Sickle Cell Disease (SCD) for Primary Care Providers in Resource-Limited Health Settings

/ Educational Manual /

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Preface:

TCH Global HOPE sickle cell disease (SCD) training program for primary care providers was inspired by the observation that unlike in high-income countries where children with SCD are treated by specialists, most affected children in sub-Saharan Africa do not receive organized care and the few who do are treated in large clinics located in general hospitals far from where most of them live. This course aims to remedy this issue by teaching local health care providers on how to manage SCD. It is designed for clinicians who provide the initial care for children with an undiagnosed health concern or continuing care for those already diagnosed with SCD. Training nurses and physicians who practice in community health centers and district hospitals will bring SCD care closer to where affected children live, and improve efficiency in referral hospitals by allowing these hospitals to focus on children with complications. This manual and its accompanying video lectures, and quizzes in TCH Global HOPE's online education website [*https://txchglobalhope.moodle.school/my/*] will introduce course participants to the essential components of the diagnosis and management of SCD in children.

Acknowledgements:

This work would not have been possible without the support of US- and Angola-based colleagues on Angola Sickle Cell Initiative (ASCI) – a collaboration between Chevron, Texas Children's Hospital, Baylor International Pediatric AIDS Initiative (BIPAI), and the Ministry of Health. I am especially indebted to **Silvina Kahan** (ASCI's Angola country director), and **Emily Freedman**, ASCI administrator in Houston, Texas. I am also grateful to **Titilope Fasipe**, my colleague at the Texas Children's Hematology Center for editorial assistance, and to Marilyn Hockenberry and Jennifer Higgins for their help in organizing the online component of this course.

Financial and other support to complete this work was provided by Chevron and Texas Children's Hospital.

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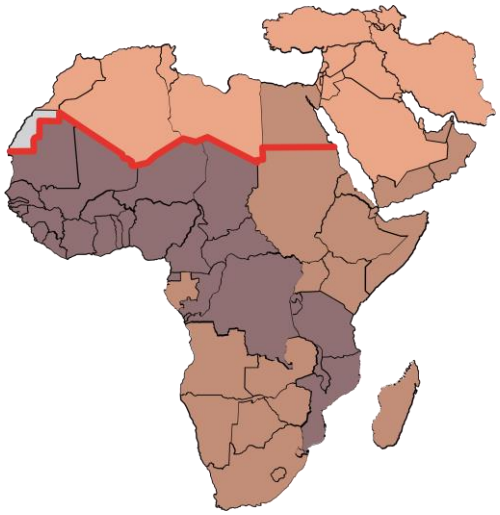
Acronyms

ACS	Acute chest syndrome
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ARC	Absolute reticulocyte count
ASCI	Angola Sickle Cell Initiative
ASS	Acute spleen sequestration
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
CBC	Complete blood count (also called FBC)
CDC	US Centers for Disease Control and Prevention
DMT	Disease-modifying therapy
ESR	Erythrocyte sedimentation rate
FBC	Full blood count (also called CBC)
G6PD	Glucose-6-phosphate dehydrogenase
H. flu	Haemophilus influenzae
Hgb	Hemoglobin
Hgb F	Fetal hemoglobin
Hgb S	Sickle hemoglobin
Hib	Haemophilus influenzae type b
HIC	High-income countries
HPLC	High-performance liquid chromatography
IEF	Isoelectric focusing
IM	Intramuscular
IV	Intravenous
LDH	Lactate dehydrogenase
MCV	Mean cell volume (also called mean corpuscular volume)
MCV4	Meningococcal conjugate vaccine
MMR	Measles, mumps, and rubella
MRI	Magnetic resonance imaging
MUAC	Mid-upper arm circumference
NSAID	Nonsteroidal anti-inflammatory drug

PCV13	Pneumococcal conjugate vaccine
PLT	Platelet count
POC	Point-of-care
PPSV23	Pneumococcal polysaccharide vaccine
RBC	Red blood cells
RDT	Rapid diagnostic test
S. aureus	Staphylococcus aureus
S. pneumoniae	Streptococcus pneumoniae (also called pneumococcus)
SAM	Severe acute malnutrition
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCT	Sickle cell trait
SSA	Sub-Saharan Africa
TCD	Transcranial Doppler
TCH Global HOPE	Texas Children's Hospital Global Hematology-Oncology Pediatric Excellence
WBC	White blood cells
WHO	World Health Organization

UNIT 1:
OVERVIEW OF ANEMIA

Prevalence and Definition of Anemia



Michael Stencel, 2020
Anemia prevalence in SSA

Anemia is a condition that occurs when the body does not have enough normal red blood cells or hemoglobin. Red blood cells (RBC) contain hemoglobin, a protein that transports oxygen from the lungs to the rest of the body and then carries carbon dioxide back to the lungs where we breathe it out. Red blood cells are produced in the bone marrow, the semi-solid tissue found within the bones. To effectively make red blood cells, the bone marrow requires protein, iron, and vitamins such as folate, vitamin B12, vitamin A, etc. Significant anemia commonly results in pale skin and tiredness.

Globally, anemia affects billions of people. Based on population surveys, the prevalence of anemia in children younger than 5 years is 40% or higher in all sub-Saharan Africa (SSA) countries. In the countries shaded dark brown in this SSA map, anemia affects more than 60 percent of young children.

Because normal hemoglobin level varies according to age and gender, the World Health Organization (WHO) defines anemia as a hemoglobin concentration less than 11.0 g/dL for children 6 months to 5 years old, hemoglobin less than 11.5 g/dL for those who are 5–11 years old, and hemoglobin less than 12.0 g/dL for children who are 12–14 years old. Hemoglobin concentration less than 7.0 g/dL in children younger than 5 years, or less than 8.0 g/dL in children older than 5 years is severe anemia.

Causes of Anemia

Anemia results from three possible methods: decreased production of red blood cells in the bone marrow, increased breakage of red blood cells, or blood loss. Some patients may have more than one of these three mechanisms at the same time. The main etiologies of anemia vary widely in different settings. In Africa, common causes include deficiencies of iron, folate, vitamin A, vitamin B12, etc. that hinder the production of red blood cells; infections such as malaria that cause both decreased production and increased breakage of red blood cells; and infections such as schistosomiasis or hookworm that cause both decreased production of red blood cells and blood loss. Other common causes of anemia in Africa include inherited conditions such as sickle cell disease (SCD) and glucose-6-phosphate dehydrogenase (G6PD) deficiency that cause increased breakage of red blood cells.

Laboratory Testing

When anemia is suspected, a test to directly measure the hemoglobin level should be performed. Although bedside or point-of-care (POC) devices such as the hemoglobin color scale and portable hemoglobin meters, e.g., HemoCue® are convenient, automated laboratory-based machines that analyze the three main types of blood cells – red blood cells, platelets, and white blood cells (WBC) including the percentage of each WBC type (neutrophils, eosinophils, basophils, monocytes, and lymphocytes) are more accurate and should be used if available. This is called a complete blood count (CBC) or full blood count (FBC).

Complete Blood Count

To assess red blood cells, automated laboratory-based machines directly measure hemoglobin concentration, number of RBC, and the average size of the red cells (also called the mean cell volume – MCV). An example of an actual CBC report from a patient is below.

CBC W/Plat & Diff

	Ref Range & Units	
WBC	5.0 – 14.5 10^3/µL	5.22
RBC	4.0 – 5.2 10^6/µL	4.49
HGB	11.5 – 15.5 G/DL	12.5
HCT	35.0 – 45.0%	37.6
MCV	76.0 – 90.0 FL	83.7
MCH	26.0 – 30.0 PG	27.8
MCHC	32.0 – 36.0 G/DL	33.2
RDWCV	11.5 – 14.0 %	13.2
RDWSD	38.5 – 49.0 FL	40.4
Platelet	150 – 450 10^3/µL	338
MPV	6 – 10 FL	9.7
Differential Type		AUTO
Seg%	33 – 76%	68.0
Lymph%	15 – 61 %	19.3
Mono%	0 – 5%	8.8^
EOS%	0 – 3%	3.1^
Baso%	0 – 1%	0.6
IG%	0%	0.2^
ANC	1.5 – 8.0 10^3/µL	3.55
NRBC%	0%	0
NRBC Absolute	10^3/µL	0.00

The MCV is helpful to determine the cause of anemia. In general, a high MCV (macrocytosis) suggests vitamin B12 or folate deficiency while a low MCV (microcytosis) suggests iron deficiency or thalassemia. Normal MCV varies depending on age. During childhood, MCV higher than 90 fL is higher than average. The expected lower limit of MCV in children can be estimated by adding 70 to the child's age in years. For example, the MCV of a 6-year-old is low if it is less than 76 fL. Most children with SCD have normal MCV.

Some automated machines are also able to count reticulocytes in blood. Reticulocytes are newly formed red blood cells released from the bone marrow to replace red cells that are destroyed by disease, or as part of the normal process of replacing old red cells. In normal children, about 0.5%–2% of circulating red cells are reticulocytes. The number of these 'newborn red cells' (reticulocytes) in the blood is a useful indicator of production activity in the bone marrow where red blood cells are made. A reticulocyte count below 0.5% is typical of conditions where the production of red blood cells is reduced such as infection, replacement of bone marrow by leukemia, and a deficiency of materials such as iron, vitamin B12, or folate that are required to make red cells. On the other hand, blood loss or conditions characterized by fragile red blood cells such as SCD, cause the bone marrow to increase production to replace the red blood cells that are lost. Consequently, a reticulocyte count that is much higher than 2% is seen in these conditions.

Management of Anemia

Children with fever should be checked for infections — especially malaria — and then treated appropriately. Specific treatment should be based on the cause of anemia. CBC with reticulocytes plus a review of a blood smear may help to determine etiology. For example, the involvement of other blood cells such as platelets and white cells in addition to anemia may indicate leukemia or bone marrow failure. Elevated MCV may be seen in vitamin B12, folate deficiency, liver disease, bone marrow failure, or red cell production defects. As previously mentioned, elevated reticulocytes suggest hemolysis, and when hemolysis is seen, a blood smear may suggest the cause such as sickled cells in SCD, spherocytes (autoimmune hemolysis), or neutrophils with abnormal appearing nuclei in B12 or folate deficiency.

Transfuse anemic children with Hgb less than 4 g/dL or those with Hgb between 4 g/dL–6 g/dL if signs of shock, heart failure, or severe malaria are also present. Children suspected to have iron deficiency should receive oral iron. However, iron therapy should be delayed in children with acute infection or severe acute malnutrition (SAM).

Prevention of Anemia

Since anemia affects more than half of all children living in SSA and is associated with poor cognitive and motor development and an increased risk of death, effort to bring awareness and prevent this problem is a priority. Anemia in SSA children is usually due to multiple factors in the same child. In addition to malaria, micronutrient deficiencies (iron, vitamin B12, vitamin A, folate, etc.) due to malnutrition, intestinal helminths such as hookworm, HIV infection, schistosomiasis, and hemoglobinopathies such as SCD are important contributors.

Some recommended strategies to combat anemia include the following:

- Promote late clamping of umbilical cord (not earlier than 1 minute after birth) in term and preterm newborns who do not require positive-pressure ventilation. This delay increases iron stores of babies
- Control malaria in pregnant women and young children through the prompt treatment of acute malaria and through the use of chemoprophylaxis/intermittent preventative treatment depending on region of SSA. Other effective malaria control strategies include use of insecticide-treated nets, and vector (mosquito) elimination with indoor spraying, etc.
- Regularly deworm children who live in areas where baseline prevalence of worm infestation is 20% or higher. Most regions of SSA meet this criterion
- Promote a diet containing adequate amounts of micronutrients including iron, folate, etc., and in areas where baseline prevalence of anemia in young children is 40% or higher, give iron-containing micronutrient supplements. Most regions of SSA meet this criterion
- Teach basic hygiene to reduce the risk of infection. Interventions to improve water and sanitation help to reduce the extent of inflammation and reduce nutritional losses due to infection
- Screen all newborns for SCD. If this is not yet possible, be quick to test children who present with anemia or other signs that suggest SCD.

Unit 1 Case Study / Quiz

1-1:	True (T) or False (F)?
	Normal hemoglobin level in children younger than 14 years varies according to whether patient is male or female?
1-2:	True (T) or False (F)?
	While evaluating anemia with a complete blood count from an automated machine, the mean cell volume (MCV) is very important in suggesting the cause of the anemia
1-3:	True (T) or False (F)?
	An African child who is noted to have anemia during a malaria illness is not likely to have other factors in addition to malaria to explain the anemia.

UNIT 2:
EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF SCD

What is SCD?

SCD is a group of inherited diseases in which sickle hemoglobin (Hgb S) is the predominant type of hemoglobin within the red blood cells. Red cells that contain mostly Hgb S do not function normally in the body. In patients with SCD, normal Hgb A is absent or reduced below 50%.

Hemoglobin is the protein within RBC that carries oxygen and supplies it to the body's tissues including the brain, bones, kidneys, etc. RBC that contain mostly Hgb S are called sickle cells, and they do not function normally.

What is sickle cell trait (SCT)?

A person who inherits one sickle hemoglobin (Hgb S) gene from one parent plus one normal (Hgb A) gene from the other parent is said to have sickle cell trait. SCT is also called Hgb AS because the RBC contain both normal and sickle hemoglobin. Unlike individuals with SCD, people with SCT have normal hemoglobin and reticulocyte count. SCT individuals are healthy because their RBC contain mostly Hgb A and therefore function normally to carry oxygen to the body's tissues. While people with SCT are healthy and do not have SCD, they can pass the sickle cell gene to their children. Although individuals with SCT may have malaria, children with SCT are less likely to die from malaria compared to unaffected children with Hgb AA.

Inheritance of SCD

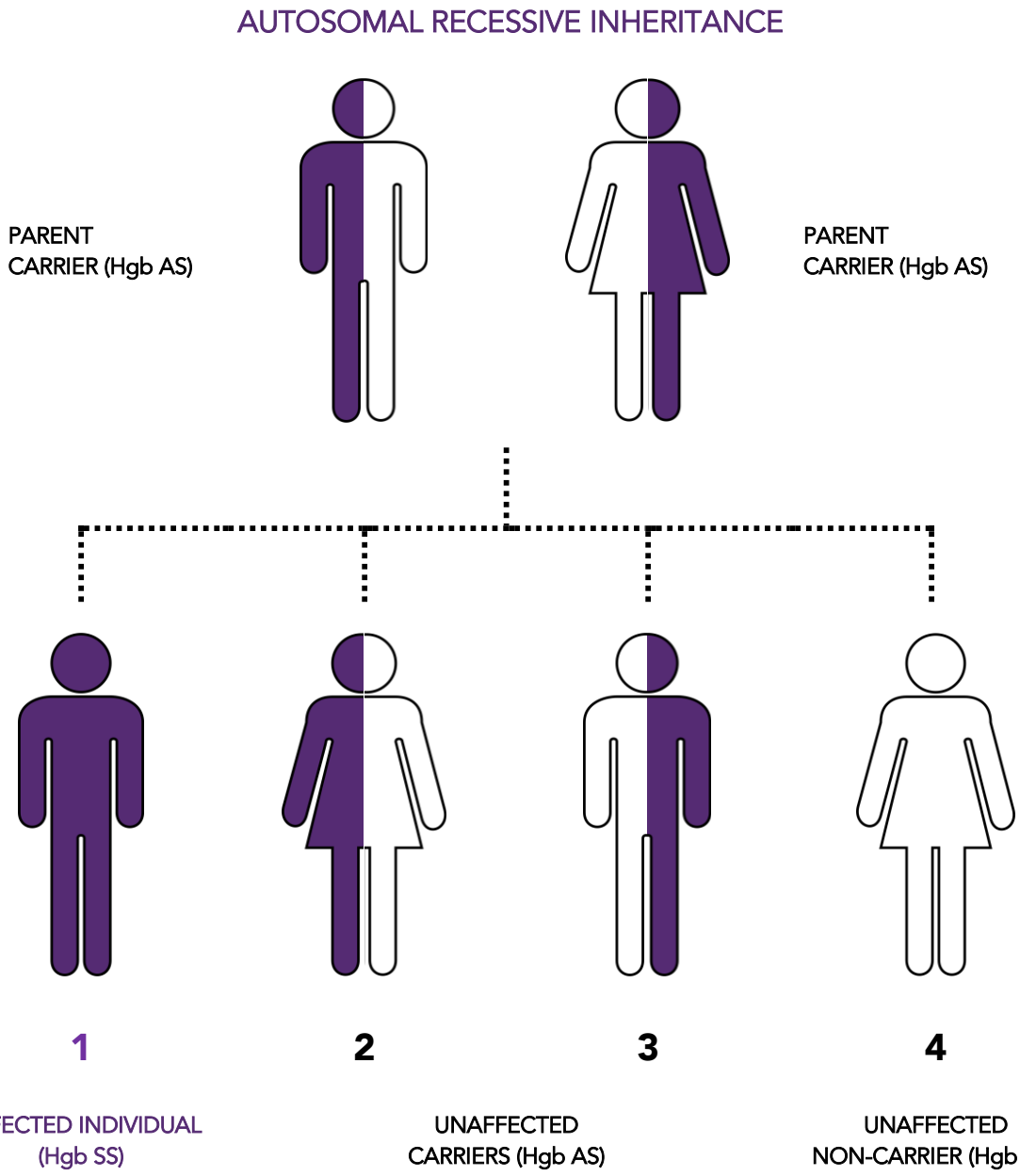
SCD is inherited — i.e., passed from parents to their children through their genes. Genes store information about us such as skin color, height, and the type of hemoglobin contained in our red blood cells. Each person's genes occur in pairs — one from each parent. For example, each individual inherits two beta-globin genes (one from each parent) that determine the type of hemoglobin contained within the red cells. However, only one of these genes can be passed on to a child. The specific one of the two genes that is passed on to a child is random — i.e., similar to tossing a coin.

