 cm/sec</td>
<td>Next TCD in 26 weeks</td>
</tr>
<tr>
<td>≥ 200 cm/sec</td>
<td>Next TCD + MR in 4 weeks</td>
<td>≥ 200 cm/sec</td>
<td>Offer transfusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 200 cm/sec + MR abnormal</td>
<td>TCD in 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 200 cm/sec + MR normal</td>
<td>TCD in 16 weeks</td>
</tr>
</tbody>
</table>
Transfusion Therapy

Red cell transfusions or partial exchange transfusions may be used as primary treatments for the following conditions:

- Anaemia
- Aplastic crisis
- Splenic sequestration crisis
- Hyperhaemolytic crisis
- Refractory painful crisis
- Acute chest syndrome
- Congestive heart failure
- Priapism
- Chronic leg ulcers
- CVA (HbSS must be reduced to <20% at all times)
- Serious infections (i.e., sepsis, meningitis)
- Pregnancy
- Elective surgical procedures
Transfusion Therapy

Always consider the risk of infection when you decide to transfuse blood (hepatitis B virus, hepatitis C virus, HIV), iron overload, and alloimmunization and dearth of blood for transfusion in our setting.

Ideally, patients should receive blood that is
- leukocyte depleted,
- sickle cell negative, and
- phenotypically matched to the patient for the Rh and Kell antigens.

Recombinant human erythropoietin may ameliorate the anaemia of sickle cell disease.
Adolescents and Transition of Care

- Young adults (>20 years) with frequent pain crises at greatest risk for early death

- Barriers to care for young adults
  - Lack of adult SCD providers
  - Loss of medical coverage
  - Developmental (level of independence, denial of chronic illness)
  - Ineffective coping skills (passive versus active)
Adolescents and Transition of Care

- Develop explicit plan for transition

- Team approach - pediatric and adult providers, social work, school/vocational staff, support groups

- Plan gradual transition (start 1 year before)

- Continue communication between pediatric & adult providers after transition
References:


Thank You For Listening