SCD occurs when a child inherits at least one sickle hemoglobin (Hgb S) gene from one parent plus another abnormal beta-globin gene from the other parent. Most often, the second abnormal beta-globin gene is another sickle hemoglobin (Hgb S) — these children have Hgb SS disease. However, the second abnormal beta-globin gene may be a gene for Hgb C (these children have Hgb SC disease), or Hgb D (affected children have Hgb SD disease), or a beta (ß) thalassemia globin gene (these children are said to have Hgb Sß-thalassemia).

Unlike the genes for Hgb S, C, and D that make Hgb S, Hgb C, and Hgb D respectively, the beta thalassemia gene is abnormal because it does not make hemoglobin at all (beta zero thalassemia; $ß^0$-thal), or makes a reduced amount of Hgb A (beta plus thalassemia; $ß^+$-thal). Children who inherit the sickle hemoglobin gene and the thalassemia zero gene are said to have Hgb Sbeta zero thalassemia or Hgb S$ß^0$-thal. These individuals have only Hgb S in their RBC since the beta zero thalassemia gene does not make any hemoglobin. Patients with Hgb Sbeta plus thalassemia (Hgb S$ß^+$-thal) have Hgb S and a small amount of Hgb A (usually 5%–30%) in their RBC since the beta plus thalassemia gene can make a small amount of normal hemoglobin (Hgb A).

In summary, to have SCD a child inherits two abnormal beta-globin genes – one from each parent. At least one of these abnormal genes must be a sickle cell gene. This is described as autosomal

recessive inheritance. You cannot catch SCD through witchcraft or by touching someone with the disease.



Two parents with sickle cell trait (Hgb AS) have a 1 in 4 chance (25%) of having a child with SCD (Hgb SS), 2 in 4 chance (50%) of a healthy child with Hgb AS (unaffected carrier), and 1 in 4 chance (25%) of a healthy child who does not carry the sickle cell gene (Hgb AA). These percentages apply to each pregnancy.

Types of SCD

Recall that SCD occurs when a child inherits at least one sickle hemoglobin (Hgb S) gene from one parent plus another abnormal beta-globin gene from the other parent. There are several types of SCD – depending on the specific abnormal beta-globin gene inherited with the Hgb S gene. The most common type of SCD is the Hgb SS form (beta-globin gene for Hgb S is inherited from both parents). The Hgb SS form of SCD is also called sickle cell anemia (SCA). Other types include Hgb SC (Hgb S gene from one parent and Hgb C gene from the other parent); Hgb Sß^0-thal (Hgb S gene from one parent and ß^0-thal gene from the other parent); Hgb Sß$^+$-thal, and so on. Although it is not possible to accurately predict how severely the disease will affect any particular person, on average, Hgb SS and Hgb Sß^0-thal tend to be more severe than Hgb SC and Hgb Sß$^+$-thal. The amount of Hgb A present within RBC in patients with Hgb Sß$^+$-thal typically varies from 5%–30% but tends to be stable in an individual patient. In general, Sß$^+$-thal patients with higher Hgb A level are less severely affected than those with Hgb A level in the lower end of the range.

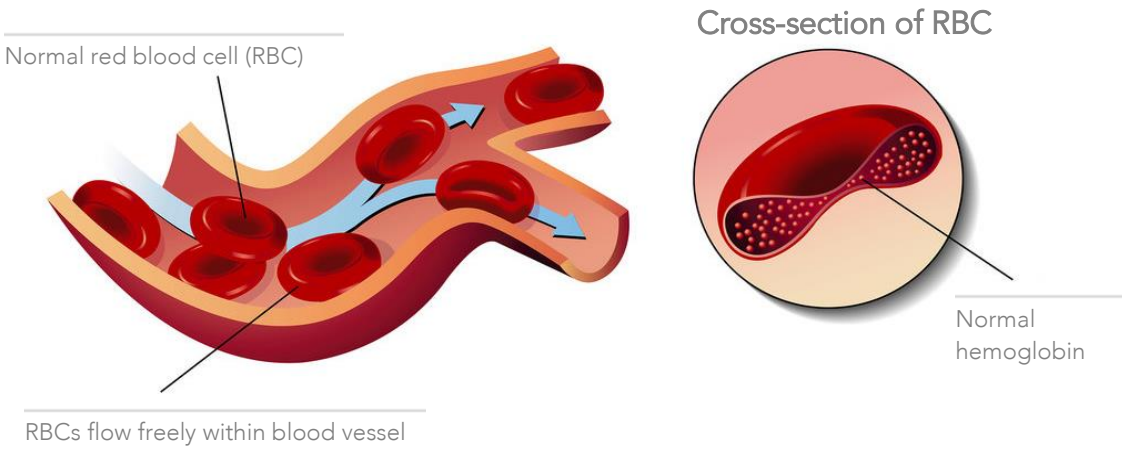
Some Types of SCD

	Inheritance	Comments
Hgb SS (SCA)	Hgb S gene from both father and mother	Most common. Severe
Hgb SC	Hgb S gene from one parent and Hgb C from the other parent	Less common. Moderate severity
Hgb Sß$^+$-thal	Hgb S gene from one parent and ß$^+$-thal from the other parent	Uncommon. Mild-moderate disease depending on how much Hgb A
Hgb Sß^0-thal	Hgb S gene from one parent and ß^0-thal from the other parent	Uncommon. Severe

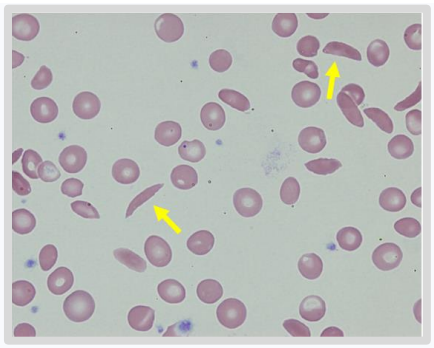
Functional changes in red blood cells due to SCD

- Red blood cells from unaffected individuals including those with SCT (Hgb AS) mostly contain Hgb A. These red cells can bend easily without breaking as they travel through small blood vessels to supply oxygen to tissues. As a result, blood flows smoothly and without hindrance.

Normal red blood cells



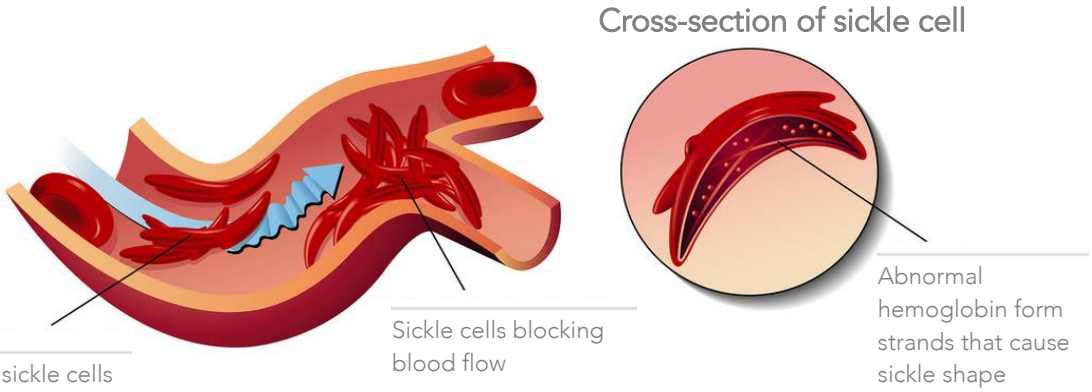
- Hgb S is less soluble within the red blood cell compared to Hgb A. In conditions of low oxygen deep inside the body, solid forms of Hgb S come out of the solution inside the red cell and damages the covering (membrane) of the red cells from within. These solid forms of Hgb S also distort the red cells into a curved shape that resembles an agricultural sickle tool or the letter C. Some of the crescent- or C-shaped sickle cells are highlighted on this blood smear from a patient with SCD.



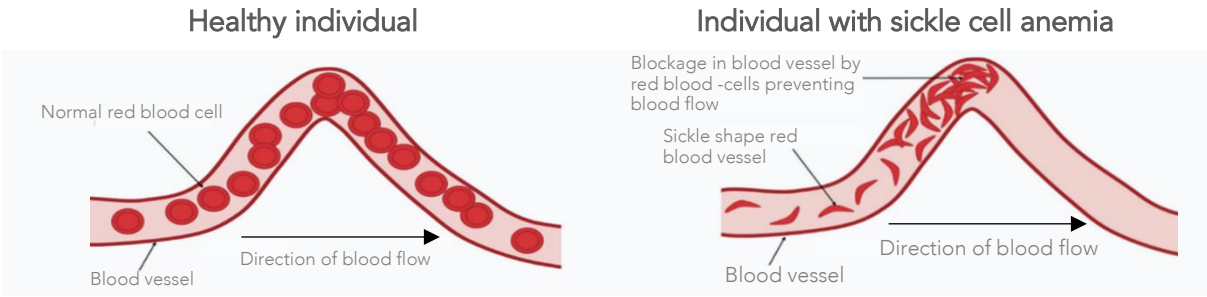
Source: Texas Children's Hospital

Within the bloodstream, these sickle RBC are deformed, not capable of bending easily without breaking apart as they travel through small blood vessels, and attach to the inside wall of blood vessels. As a result, blood flow is blocked, and the body's tissues do not get an adequate supply of oxygen. When the RBC break apart, the release of hemoglobin and other chemicals directly into the blood further damages the inside of the blood vessels causing further disruption in oxygen supply to the body's tissues. In response, the bone marrow increases production of red blood cells to compensate for the red cells that are destroyed.

Abnormal, sickled, red blood cells (sickle cells)



To summarize, compared to normal cells, sickle cells are sticky, stiff, and fragile. Sticky and stiff RBC block blood flow and cause damage to body organs due to reduced blood flow and oxygen supply. Examples of symptoms that occur due to poor supply of oxygen to body organs include pain (bones), stroke (brain), difficulty with breathing (lungs), and so on. Similar damage to the spleen (an organ that is very important to protect the body against microorganisms such as bacteria, viruses, and parasites) results in a high risk of infection.



By Kep17 - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=88943344

Additionally, these fragile sickle cells break up easily and release their contents in the circulation. This results in a low number of RBC and hemoglobin (anemia), and yellow discoloration of eyes (jaundice) as these RBC contents accumulate in the blood and stain the eyes. A typical CBC report from an actual child with SCD is below. Note the low hemoglobin (anemia) and high reticulocyte count that results from the abnormal breakdown of RBC and the bone marrow's attempt to correct the anemia by producing more RBC.

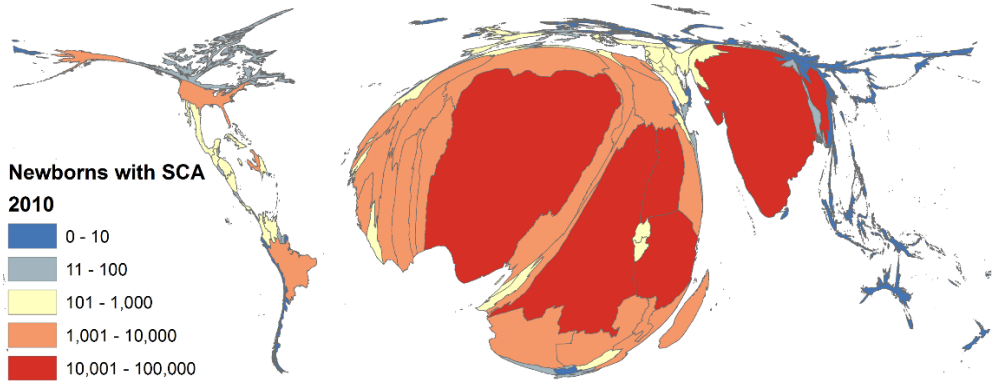
CBC W/Plat & Diff

	Ref Range & Units	
WBC	4.5 –13.5 10^3/µL	9.91
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	4.1 – 5.1 10^6/µL	2.44ᵛ
HGB	12.0 – 16.0 G/DL	6.8ᵛ
HCT	36.0 – 45.0%	20.3ᵛ
MCV	78.0 – 95.0 FL	83.2
MCH	26.0 – 32.0 PG	27.9
MCHC	32.0 – 36.0 G/DL	33.5
RDWCV	11.5 – 14.0 %	18.7^
RDWSD	38.5 – 49.0 FL	55.8^
Platelet	150 – 450 10^3/µL	412
MPV	6 – 10 FL	8.6
Differential Type		**AUTO**
Seg%	33 – 76%	39.5
Lymph%	15 – 55%	46.4
Mono%	0 – 4%	10.5^
EOS%	0 – 3%	2.6
Baso%	0 – 1%	0.9
IG%	0%	0.1^
ANC	1.8 – 8.0 10^3/µL	3.91
NRBC%	0%	2^
NRBC Absolute	10^3/3/µL	0.14
Reticulocyte Count		
Retic Percent	0.5 – 2.0%	17.6^
Retic Absolute	0.029 – 0.099 10^6/µL	0.430^

Who is at risk for SCD?

About one in every 50–100 newborns in Africa has SCD — i.e., 1%–2% of all babies. Although SCD is more common in Africans, the disease occurs in all racial groups. Any person can inherit SCD. Outside Africa, SCD also occurs in India, Saudi Arabia, and in Mediterranean countries such as Greece, Italy, Spain, and Turkey. It also occurs in Caribbean countries such as Jamaica, Cuba, Bahamas, etc., and in South, Central, and North American countries such as Brazil, Guatemala, Nicaragua, USA, and so on.

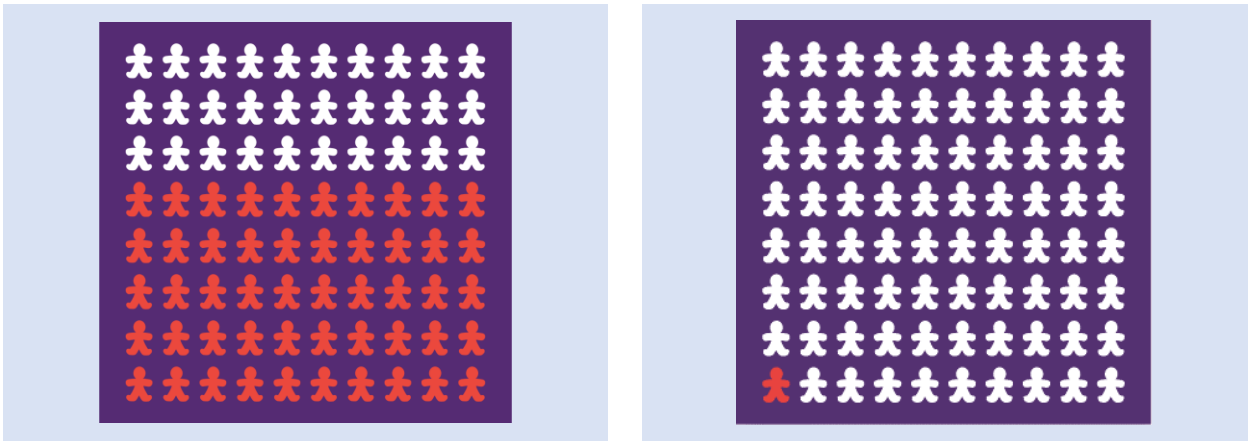
Each country's size on the following map is based on the number of newborns with SCD in 2010. Although most of the births occurred in Africa, many babies with SCD were also born in India, America (North, Central, and South), and Europe.



By Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN (2013) PLoS Medicine 10(7)

Is SCD a problem in Africa?

Worldwide, over 300,000 babies are born with SCD every year. Most of these babies are born in SSA. Unfortunately, it is estimated that more than 50% of all babies born with SCD in SSA die before 5 years of age. Most deaths occur before a diagnosis is made, and can be prevented by early diagnosis followed with simple treatments and education of the family. In contrast, almost all children born with SCD in the US and Europe survive into adulthood.



Deaths (red symbol) of children with SCD – sub-Saharan Africa (SSA) versus high-income countries (HIC)

Unit 2 Case Study / Quiz

2-1:	**True (T) or False (F)?**
	Sickle cell disease only occurs in Africans or black people living outside Africa.
2-2:	**True (T) or False (F)?**
	It is possible for a child to be born with sickle cell disease even if only one parent has sickle cell trait.
2-3:	**True (T) or False (F)?**
	While sickle cell trait (SCT or Hb AS) does not cause pain crisis, it may cause a mild anemia.
2-4:	**True (T) or False (F)?**
	Children with sickle cell trait (SCT or Hb AS) are less likely to die from malaria.
2-5:	**True (T) or False (F)?**
	Patients with SCD are expected to have a high reticulocyte count.

UNIT 3:
CLINICAL MANIFESTATIONS AND DIAGNOSIS OF SCD

Finding children with SCD

In high-income countries, all newborns are tested for SCD at birth. In the absence of newborn testing (as in Africa), all health care workers must know when to suspect SCD and how to diagnose SCD.

Keep a high suspicion for SCD in children since one in every 50–100 newborns has SCD in Africa. Death from SCD is preventable if the disease is diagnosed early in life and then treated.

Common symptoms of SCD

Typically, newborns with SCD do not experience any symptoms for the first 3–6 months. This is because the high level of fetal Hgb that is present in the RBC of all newborns prevents Hgb S from coming out of solution to form solids that deform the RBC into sickle shapes. Babies start to suffer from SCD symptoms when the Hgb F level drops after 3–6 months of age.

The severity of SCD varies a lot between affected patients, even among those who have the same type of SCD. Although we do not fully understand why some patients with SCD have many complications while others have very few, we know that patients whose Hgb F drops to very low level after 6 months of age suffer more complications compared to those whose Hgb F level remains high.

Common symptoms of SCD include:

- Pain events: Due to blocked blood flow to tissues. Typical first symptom in infants is pain involving hands and feet (dactylitis). Pain events occurs in abdomen, arms, legs, chest, and back in older children
- Chronic anemia: From breakdown of red blood cells
- Jaundice: From breakdown of red blood cells.

Less common symptoms of SCD

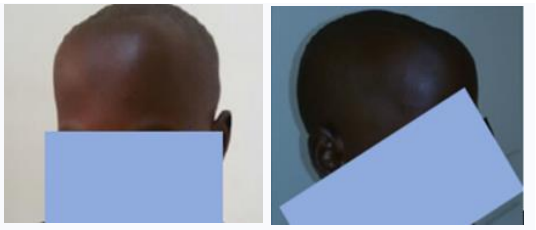
Poor oxygen delivery to tissues can also cause damage to:

- Brain – stroke with convulsions or inability to walk or talk
- Spleen – infection and spleen enlargement
- Lungs – shortness of breath or pneumonia
- Bones and joints – infection (osteomyelitis or septic arthritis), limp, deformity
- Kidney – protein or blood in urine with kidney failure
- Skin – sores on leg
- Eyes – loss of vision
- Penis – prolonged painful erection (priapism)
- Poor growth

Which children should be tested for SCD?

SCD should be suspected or ruled out in a child with history of any of the following symptoms:

- Unexplained chronic anemia
- Need for blood transfusion after 3 months of age
- Unexplained bone pain
- Jaundice (yellow eyes)
- A brother or sister already diagnosed with SCD
- Stroke
- Enlarged spleen
- Severe infection, especially if due to Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. flu), Salmonella, Staphylococcus aureus (S. aureus), or gram-negative bacteria
- Unusually prominent forehead (frontal bossing) as in the picture



Source: TCH Global HOPE

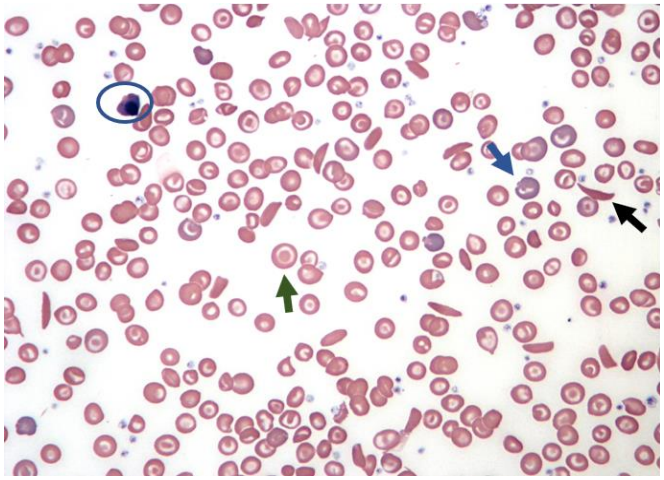
Methods to Confirm Diagnosis of SCD

Microscopy

Microscopy can confirm SCD in a child with chronic anemia plus jaundice and high reticulocytes. A microscope can be used to see sickle cells on a fresh blood smear after it is stained.

Blood smears from patients with SCD may also show target cells or a high number of bluish cells. A high number of bluish red cells on a smear is called polychromasia. These bluish cells are immature 'newborn' red cells released from the bone marrow to replace the excess number of sickle red cells that are destroyed.

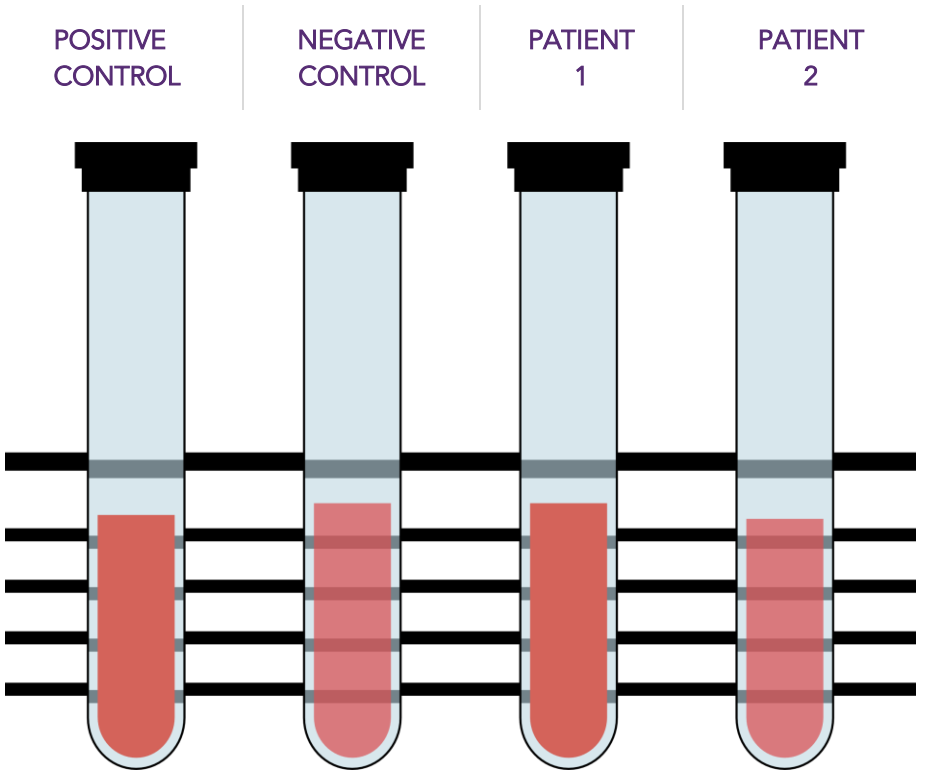
While microscopy can help diagnose SCD in general, it cannot specify the type of SCD – i.e., if it is Hgb SS or Hgb SC, etc. While the presence of sickle cells plus accompanying symptoms confirms SCD, some children with relatively mild forms of SCD such as Hgb SC or Hgb Sß$^{+}$-thal may not have sickle cells on a blood smear.



By Keith Chambers - https://commons.wikimedia.org/w/index.php?curid=31705671), CC BY-SA 3.0, – picture was modified to highlight sickle, target, and immature cells

This blood smear from a patient with SCD is typical. Note sickle cells (black arrow), target cells (green arrow), and bluish immature or 'newborn' reds cells (blue arrow). Numerous bluish cells or nucleated red cells (blue circle) strongly suggests a high reticulocyte count

Positive sickle solubility test



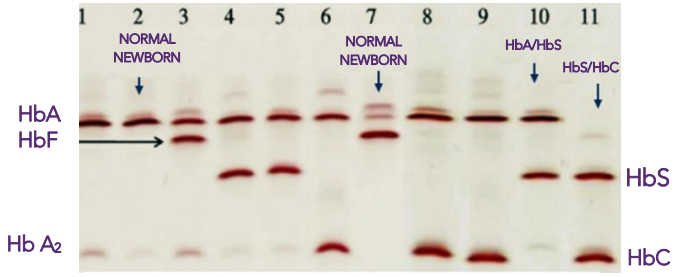
Michael Stencel, 2020

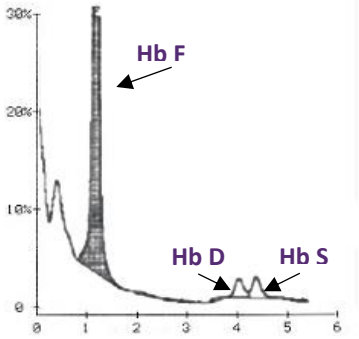
The sickle cell solubility test is based on the relative insolubility of Hgb S in reducing solutions compared to other hemoglobin types such as Hgb A. The above picture shows 2 positive and 2 negative tests. The positive tests are opaque while negative tests are clear. The sickle solubility test is positive whenever 'insoluble' sickle hemoglobin is present. Therefore, individuals with SCT will also be positive.

Additional testing such as Hgb electrophoresis, isoelectric focusing, or high-performance liquid chromatography (HPLC) is needed to clarify a positive sickle solubility test. In places where these sophisticated tests are not available, simple tests may also help. For example, patients with SCT should not have anemia or jaundice. Therefore, a positive sickle solubility test in a patient with chronic anemia, jaundice, and high reticulocyte count strongly suggests SCD. Similar to blood smear, sickle solubility test cannot specify the type of SCD — i.e., tell us whether it is Hgb SS or Hgb SC, and so on.

Hemoglobin electrophoresis, isoelectric focusing (IEF), and HPLC

Hemoglobin electrophoresis, IEF, and HPLC are techniques commonly used to identify specific Hgb. To do this, these methods rely on the unique properties of each type of Hgb. Hemoglobin electrophoresis and IEF rely on the fact that each hemoglobin has a different electrical charge, and how far they move on a gel depends on the amount of that charge. The finding of Hgb S without Hgb A (or reduced Hgb A) is common to all patients with SCD (Hgb SS, Hgb SC, and Hgb $S\beta^0$-thal patients do not have any Hgb A; Hgb $S\beta^+$-thal individuals have Hgb A of 5%–30%).





Waicman H. Moradkhani K - The Indian journal of medical research (2011) – IEF was modified to label 4 results

This picture shows the IEF results of 11 individuals. IEF is a form of electrophoresis that separates proteins such as hemoglobin by relying on the differences in their electric charge.

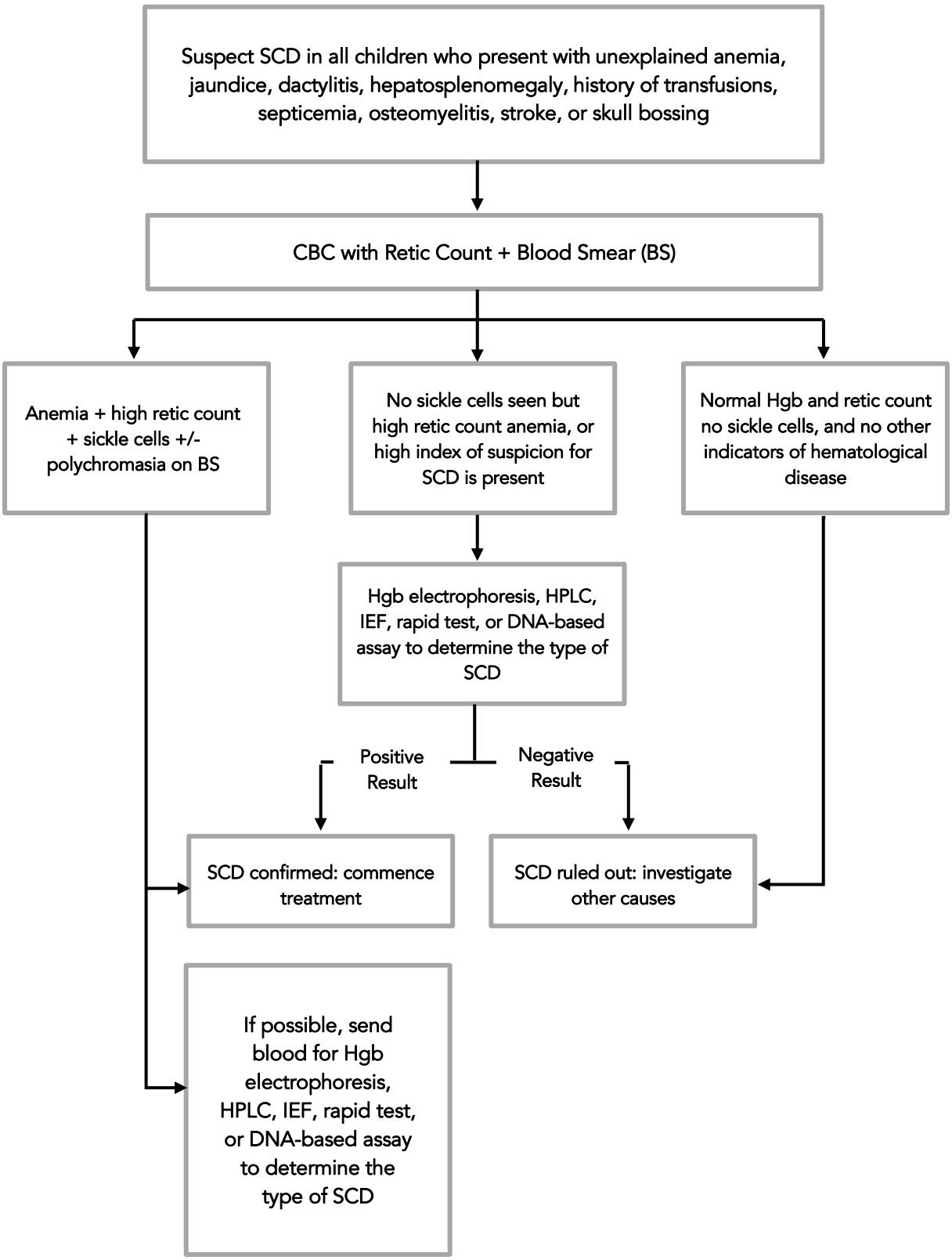
This HPLC shows a newborn with sickle cell-hemoglobin D disease (Hgb SD). Hgb SD is a type of SCD. The high level of Hgb F is common to all newborns.

Hemoglobin electrophoresis, IEF, and HPLC are excellent diagnostic tests that can also specify the type of SCD. However, they are not widely available in resource-limited health settings because they require sophisticated equipment, and specially trained laboratory technologists. Many newborn screening programs use Hgb electrophoresis, IEF, or HPLC.

Other possible methods

Other possible methods include genetic (DNA) testing, and rapid tests such as HemoTypeSC™ and Sickle SCAN™. A blood transfusion within the previous 2–3 months may result in a false normal test for SCD. DNA-based assay for diagnosis is the only type of test that is not affected by blood transfusion.

Schematic summary of SCD diagnosis



Unit 3 Case Study / Quiz

3-1:	**True (T) or False (F)?**
	Every child who is diagnosed with stroke should be tested for SCD.
3-2:	**True (T) or False (F)?**
	A child with anemia, jaundice, elevated reticulocyte count, plus obvious sickle cells on peripheral blood smear may or may not have SCD.
3-3:	**True (T) or False (F)?**
	Apart from jaundice, SCD does not affect the eyes
3-4:	**True (T) or False (F)?**
	The first symptom of SCD in most young children is pain crisis involving hands and or feet?

UNIT 4:
ROUTINE MANAGEMENT OF SCD

Maintaining health in children with SCD

General guidance: Diagnose children suspected to have SCD as early as possible to reduce morbidity and mortality. Arrange to see affected patients for routine 'well-child' visits every 3–6 months. The well-child clinic visit is an opportunity for general guidance on how to maintain health plus special laboratory tests and screenings to find problems early when they are easier to manage. Pay attention to the following general guidance for all patients with SCD:

- Hydration: Counsel patients on the need to always stay well hydrated because dehydration may provoke crises in SCD. They should drink enough water to keep their urine clear or pale yellow and without any odor. The easiest way to accomplish this is to develop the habit of carrying a water bottle at all times. The following table is a rough guide to show the minimum number of cups (240 ml or 8 ounces) to drink daily. Adjust number of cups downwards for children with a normal appetite (table does not account for natural water in food) and upwards for patients with fever.

Age (years)	Weight (kg)	Cups per Day
1–2	10–13	5
3–4	13–19	6
5–6	19–23	7
7–10	23–35	8
11–14	35–45	9
> 15	> 45	10

- **Nutrition:** Children with SCD are at risk for poor growth partly due to the extra metabolic demands arising from the need to replace blood cells in the bone marrow. The bone marrow needs folate and other nutrients to make new red blood cells. To meet the extra nutritional demands of making so many new red cells, you should counsel families that children with SCD need to eat a well-balanced diet that includes:
  - Fruits and vegetables of different colors
  - Beans
  - Nuts
  - Whole grains such as maize, millet, brown rice, etc.
  - Animal proteins such as eggs, fish, chicken, edible insects, etc.

  Review nutrition and growth during every routine visit by recording weight, and height or length and plotting them on growth charts such as the growth charts from the World Health Organization. Weight-for-height Z-score less than -3, bilateral pitting edema, or mid-upper arm circumference less than 115 mm indicates severe acute malnutrition in children younger than 5 years.

- **Folic Acid:** Because children with SCD need to make more cells compared to healthy children, many clinicians prescribe folic acid supplements to children with SCD. However, children with SCD can get sufficient folic acid by eating a well-balanced diet. The recommended daily amount of folic acid in healthy children without SCD ranges from 100 mcg (0.1 mg) in infants to 400 mcg (0.4 mg) in teenagers. If eating a well-balanced diet is not possible, folic acid tablets may be prescribed. It is customary in many SCD clinics in SSA to prescribe 1–5 mg of folic acid per day or 5 mg per week. Although these amounts of folic acid are probably more than the body needs, excess folic acid is usually not harmful
- **Vitamin A:** The WHO recommends routine vitamin A supplementation in children 6–59 months old in places where more than 1 in 5 children (20%) have vitamin A deficiency. Because the prevalence of vitamin A deficiency is 40% or greater in all SSA countries, administer vitamin A supplements to all 6- to 59-month-old children, especially those who do not have access to a well-balanced diet. Dose of vitamin A to administer by mouth every 6 months: 100,000 units in infants 6–11 months old; 200,000 units in children 12–59 months old

- **Routine Laboratory Assessments:**
  - CBC with reticulocytes every 3–6 months to establish baseline (Hgb by POC device may be used if CBC with reticulocytes is not available)
  - Blood bank screen for antibodies before every blood transfusion
  - Check for hepatitis B, hepatitis C, and HIV infection every 2 years in patients who have a history of blood transfusion in the previous 2 years
  - Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin), ferritin, fetal hemoglobin, lactate dehydrogenase (LDH), etc. should be done only if needed based on clinical presentation on a case-by-case basis
  - Serum creatinine and urine analysis yearly from 10 years of age

Preventing bacterial infection

Start penicillin as soon as possible in those who are diagnosed on newborn screen, or as soon as the diagnosis of SCD is confirmed in children who are younger than 5 years old. Penicillin should only be routinely used for children with Hgb SS or Hgb Sβ^0-thal types of SCD.

- Take penicillin two times daily by mouth until 5 years of age

  Dose:
  - 125 mg (half of a 250 mg tablet) twice daily until 3 years old
  - 250 mg (whole of a 250 mg tablet) twice daily from 3 years – 5 years.

Penicillin-VK

* Tablets must be crushed and dissolved in milk or water before administration.

* Twice daily amoxicillin or erythromycin by mouth, and monthly intramuscular (IM) benzathine penicillin are alternatives

Preventing malaria

- Always sleep under an insecticide-treated bed net
- Use insect repellants to reduce mosquito bites
- In addition to insecticide-treated bed net, prophylaxis medicines against malaria should be considered based on local patterns of resistance.

Vaccinations

- Take ALL childhood vaccines including yellow fever vaccine, polio vaccine; measles, mumps, and rubella (MMR) vaccine; and Bacillus Calmette-Guérin (BCG) vaccine
- Pay particular attention to the following vaccines since children with SCD are especially susceptible to the infections they prevent compared to children who do not have SCD:
    - Haemophilus influenzae type b (Hib) vaccine
    - Pneumococcal conjugate vaccine (PCV13)
    - Hepatitis B vaccine (patients with SCD are at risk since many of them need blood transfusion).

The US Centers for Disease Control and Prevention (CDC) recommends a 4-dose schedule (at 2, 4, 6, and 12-15 months) for both Hib vaccine and PCV13 for all children in the US.

** If available, the following vaccinations should be given:*

- Pneumococcal polysaccharide vaccine (PPSV23): First dose at 2 years of age, then an additional dose at 3–5 years after the initial dose
- Meningococcal conjugate vaccine (MCV4): especially if child lives in the meningitis belt
- Hepatitis A vaccine
- Yearly influenza vaccine: if recommended by local public health service.

Since SCD patients are highly prone to H. flu and S. pneumoniae infections, children with SCD who were not completely vaccinated or not vaccinated at all against H. flu or S. pneumoniae should receive the Hib vaccine and PCV13 regardless of the age when the child first presents. The actual number of doses of Hib vaccine or PCV13 to administer should be based on the age of the child and the number of previous doses given. Refer to specific public health guidance in the place where you practice for recommendations for catch-up vaccinations in this vulnerable population. The current CDC recommendations for children with SCD who were incompletely vaccinated against S. pneumoniae and H. flu are as follows:

Recommended catch-up vaccinations for children with SCD

	History	Recommendation
S. pneumoniae		
2–5 years old	▪ Only 3 doses of PCV13	▪ Give 1 dose of PCV13 at least 8 weeks after last dose
	▪ Zero, 1, or 2 doses of PCV13	▪ Give 2 doses of PCV13 at least 8 weeks after most recent dose, then 8 weeks later
	▪ No previous PPSV23	▪ Give 1 dose of PPSV23 (at least 8 weeks after last PCV13), then repeat PPSV23 after 5 years
6–18 years old	▪ No previous PCV13 or PPSV23	▪ Give 1 dose of PCV13, followed by 1 dose of PPSV23 (at least 8 weeks after PCV13), then repeat PPSV23 after 5 years
	▪ One previous PPSV23 but no PCV13	▪ Give 1 dose of PCV13 (at least 8 weeks after PPSV23), then repeat PPSV23 after 5 years after the first PPSV23
	▪ Any previous PCV13 but no PPSV23	▪ Give 1 dose of PPSV23 (at least 8 weeks after last PCV13), then repeat PPSV23 after 5 years
H. flu (Hib)		
12–59 months old	▪ No previous Hib vaccine or only 1 dose before 1 year of age	▪ Give 2 doses of Hib vaccine at least 8 weeks apart
	▪ 2 or more doses of Hib vaccine before 1 year of age	▪ Give 1 dose of Hib vaccine at least 8 weeks after most recent dose
5–18 years old	▪ No previous Hib vaccine	▪ Give 1 dose of Hib vaccine

The following table is a general overview of some of the care for affected children.

Age	Visit Frequency	Counseling	Tests / Referral
0–6 months	2 months	▪ Educate about SCD, fever, penicillin, etc. ▪ Start penicillin and emphasize value of vaccination and need for prompt response to fever ▪ Screen brothers and sisters of patient for SCD	▪ Hgb electrophoresis, IEF, or HPLC to confirm the diagnosis if possible
6–12 months	3 months	▪ Teach spleen palpation and about spleen crisis ▪ Educate about penicillin, fever, and vaccines ▪ Teach about pain events and how to manage	▪ CBC with diff every 3–6 months
1–4.99 years	3–6 months	▪ Teach spleen palpation and about spleen crisis ▪ Continue education about penicillin, fever, spleen, crisis, and vaccines ▪ Educate about acute chest, stroke, and other complications ▪ Importance of staying well hydrated always ▪ Importance (and components) of a well-balanced diet ▪ Offer hydroxyurea if available. ▪ Answer questions about DMT including stem cell transplants as needed	▪ TCD stroke screen yearly from 2–16 years old ▪ CBC with diff every 3–6 months
5–9.99 years	3–6 months	▪ Stop routine penicillin if eligible ▪ Continue education about hydration, nutrition, and complications such as acute chest syndrome, stroke, etc. ▪ Assess school performance ▪ Continue hydroxyurea therapy	▪ TCD yearly ▪ CBC with diff every 3–6 months
10–14.99 years	3–6 months	▪ Direct genetic counseling of patient ▪ Continue education about fever, acute chest, stroke, and other complications of SCD ▪ Assess school performance ▪ Assess psychological and social adjustment ▪ Continue hydroxyurea	▪ Eye exam yearly ▪ Urinalysis yearly ▪ Serum creatinine yearly ▪ TCD yearly

Disease-Modifying Therapy of SCD

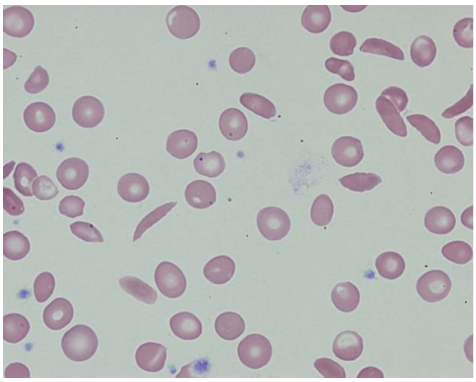
Disease-modifying therapy of SCD refers to medical interventions including medicines that can reduce SCD complications or crises by improving the underlying problem in SCD. The following are established disease-modifying therapies.

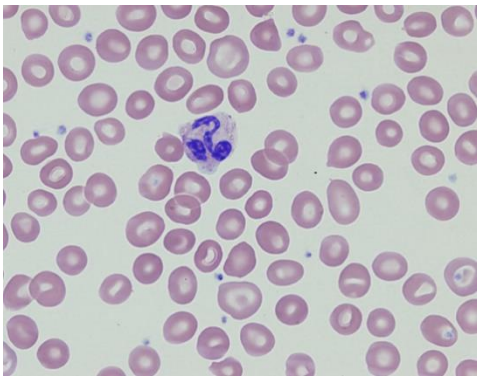
Hydroxyurea

Hydroxyurea is the first medicine known to definitely reduce the tendency of sickle cells to block blood flow. It is the most used option for direct modification of SCD. Note the following essential points about hydroxyurea:

- Hydroxyurea stimulates the body to produce fetal hemoglobin (Hgb F). Elevated Hgb F prevents Hgb S from coming out of solution within RBC to form solids that damage and deform the RBC
- Hydroxyurea is proven to raise hemoglobin level and hence reduces the likelihood of blood transfusion
- Hydroxyurea reduces the frequency of vaso-occlusive events including pain crisis, and acute chest syndrome. Hence, it reduces the likelihood of admission to hospital
- Hydroxyurea reduces the risk of malaria in children with SCD
- Hydroxyurea must be taken every day by mouth
- Children with Hgb SS or Hgb Sß^{0}-thal disease may take hydroxyurea beginning around 9 months of age
- Children on hydroxyurea must be monitored with blood tests at regular intervals. At a minimum, CBC with reticulocytes should be performed periodically since the most common side effects of hydroxyurea are low white blood count, low reticulocyte count with anemia, and low platelet count
- Discuss any questions you have about hydroxyurea treatment with the pediatrician or hematologist.
- Refer to Unit 7 of this manual for additional information about hydroxyurea.

These pictures show blood smears in the same patient before, and months after starting hydroxyurea treatment. The reds cells in the second smear are larger, more numerous, and none with a sickle shape is seen.





Source: Texas Children's Hospital

Blood Transfusions

Ongoing transfusions every 3–4 weeks can reduce the frequency of SCD complications. This strategy is most often used to prevent stroke in children with abnormal transcranial Doppler (TCD), or to prevent a second stroke in those who have already experienced a stroke. Transfusion of healthy blood every 3–4 weeks works by suppressing the need for the SCD patient's bone marrow to produce sickle red blood cells. As a result, most of the red cells circulating in the patient are Hgb AA or Hgb AS cells from the donor that do not sickle and block blood vessels. Unfortunately, ongoing blood transfusions is not a suitable method for preventing complications in most patients due to the short- and long-term risks of blood transfusions. These risks include infection, iron overload, and alloimmunization. Alloimmunization occurs when a patient develops antibodies to donated blood such that future transfusions are difficult or impossible. Like hydroxyurea, the effect wears off over time if the blood transfusions are discontinued. Refer to Unit 6 of this manual for additional information about blood transfusion.

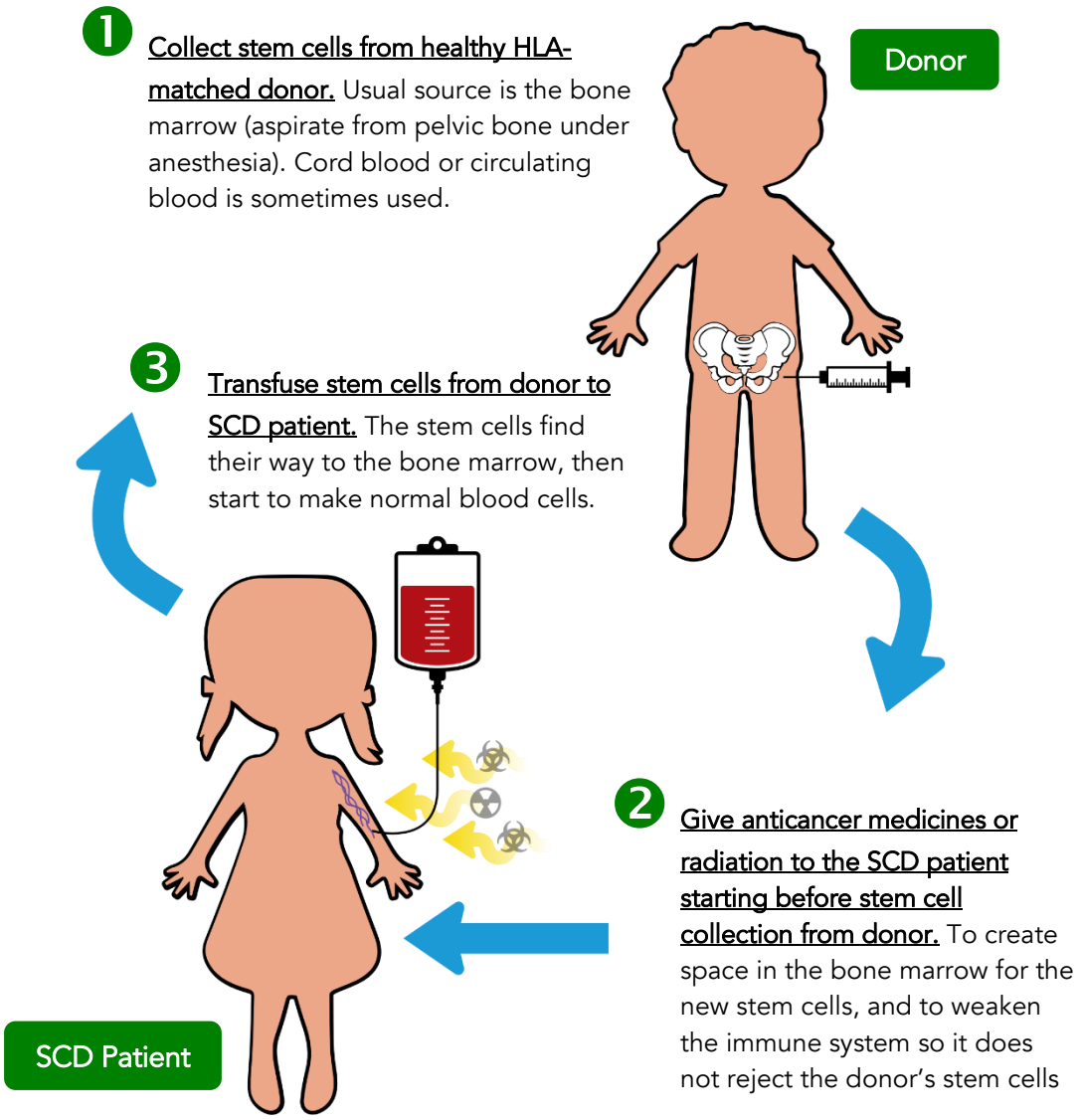
Stem Cell (Bone Marrow) Transplant

A stem cell transplant (also called bone marrow transplant) is currently the only cure for SCD. In a transplant, stem cells from a healthy donor who does not have SCD are infused into a patient with SCD. Prior to this infusion, doctors administer anticancer medicines or radiation to the patient with SCD. The anticancer medicines or radiation is used to 'create space' in the patient's bone marrow and to weaken the patient's immune system so it does not reject the stem cells from the donor.

A transplant works best if there is a well-matched person to donate the normal bone marrow cells. Two people are said to be well matched for transplant if they share similar immune response genes so that their stem cells are very similar. The process of finding a match involves sophisticated genetic (DNA) testing of patient and potential donors. This genetic test is usually referred to as human leukocyte antigen (HLA) typing. This step is necessary to reduce the risk that the patient's immune system will reject the donor's stem cells. Although it is possible to find a match in the general population registry (matched unrelated donor), a brother or sister who shares the same mom and dad as the patient provides the best chance of a match. There's only a 25% probability that each brother or sister who has the same mom and dad as the patient will be a complete match for transplantation. In addition to being a match, the donor must not have SCD (SCT is acceptable), be healthy, and not have any chronic infectious disease such as HIV, hepatitis viruses, and so on.

It is likely that in the future, research will discover new ways for affected patients who do not have well-matched donors to be permanently cured. Research to make it possible for the patient's own stem cells to be collected, then genetically engineered, and afterward returned to the patient is currently in progress. Although transplant is successful in most patients, up to 5%–10% of patients who undergo a transplant do not survive mainly due to infection that develops after the immune system is weakened by anticancer medicines or radiation. In addition, SCD may recur in some survivors because the patients' immune system rejects the normal stem cells, and other survivors develop chronic complications such as reduced fertility due to damage to the testes or ovaries from anticancer medicines or radiation that is used to prepare the patient. Therefore, transplant is usually reserved for SCD patients with complications.

Schematic summary of stem cell transplantation for SCD



Newer Disease-Modifying Therapies

A number of disease-modifying therapies were recently approved in the USA. They include L-glutamine, voxelotor, and crizanlizumab. Besides being very expensive, the long-term benefits and harms of these new medicines are not yet known.

a) Oral L-glutamine (Endari™) was shown to reduce the frequency of pain events and acute chest syndrome in patients with SCD over 5 years old. L-glutamine, an oral medicine that increases the amount of glutamine in the blood, is thought to reduce oxidative stress on sickle cells. Since high oxidative stress is associated with increased stiffness of red cells, some experts think that L-glutamine improves SCD by making the sickle cell less stiff. Most patients on L-glutamine oral powder also take hydroxyurea.

b) Oral voxelotor (Oxbryta™) makes red blood cells less likely to form the sickle shape by binding to Hgb S and increasing its capacity to hold on to oxygen. Since Hgb S that holds on to oxygen is less likely to come out of solution within the RBC to form solids that damage and deform the RBC into sickle shapes, they are also less fragile or sticky. In a recent study, patients 12 years and older who took voxelotor increased their baseline Hgb level. Most of the patients on voxelotor on this study were also taking hydroxyurea.

c) Crizanlizumab (Adakveo™) makes red cells less likely to stick together. As a result, these red cells do not block the blood vessels. In a recent study, patients 16 years and older on crizanlizumab were less likely to experience vaso-occlusive events such as pain and acute chest syndrome. Most of the patients on crizanlizumab on this study were also taking hydroxyurea. Unlike L-glutamine and voxelotor that are given by mouth daily, crizanlizumab must be administered through a vein every 2–4 weeks.

Spleen counseling

- Teach all parents and guardians of children younger than 6 years how to palpate the spleen and check for pallor
- A child with new spleen enlargement plus severe pallor has acute spleen sequestration. Refer these children for blood transfusion

Fever counseling

- Infection is the most common cause of death in SCD
- Teach parents and guardians how to use a thermometer for early detection of infection
- Take children to emergency room or hospital for any fever greater than 37.5°C. The risk of bacterial infection is even higher for temperature > 38.5^0C.

Counseling adolescents about risk to their own children

- Since SCD is inherited, those who plan to have children should know the risk of SCD in their own children
- The sickle cell status of the future partner determines the risk of having a child with SCD. A person with SCD may have a child with SCD if their partner has beta thalassemia trait, Hgb C trait, or SCT.

Unit 4 Case Study / Quiz

4-1:	**True (T) or False (F)?**
	All children younger than five years with Hgb SC or Hgb Sß$^{+}$-thal types of SCD should be treated with twice daily penicillin V K?
4-2:	**True (T) or False (F)?**
	Parents of young children with any type of SCD should be taught how to feel for the spleen.
4-3:	**True (T) or False (F)?**
	While it is possible to prevent infections and treat SCD symptoms as they occur, there is currently no way to directly modify SCD or to permanently cure the disease.
4-4:	**True (T) or False (F)?**
	It is possible for the individual whose CBC /reticulocyte count and hemoglobin profile electrophoresis are shown to have a child with SCD in the future?

CBC W/Plat & Diff

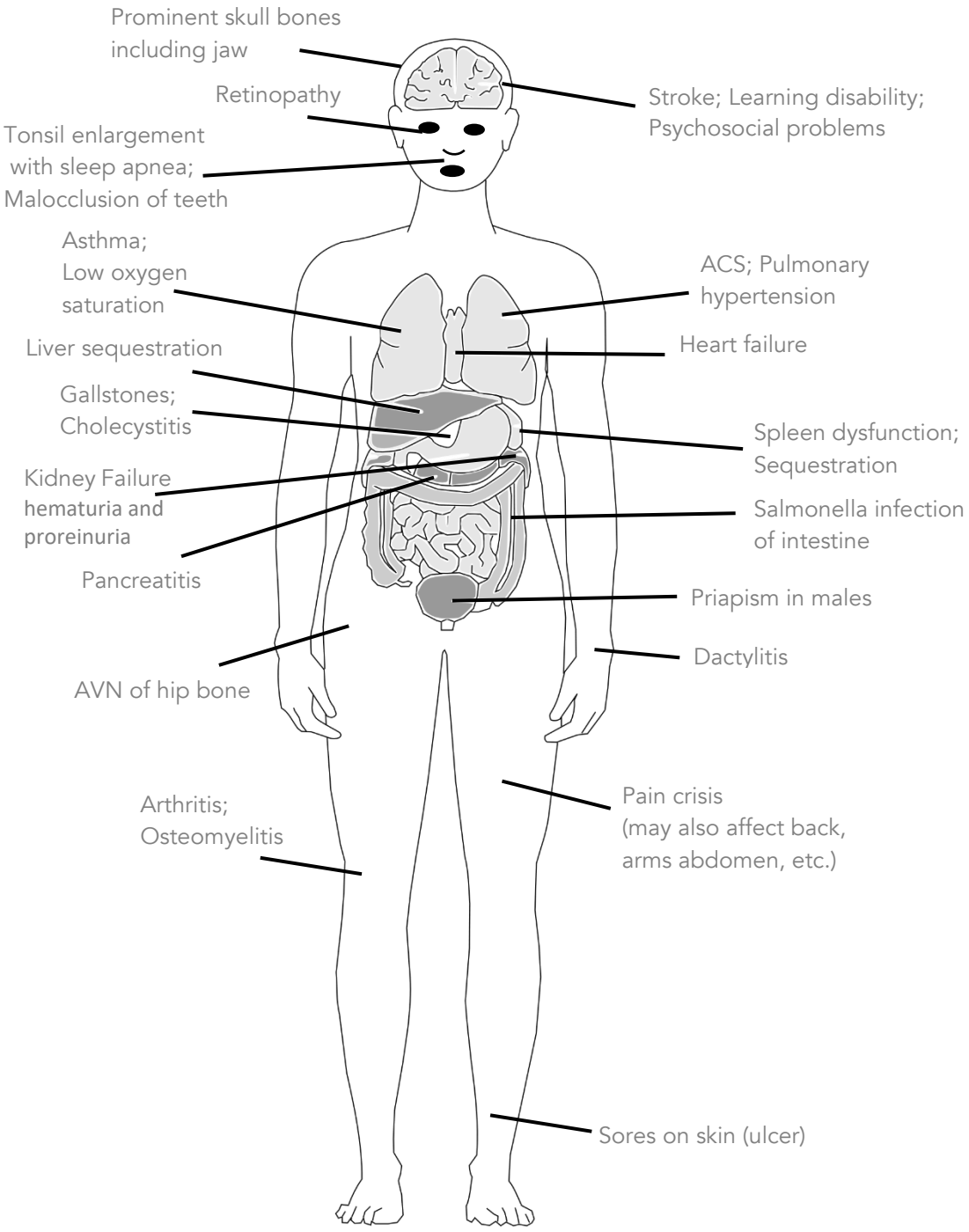
	Ref Range & Units	
WBC	5.0 – 14.5 10^3/µL	12.8
RBC	4.1 – 5.1 10^6/ µL	5.12
HGB	12.0 – 16.0 G/DL	11.1 v
HCT	36.0 – 45.0 %	33.3 v
MCV	78.0 – 95.0 FL	65.1 v
MCH	26.0 – 32.0 PG	21.7v
MCHC	32.0 – 36.0 G/DL	33.3
RDWCV	11.5 – 15.0 %	13.8
Platelet	150 – 450 10^3/µL	291
MPV	6 – 10 FL	8.6
Differential Type		**AUTO**
Seg%	33 – 71 %	48.6
Lymph%	15 – 55 %	43.8
Mono%	0 – 4%	4.9
EOS%	0 – 3%	2.7
Baso%	0 – 1%	0.9
ANC	1.8 – 8.0 10^3/µL	6.2
Reticulocyte Count		
Retic Percent	0.5 – 2.0%	0.9
Retic Absolute	0.029 – 0.099 10^6/µL	0.046
Hemoglobin Electrophoresis		
Hemoglobin A	90 – 100%	90.8
Hemoglobin A2	<4%	6.3^
Hemoglobin F	0 – 3%	2.9
Hemoglobin S	%	0.0
Hemoglobin C	%	0.0
Hemoglobin Other	%	0.0

UNIT 5:
MANAGEMENT OF SCD EMERGENCIES

Complications

- SCD may affect any body organ that gets blood flow. The following are some of the complications that may occur:
  - Bones — infarction (thigh bone, arm bone, back), deformity (frontal bossing, tooth malocclusion)
  - Brain — stroke, learning problems, psychological and social dysfunction
  - Ears — deafness
  - Eyes — vision loss (retinopathy)
  - Growth — Delayed growth and delayed puberty
  - Heart — heart failure
  - Kidney — blood in urine, kidney failure, hypertension
  - Lungs — acute chest syndrome, asthma, pulmonary hypertension, sleep apnea
  - Skin — leg sores
  - Spleen — acute sequestration, infection of the brain, bloodstream, lungs, bones, joints, etc.
  - Penis — priapism
  - Liver and gall bladder — jaundice, gallstones, sequestration
  - Veins — blood clots (deep vein thrombosis)
- It is better to prevent or delay a complication than to treat it after it occurs
- Most deaths result from bacterial infection (especially S. pneumoniae, H. flu, E. coli, and Salmonella), and malaria
- Prevent infections (daily penicillin, vaccinations, insecticide-treated nets) and promptly manage fever so that any infection can be quickly identified and treated.

Schematic of SCD complications



Danger Signs

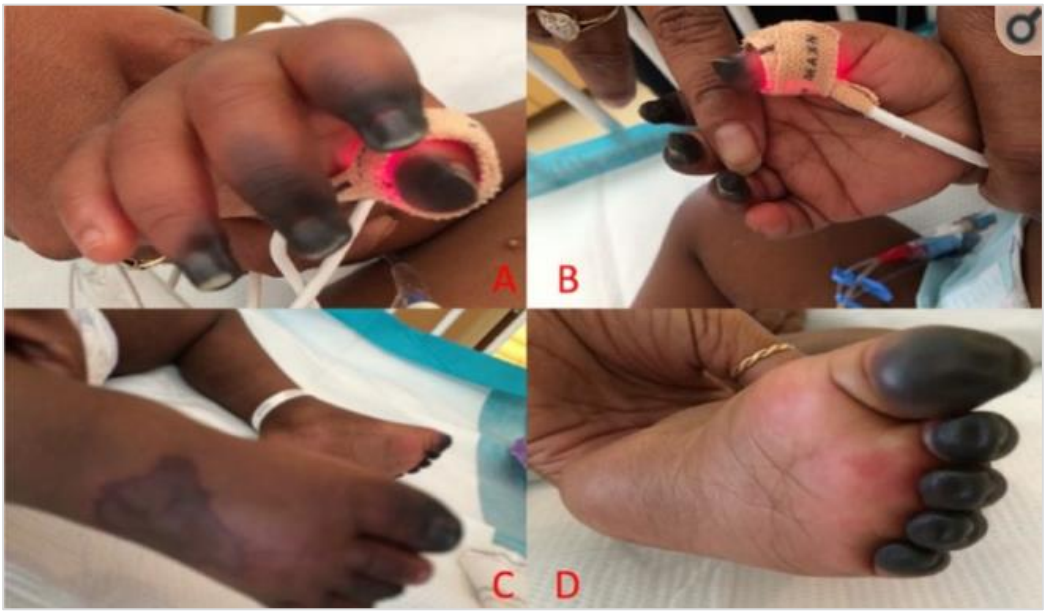
Since SCD may cause severe life-threatening illnesses, always check for danger signs in sick children especially those who are younger than 5 years. Checking for danger signs involves asking and looking. Ask if the child can drink or breastfeed, if the child vomits everything, and if they have had any convulsions. Then look to see if the child is lethargic or unconscious and if the child is convulsing.

The presence of any danger sign indicates the need for urgent medical attention. Therefore, refer or consult a pediatrician immediately if any danger sign is present.

Fever / Infection

Children with SCD are highly prone to bacterial infections of the lungs (pneumonia), bones (osteomyelitis), joints (septic arthritis), brain (meningitis), and bloodstream (septicemia). Common bacteria are S. pneumoniae, Salmonella, H. flu, and S. aureus. Malaria is also a common cause of severe illness and death in children with SCD. Infection should be promptly treated in patients with SCD because death may occur within a few hours. Infections occur because SCD patients sustain vaso-occlusive damage to the spleen early in life. The spleen is an organ in the abdomen that helps protect against infection by producing antibodies and filtering bacteria from blood. As a result, bacteria circulate in the blood to infect tissues such as bone that have also been damaged by blockage of their blood supply. Compared to healthy tissues, damaged tissues are not as able to resist infection.

Presentation: History of fever, or temperature > 37.5^{0}C. The risk of bacterial infection is even higher for temperature > 38.5^{0}C. Even when it does not result in death, infections caused by S. pneumoniae, Salmonella, H. flu, or S. aureus can be very severe. The child in the following pictures presented with fever and was found to have a bloodstream infection due to S. pneumoniae. The infection led to gangrene of her fingers and toes (black tissue in pictures). The affected fingers and toes eventually fell off on their own (auto amputated).



Source: Pangonis S, Patamasucon P, Fitzpatrick E - Journal of investigative medicine high impact case reports (2016)

Assessment

- Check for general danger signs
- Assess for causes of fever
  - Does the child have recent measles (cough, runny nose, or red eyes, corneal clouding); bloody diarrhea; chest pain; cough; painful or frequent urination; and so on?
  - Check for stiff neck; fast breathing or chest indrawing; bone or joint tenderness or swelling
- Check spleen size (spleen sequestration often accompanies infection)

Laboratory Evaluation:

- Perform a test for malaria – blood smear or rapid diagnostic test (RDT)
- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)
- Order a blood culture
- Depending on presentation, chest X-ray, urine culture, or lumbar puncture may also be required

Treatment:

Refer immediately if any danger sign or a source of fever such as stiff neck or fast breathing is present.

Children who are diagnosed with malaria should be treated with appropriate antimalarial medicines. In addition to malaria, ALL children with SCD and fever should be assumed to have a life-threatening bacterial infection. If no obvious source of fever is present, do a blood culture if possible and give one of the following antibiotics:

- Ceftriaxone – 50 mg/kg intravenously (IV) or intramuscularly (IM)
- Amoxicillin – 45 mg/kg twice daily by mouth
- Amoxicillin-clavulanate – 45 mg/kg twice daily (of amoxicillin component) by mouth

After the initial dose of antibiotics, quickly determine whether the child can be discharged home to continue treatment. Patients who do not meet criteria for hospital admission should be discharged home and instructed to return for follow up within 1–3 days. These antibiotic options may be continued for 1–3 days to allow time to exclude infection by means of microbial cultures or resolution of symptoms.

Admit or transfer patients with SCD and fever who have any of the following findings:

- Presence of any danger sign
- Signs of serious infection such as septic shock, meningitis, osteomyelitis, or pneumonia
- Temperature > 40^0C
- Younger than 6 months OR not up to date with immunizations
- CBC showing WBC greater than 30,000/µL OR less than 5,000/µL OR ANC > 20,000/µL
- Hgb less than 5.0 g/dL OR more than 2.0 g/dL lower than patient's usual baseline
- Concern about family's ability to return for follow up or to administer oral antibiotics

Stop antibiotics within 3 days if blood culture is sterile or fever resolves, and patient improves.

Pain

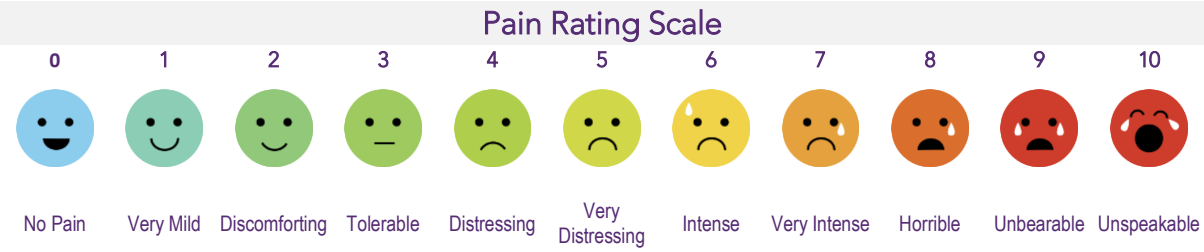
Pain is the most common complication of SCD. It happens partly because sickle cells block the flow of blood to bones and other organs, thus depriving these tissues of oxygen. Typically, pain starts suddenly and most often affects legs, arms, chest, back, knees, or abdomen. How often it occurs and whether it lasts only a few hours or several days varies from patient to patient and even varies in the same person over time. While pain that starts and then ends is typical in young children, some teenagers and adults may have pain all the time because of permanent damage to bones and joints.

Presentation: Pain, and swelling in legs, arms, chest, back, knees, or abdomen. Fever may occur.

Assessment

- Check for general danger signs
- Assess for other conditions that may imitate pain crisis such as bone/joint infection, fracture, gallstone disease, stroke, acute chest syndrome, etc.

  - Persistent fever especially if T > 38.5°C or joint swelling suggests an infection of bone or joint
  - Severe tenderness in the upper right side of abdomen suggests liver or gall bladder disease
  - History of injury or pain that is unusual for a particular patient suggests bone or soft tissue injury or infection
  - Severe headache, drowsiness, or severe weakness of a limb suggests a stroke
  - Cough, fast breathing, or chest indrawing suggests acute chest syndrome
  - Back pain with painful or frequent urination may be due to urinary infection
  - Severe pallor with abdominal pain suggests spleen or liver sequestration
- Use a pain scale to assess severity at the beginning and at regular intervals such as every 2–4 hours to see if the pain is improving or getting worse. Several pain scales exist. The most common ones combine numbers and images. One such scale is the faces scale pictured below. This scale is useful for children older than 3 years who are able to express themselves. For patients younger than 3 years, the parent or guardian's perception of their child's pain should be used.



Laboratory Evaluation:

- Believe what the patient says since there is no laboratory test to diagnose pain or its severity.
- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)

Treatment:

Refer immediately if danger signs or if concern for serious conditions that imitate pain crisis are present.

The following measures help all patients with pain crisis:

- Treat pain promptly
- Rest affected limb or body part
- Encourage hydration because dehydration may worsen or provoke pain crisis
- Apply warm pack to affected body part (avoid cold packs)
- Offer psychological support to reduce anxiety

To reduce risk of acute chest syndrome complicating pain crisis, encourage patients with pain to remain active. If the pain is so severe that the patient has difficulty staying active, encourage the patient to do breathing exercises using an incentive spirometer (pictured). If an incentive spirometer is unavailable, balloons, pinwheels, or bubbles should be used for breathing exercises.

Pain (Analgesic) Ladder

- Patients should be started on pain medicine that matches the assessed pain severity:

  For patients with mild pain – i.e., faces scale score 1–3

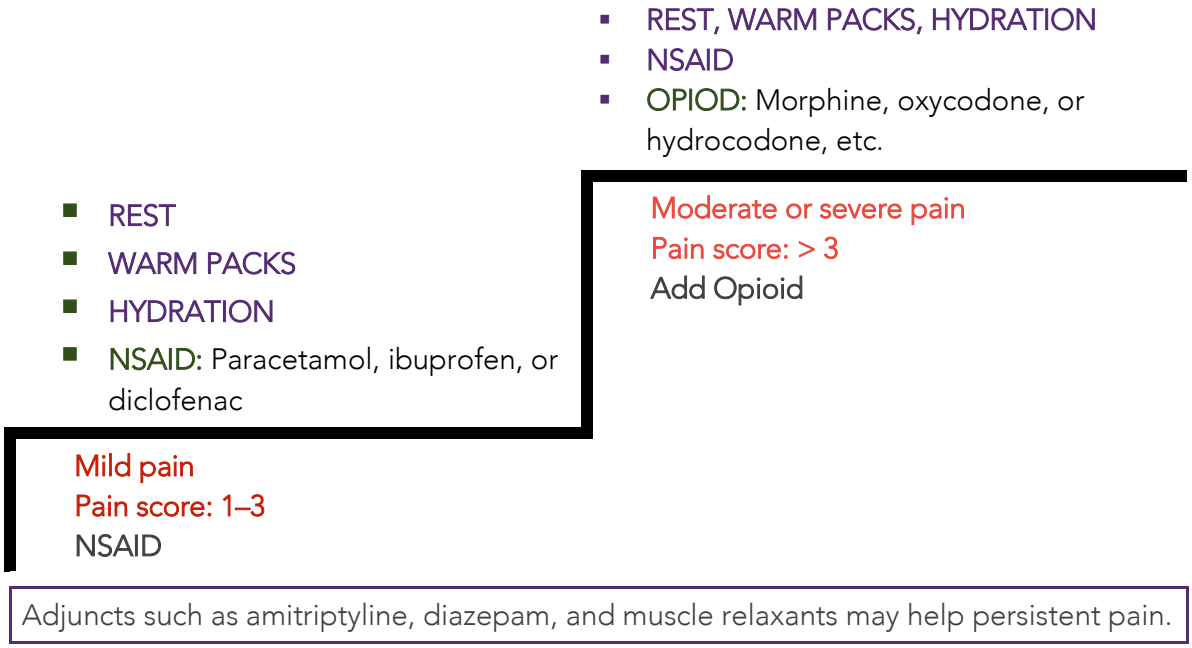
  - Oral medicines are preferable to IM or IV route
  - Paracetamol (10–15 mg/kg every 4–6 hours) or nonsteroidal anti-inflammatory drug (NSAID) such as Ibuprofen (5–10 mg/kg every 6–8 hours). Other examples of NSAIDs are dipyrone, diclofenac, and naproxen
  - Give medicines on a fixed schedule rather than as needed until pain resolves or improves
  - Some patients benefit from alternating paracetamol with ibuprofen every 3 hours — i.e., give each medicine every 6 hours but alternate them
  - Monitor for a few hours and if stable, send home, and request return to clinic the next day for another evaluation
  - Continue medicines until the pain has resolved for at least 24 hours, then stop
  - If the patient is improving, may continue oral medicines for a maximum of 7 days.

  For patients with moderate to severe pain — i.e., faces scale score 4–10

- Consult pediatrician or hematologist
- Oral medicines are preferable to IM or IV route
- Paracetamol (10–15 mg/kg every 4–6 hours) **or** NSAID such as Ibuprofen (5—10 mg/kg every 6–8 hours)
- Some patients benefit from alternating paracetamol with ibuprofen every 3 hours — i.e., give each medicine every 6 hours but alternate them

- Add opiate medicine such as morphine, hydrocodone, or hydromorphone administered by mouth
- When it is not possible to administer morphine or another opioid by the oral route, give subcutaneously or intravenously since these routes are less painful than intramuscular injection
- Give paracetamol/NSAID and opioid on a fixed schedule rather than as needed until pain resolves or improves
- If possible, codeine and tramadol should be avoided in children due to potential risks and because the response is not certain
- Responses to opioid medicines vary by patient. Thus, the correct dose of opioid is the dose that safely relieves the pain (a typical starting dose of oral morphine is 0.2 mg/kg – see table). It is usually possible to carefully increase beyond starting dose to get pain relief
- Opioid medicines such as morphine carry significant risks such as overdose, accidental death, and development of dependence. Adjunctive medicines commonly used with opioids such as diazepam, and muscle relaxants may increase these risks. Only administer opioids in collaboration with a pediatrician or hematologist who is familiar with their use
- Use a stool softener (e.g., docusate, polyethylene glycol, milk of magnesia) or a laxative (e.g., senna) to counteract constipation in patients on opioids
- DO NOT give a blood transfusion for a simple pain crisis. Blood transfusion is only necessary if severe anemia, ACS, or another complication develops
- Patients with chronic pain may benefit from additional medicines such as amitriptyline, diazepam, muscle relaxants, etc. However, these medicines increase the risks associated with the use of opioids
- Continue medicines until the pain has resolved for at least 24 hours, then stop.

Schematic of Analgesic Ladder

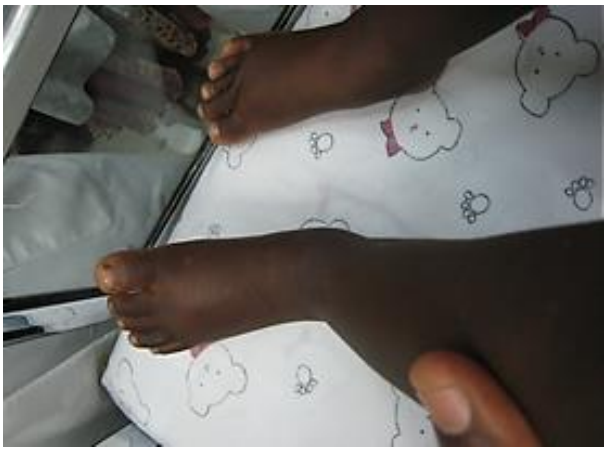


Typical Starting Doses of Paracetamol, Ibuprofen and Morphine for ORAL use

Weight (kg)	Paracetamol dose every 4–6 hours (mg)	Ibuprofen dose every 6–8 hours (mg)	Morphine dose every 4–6 hours (mg)
5.4 to 8.1	80	50	1
8.2 to 10.8	120	75	1.5
10.9 to 16.3	160	100	2
16.4 to 21.7	240	150	3
21.8 to 27.2	320	200	4
27.3 to 32.6	400	250	5
32.7 to 43.2	480	300	6
> 43.2	500	400	8

Dactylitis

Dactylitis is a pain crisis that affects the hands and/or feet of young children — typically 6 months to 2 years of age. It is the initial presentation of SCD in many children. Commonly, it is on both right and left. Like pain crisis in other body parts, dactylitis may be associated with fever and swelling (see pictures).



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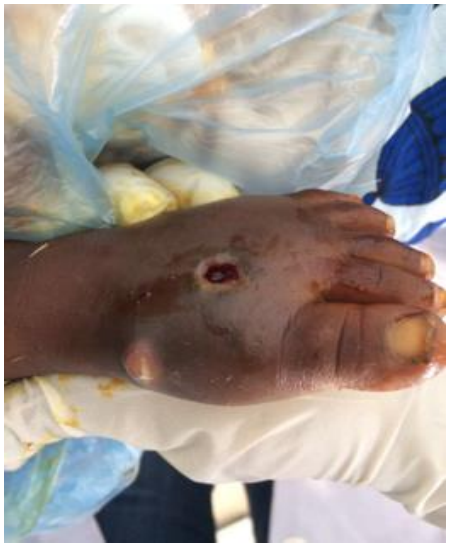
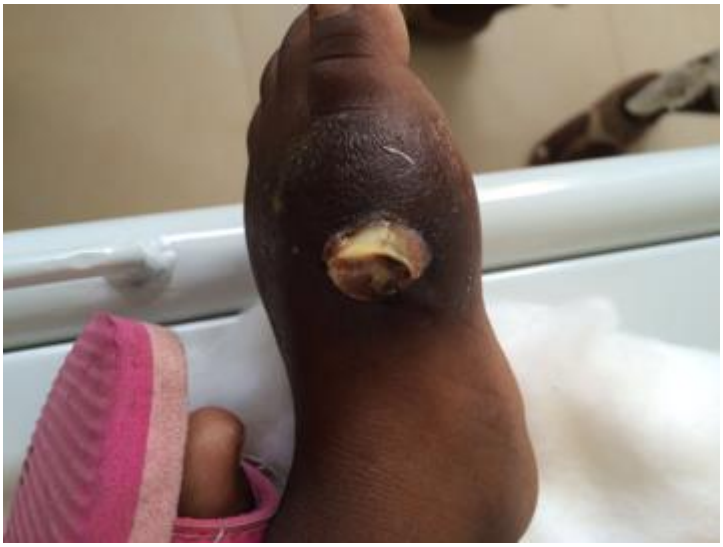
Treatment of dactylitis should proceed as for other pain events in SCD. However, suspect bone infection (osteomyelitis) and consult a pediatrician or hematologist if fever persists. The child in the picture below presented with foot pain, swelling, and persistent fever. She was incorrectly diagnosed with dactylitis and treated with only pain medicines. Earlier recognition of bone infection (osteomyelitis) and antibiotic treatment would have prevented the bone damage and deformity that occurred.





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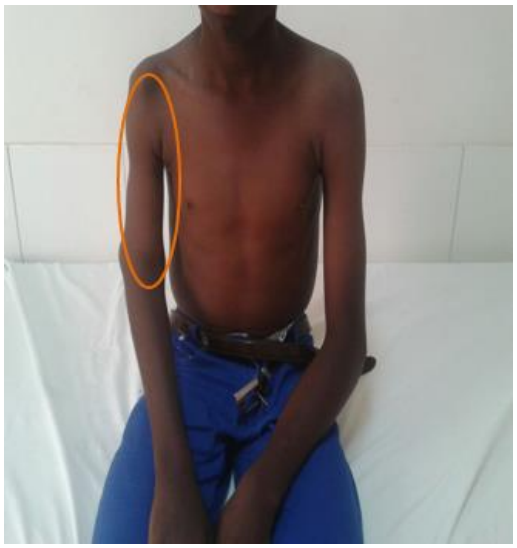
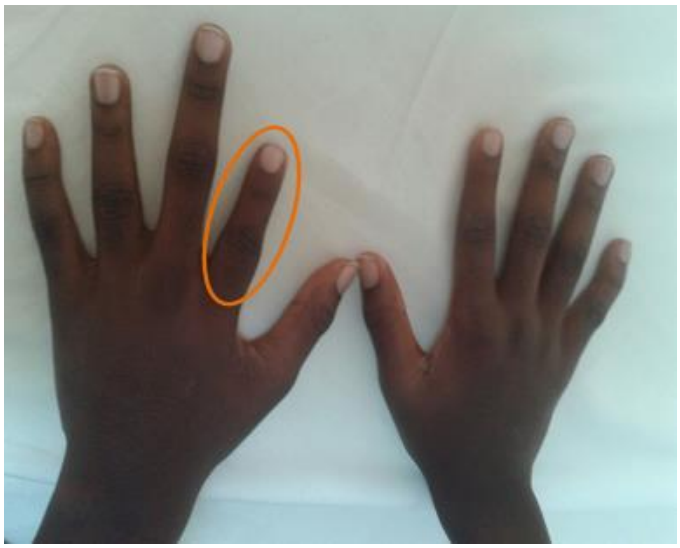
Bone Infection (Osteomyelitis) & Joint Infection (Septic Arthritis)

Bone damage from blockage of blood flow predisposes to infection of the bones (osteomyelitis) and joints (septic arthritis). The most common bacteria associated with these infections are Staphylococcus aureus and Salmonella. Delayed treatment of osteomyelitis may result in permanent deformity.

Pictures show deformities in a SCD patient that most probably resulted from poorly treated osteomyelitis





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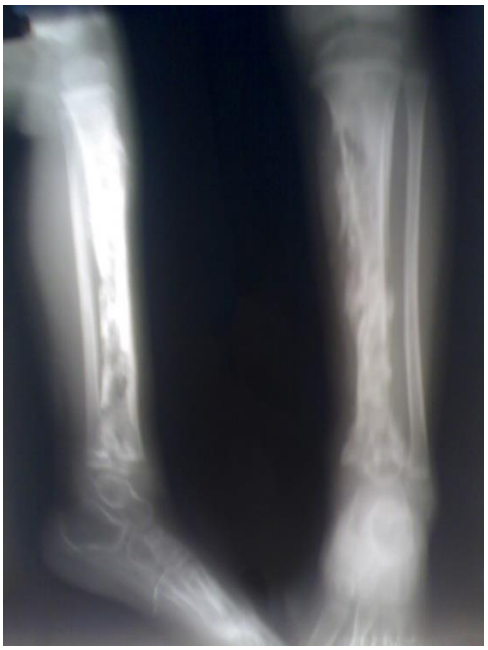
Presentation: Bone (or joint) pain and fever. The pain may be similar to a simple pain crisis. However, unusual nature of the pain, persistent fever, tenderness on a specific point, and swelling should prompt evaluation for osteomyelitis.

The X-rays in the picture below shows osteomyelitis of the tibia (leg bone). The irregular dark areas within the bone are small abscesses that are less dense than bone which appears lighter in color. Bone abnormality on X-ray, ulcers on skin, and pus drainage are late findings that indicate a delay in the diagnosis of osteomyelitis. For this reason, do not rely on these signs as signals to start treatment.



By Sarindam7 at the English Wikipedia, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=4183336

Assessment

- Check for general danger signs
- Ultrasound or magnetic resonance imaging (MRI) of bone or joint if available
- X-ray of bone (bone abnormality on X-ray does not show up for at least 2 weeks).

Laboratory Evaluation:

- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable) — very high WBC count suggests infection
- Obtain a culture of fluid or tissue from the affected joint or bone, and blood culture if available
- Check erythrocyte sedimentation rate (ESR) and C-reactive protein

Treatment:

- Admit or transfer all patients with suspected osteomyelitis or septic arthritis
- Start IV antibiotics promptly (preferably after culture of blood, joint fluid, or bone).
- Initial antibiotics must cover both Salmonella and S. aureus until specific organism is identified on microbial culture. Examples include: Cefotaxime, ceftriaxone, cefepime or ciprofloxacin (for Salmonella and other gram-negative bacteria) plus flucloxacillin, nafcillin, clindamycin, cefazolin, or vancomycin (anti-Staphylococcus aureus)
- Osteomyelitis requires antibiotic treatment for at least 4–8 weeks to prevent deformity

- Consult with pediatrician, bone surgeon, and infectious disease specialist if possible.

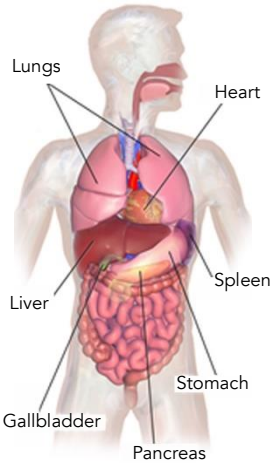
Abdominal Pain

Abdominal pain may be due to a problem in the lungs such as ACS or pneumonia, spleen (sequestration or infection), liver (liver crisis, sequestration, or infection), gallbladder (gallstones or cholecystitis), pancreas (gallstone-induced pancreatitis), abdominal pain crisis, etc. Children with SCD are more likely to develop gallstones due to the increased amount of bilirubin that is released when fragile sickle cells break down in the circulation.

Presentation: Abdominal pain. Fever, worsening jaundice, nausea, and vomiting may occur. The location and nature of the pain provide important clues in management.

Assessment

- Check for general danger signs
- When assessing abdominal pain, imagine two lines that meet at the bellybutton — the first one from top to bottom, and the second line at a right angle from left to right. This divides the abdomen into 4 sections or quadrants (right upper, right lower, left upper, and left lower quadrants).
- Make note of where the abdominal pain is most severe. As hinted by this diagram, liver, gallbladder, or pancreas crisis usually present with pain in the right upper quadrant, while spleen crisis is typically most severe in the left upper quadrant. The urinary bladder and reproductive organs are in the lower quadrants
- Check oxygen saturation.



By BruceBlaus - Own work, CC BY-SA 4.0,
https://commons.wikimedia.org/w/index.php?curid=47113847

Laboratory Evaluation:

- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)
- Abdominal ultrasound, liver function, and other tests may be needed

Treatment:

Immediately admit or transfer any SCD patient with abdominal pain who has any of the following:

- Any danger signs
- Abdominal pain is severe
- Fever
- Unable to eat or drink without vomiting
- Fast breathing or chest indrawing
- Dizziness

Consultation with a pediatrician, hematologist, or surgeon may also be required.

Acute Chest Syndrome (ACS)

ACS is sickle cell crisis involving the lungs caused by blockage of lung blood vessels by sickle red cells, trapping of blood in lungs (sequestration), or infection. Asthma is more prevalent in children with SCD, and children with SCD plus history of asthma are more likely to develop ACS. Though children may come to hospital with ACS, it also commonly develops after several days in children admitted for pain crisis or other complication. For this reason, children with pain crisis should be encouraged to do breathing exercises using an incentive spirometer. If an incentive spirometer is unavailable, balloons, pinwheels, or bubbles should be used for breathing exercises. Death from ACS may occur within a few hours, so treat promptly.

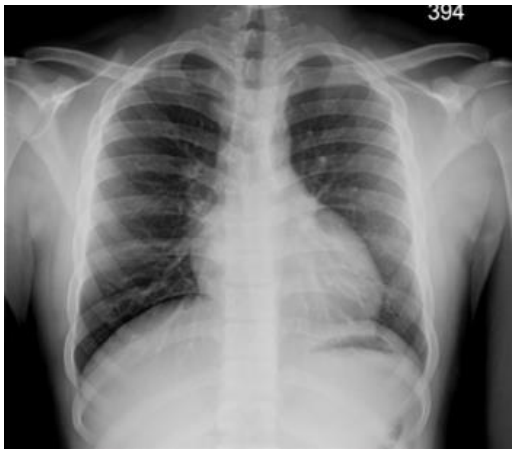
Patient using an incentive spirometer

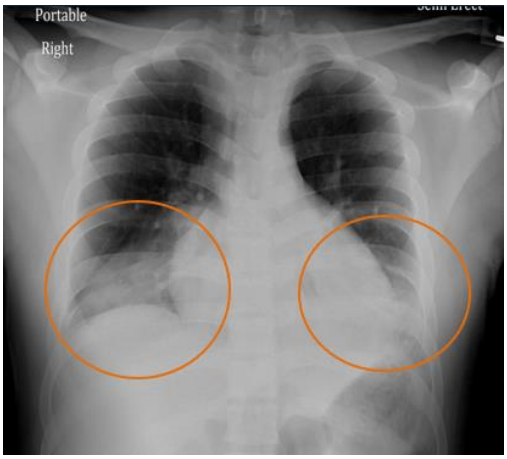
Presentation: ACS is defined as the occurrence of fever, cough, chest pain, fast breathing, or chest indrawing (i.e., lower chest wall sucks in when the patient breaths in) plus a new infiltrate* on chest X-ray. In patients with SCD, it is not possible to tell the difference between pneumonia and ACS.

Assessment

- Check for general danger signs
- Check for chest indrawing and fast breathing. Since the normal rate of breathing varies with age, fast breathing is defined as follows:
  - > 50 / minute if 2–12 months age
  - > 40 / minute from 12 months–5 years of age
  - > 30 / minute from 5–12 years of age
  - > 20 / minute if older than 12 years
- Check oxygen saturation (saturation < 90% indicates severe ACS)
- Obtain chest X-ray if fast breathing, chest indrawing, or chest pain is present.

** Chest X-rays produce black and white pictures of chest organs. The solid parts of the chest such as the bones and heart appear white because they block X-rays, unlike air in the lungs that appear darker because air does not block X-rays. Lung infiltrates refer to white patches that occur when ACS causes the air in lungs to be replaced by fluid due to inflammation, pooling of blood, etc.*





Source: Texas Children's Hospital

Both chest X-rays show the same patient admitted for back pain. The initial X-ray was normal but the repeat X-ray done after 2 days in hospital shows infiltrate (highlighted by orange circles) in the lower part of both lungs.

Laboratory Evaluation:

- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable).

Treatment:

It is not safe to manage children with suspected ACS at home. Admit or transfer patients with SCD who have any of the following findings:

- Presence of any danger sign
- Fast breathing
- Chest indrawing
- Oxygen saturation lower than 90%

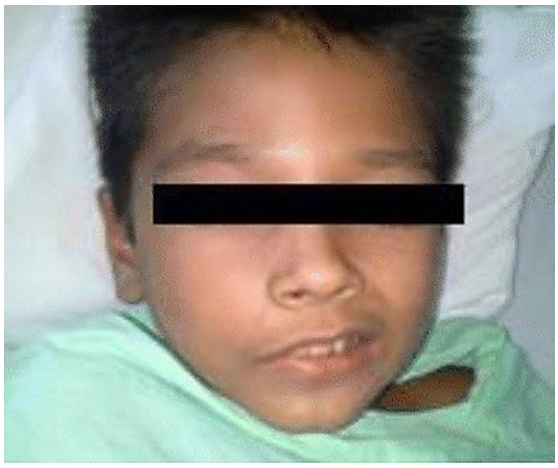
If ACS is present, antibiotics given must cover S. pneumoniae, H. flu, and atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae. Examples of initial antibiotics to treat ACS include:

- Ceftriaxone plus erythromycin or azithromycin
- Amoxicillin plus erythromycin or azithromycin
- Amoxicillin-clavulanate plus erythromycin or azithromycin

Acute Stroke

Stroke is brain damage that occurs from an insufficient supply of blood (and oxygen). Without preventive efforts, acute stroke (also called overt stroke or cerebrovascular accident) occurs in 5%–10% of children with SCD. This brain damage is severe and permanent in many children. Without treatment, more than half of all children who have an acute stroke will have another stroke within 2 years of the first one. Death may occur within a few hours, so treat promptly.

About one-third of children with SCD have silent stroke that can only be detected by taking special pictures of the brain by MRI. While silent stroke does not typically cause limb weakness, affected children may have learning difficulty, or problems with attention, impulse control, and judgement.



By de Oliveira Pardal PP, Pinheiro AC, Silva CT, Santos PR, Gadelha MA. (2015)

This child had an acute stroke that caused right-sided weakness involving leg, arm, and face. The face is drawn to the left side because of weakness on the right.

Presentation: Weakness of arms and legs, or asymmetry of the face. Convulsions, dizziness, loss of consciousness, and severe headache may also occur.

Assessment

- Check for general danger signs

- Check oxygen saturation
- Lumbar puncture to look for brain infection (meningitis) especially in young children may be needed
- Obtain MRI scan or CT scan if available

Laboratory Evaluation:

- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)

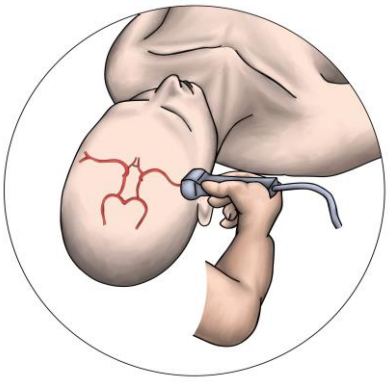
Treatment:

- Admit or transfer all patients with SCD and symptoms suggestive of stroke as soon as possible
- Observe patient closely and monitor breathing, heart rate, blood pressure, and oxygen saturation
- Early blood transfusion for acute stroke limits brain damage. While an exchange blood transfusion (i.e., procedure to replace most of the patient's sickle red cells with normal blood either manually or by a special machine) is preferred in SCD patients with stroke, a simple transfusion should be done if a manual or automated exchange transfusion is not possible.

Stroke Prevention:

Recall that 5%–10% of children with SCD experience a first stroke, and without treatment, more than half of those who have a stroke will experience another one within two years. Therefore, it is important to prevent a first stroke (primary prevention), and recurrent stroke in those who have a previous stroke (secondary prevention).

- **Secondary Prevention (Reduce risk of recurrent stroke)**
  - Immediately after a child with stroke is stabilized, they should receive a blood transfusion. These transfusions should be continued every 3–4 weeks until hydroxyurea treatment is established. Because indefinite transfusions are neither available nor practical in SSA, all affected children should also be started on hydroxyurea at the time that stroke is initially diagnosed.
- **Primary Prevention (Reduce risk of a first stroke)**
  - If available, transcranial Doppler (TCD) ultrasound to assess the flow of blood through the brain should be performed yearly in children 2–16 years old. Those with abnormal TCD should be immediately referred to a specialist (hematologist or pediatrician). Patients with abnormal TCD who are not already taking hydroxyurea should be started on hydroxyurea.



This image shows a TCD probe applied to the head for measuring the flow of blood through the arteries in the brain.

Diarrhea (>3 Watery Stools in 24-hour Period)

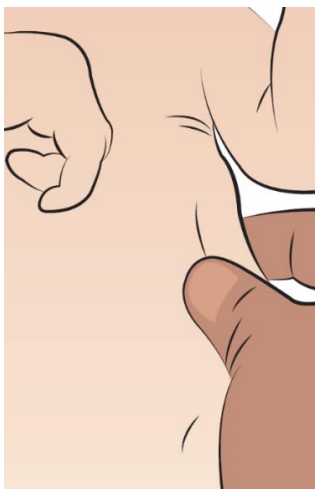
Diarrhea may be a sign of severe infection, especially when associated with fever. Children with SCD are prone to Salmonella infection of the intestines, bones, and bloodstream. Even in the absence of fever, the loss of fluids in diarrhea results in dehydration that may provoke a sickle cell pain crisis.

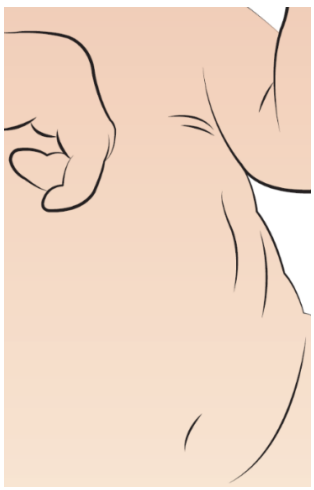
Presentation: More than 3 watery stools in a 24-hour period (diarrhea). Fever, vomiting, irritability, and jaundice may occur.

Assessment

- Check for general danger signs
- Check if there is blood in the stool (dysentery)
- Check oxygen saturation
- Check for dehydration and decide whether the child has: no evidence of dehydration, some dehydration, or severe dehydration by answering the following questions:
  - Is child very thirsty and eager to drink (some dehydration) versus unable to drink or drinks poorly (severe dehydration)?
  - Is child restless or irritable (some dehydration), versus lethargic or unconscious (severe dehydration)?
  - After child's abdominal skin is pinched, does it return to normal slowly (some dehydration) versus very slowly — longer than 2 seconds to return to normal (severe dehydration)?
  - Does child have sunken eyes? This may be seen in both forms of dehydration.

A severely dehydrated child is more likely to be lethargic or unconscious and unable to drink, compared to a child with some dehydration who though restless or irritable, is very thirsty and willingly drinks when fluid is offered.





Michael Stencel, 2020

When normal skin is pinched, it should return to normal immediately.

This child's skin did not immediately return to normal when it was pinched.

Slow return to normal slowly suggests some dehydration. Very slow return (i.e., > 2 seconds) suggests severe dehydration.

Laboratory Evaluation:

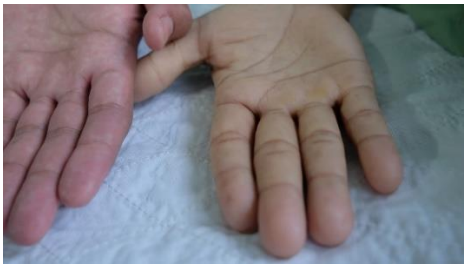
- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)
- Stool culture may be needed
- Serum electrolytes if available.

Treatment:

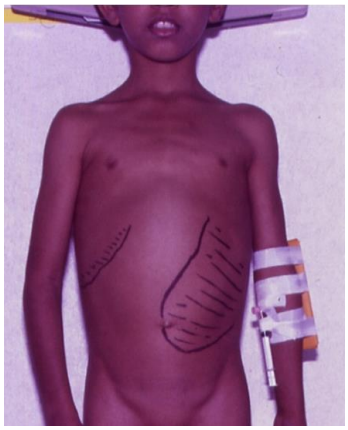
- Immediately admit all patients with SCD and diarrhea if any type of dehydration is present
- Children with severe dehydration require immediate intravenous (or nasogastric) rehydration with close monitoring, followed by oral rehydration once they improve. Those with some dehydration may be treated with oral rehydration
- Patients who have blood in stools (dysentery), or whose diarrhea is accompanied by fever or stomach cramps likely require antibiotic treatment due to the possibility of infection with Shigella or Salmonella bacteria. Recall that children with SCD are prone to Salmonella infection. In addition to intestines (diarrhea), Salmonella is notorious for causing infection of the gall bladder (cholecystitis), bloodstream (sepsis), joints (arthritis), and bones (osteomyelitis)
- Zinc is lost in greater quantities during diarrhea. Once diarrhea improves, start zinc supplements and continue for at least 14 days
- Patients with diarrhea should continue to eat a well-balanced diet as tolerated during and after illness.

Acute Severe Anemia (Palmar Pallor)

While children with SCD have chronic mild-moderate pallor, sudden severe pallor (severe anemia) may occur, especially in children younger than 6 years. This SCD complication occurs from either sudden trapping of blood in the spleen or liver (acute sequestration crisis) or bone marrow that shuts down and becomes unable to produce new red blood cells (aplastic crisis). Aplastic or sequestration crisis may be provoked by infection. Parvovirus infection — a common contagious illness in all children — is associated with aplastic crisis in children with SCD. Some experts suggest that Hgb level must drop at least 2.0 g/dL lower than the usual Hgb to call it acute sequestration. Acute severe anemia should be treated promptly because it is a common cause of death in children with SCD.



To assess pallor, compare the color of the child's palm with your own palm and with the palms of other children. The palm on the right is pale



By Al-Salem AH - ISRN Dermatology (2010)
doi: 10.5402/2011/864257

Normally, the spleen is located behind the ribs in the left upper abdomen. As shown in this picture, it usually enlarges towards the right lower abdomen.

Presentation: Severe pallor with enlargement of spleen beyond baseline (spleen sequestration) or severe pallor without spleen enlargement (aplastic crisis). In rare cases, sequestration affects the liver.

Assessment

- Check for general danger signs
- Check oxygen saturation
- Monitor pulse and blood pressure — sequestration may cause shock with fast pulse (heart rate) and low blood pressure.

Laboratory Evaluation:

- Check CBC with reticulocytes (hemoglobin by POC device if CBC with reticulocytes is unavailable)
- Reticulocyte count is low (typically < 1%) in aplastic crisis but higher than usual with acute sequestration crisis
- Type and screen for blood transfusion
- Obtain a malaria smear or RDT, and blood culture if the patient also has a fever.

Treatment:

- Admit or transfer all patients with acute severe pallor (aplastic crisis or sequestration crisis)
- Transfuse blood to increase Hgb to ~ 7.0 g/dL
- The first episode of aplastic anemia from parvovirus results in life-long immunity
- Acute spleen sequestration (ASS) often recurs. Consult a pediatrician or hematologist for any episode of ASS with Hgb < 4 g/dL, or if ASS with Hgb < 6.0 g/dL occurs more than once to help decide on the need for surgical removal of the spleen (splenectomy). Special vaccinations and arrangements are required prior to splenectomy.

Preventing death due to spleen sequestration:

Recall that acute spleen sequestration is a common cause of death in children with SCD and it often recurs. The parents of all children (especially those younger than 6 years) with SCD should be taught how to palpate the spleen and assess pallor. All parents should be told to immediately seek medical attention if sudden spleen enlargement or severe palmar pallor occurs.

Other Complications

General Appearance and Stigma

Children with SCD may have prominent foreheads, misaligned teeth, slow growth, and long, slender limbs that partly result from the expansion of bone marrow in its attempt to produce more red cells. Combined with jaundice and pallor, some individuals with SCD have features that make them identifiable to others. Consequently, people affected by SCD not only struggle with the symptoms of the disease but also suffer from the stereotypes and biases that result from other people's ideas about SCD.

Management:

Discuss the issue with patients and their families and regularly reassure them that with modern treatments, many patients with SCD lead productive lives. Additionally, referral to SCD support groups may help patients better advocate for themselves.

Eyes

Aside from jaundice, SCD affects the retina in 10%–30% of older children and adults. The retina is the tissue in the back of the eye that converts light into signals that then go to the brain to help us recognize objects. SCD retinal disease may cause blindness if not detected and treated early.

Management

- Refer patients older than 10 years to the eye doctor for examination. This should be repeated every 1–2 years
- Treatments to preserve vision are more likely to be effective if retinal damage is diagnosed early.

Kidneys

SCD affects the kidney in 10%–30% of older children and adults. Left untreated, this may result in kidney failure.

Management

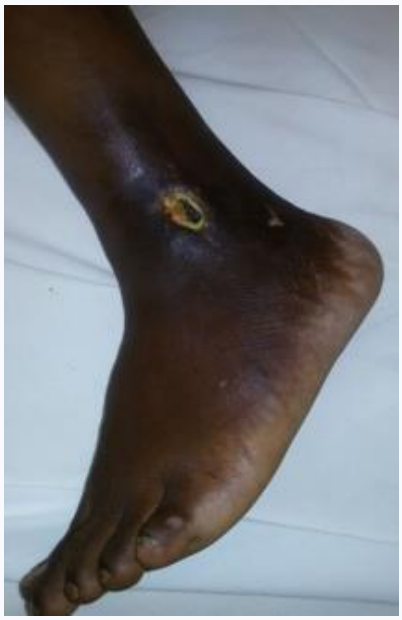
- Monitor blood pressure in older children and pay attention to the dose of medicines such as ibuprofen, diclofenac, gentamicin, etc. that may affect kidney function
- Monitor serum creatinine and check urine for protein in patients older than 10 years. This should be repeated every 1–2 years
- Refer patients with blood or protein in the urine, high blood pressure, or high serum creatinine to pediatrician or kidney specialist.

Leg Ulcer

Lower leg ulcers are common in older children and adults, especially those with Hgb SS type of SCD. Long-term blockage of skin blood vessels by sickle red cells, trauma, and infection are some possible reasons why leg ulcers develop. SCD ulcers are painful and prone to recur.

Management:

- Refer patients with large or recurrent ulcers to a pediatrician or hematologist
- Chronic leg ulcers in patients with SCD are best treated by a multidisciplinary team comprising pediatrician, hematologist, wound care specialists, surgeons, etc. Surgical removal of dead tissue and skin graft may be needed
- Start hydroxyurea if the patient is not already on this medicine
- Daily wound dressing – clean with saline and place dry gauze. Remove dressing with necrotic tissue the next day, then repeat the process
- Minimize local edema by means of rest, elevation of the lower extremity, and compression bandage
- Treat pain aggressively with topical and systemic opioids. Topical opioids also relieve swelling and facilitate healing
- Give nutritional supplements such as zinc and vitamin D if deficiency is suspected.



Source: TCH Global HOPE

Ulcers are most common around the ankle as in this patient.

Preventing leg ulcers:

- Inspect the skin often and intervene at the first sign of skin breakdown
- Always keep skin clean and moist by applying moisturizer. Drink plenty of water to stay hydrated
- Minimize skin trauma by wearing protective shoes – don't walk with bare feet.

Priapism

Painful erection of penis (priapism) may occur as brief repeated episodes or persistent pain that lasts several hours with the risk of impotence. Painful urination or retention of urine may occur.

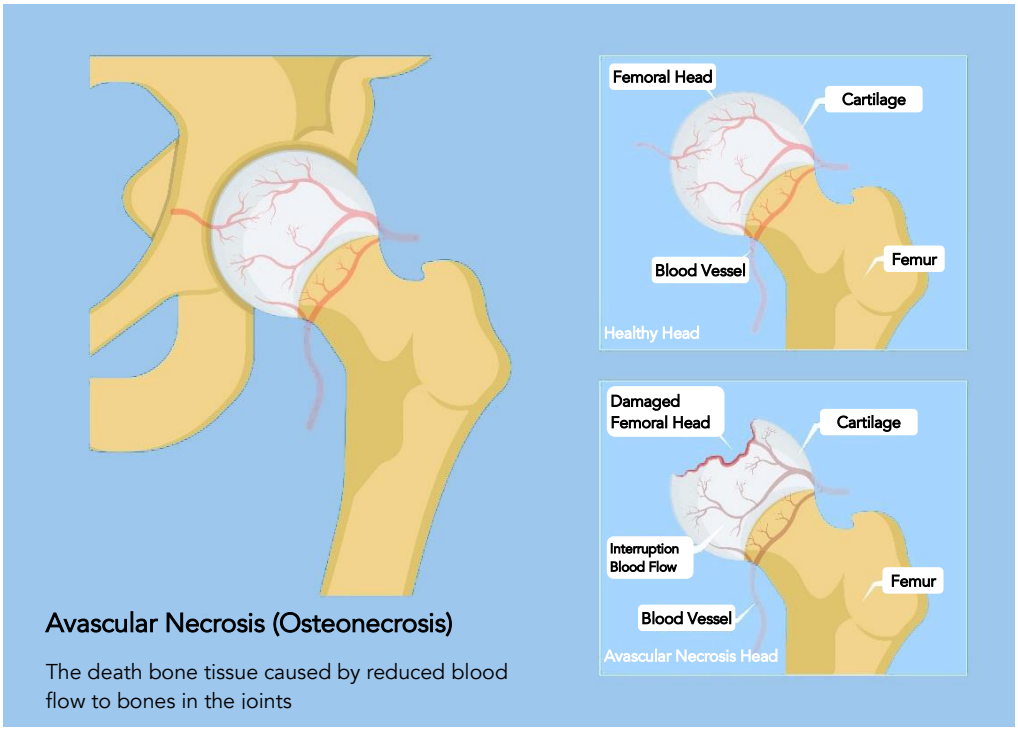
Management

- Start hydroxyurea in patients with frequent episodes of priapism
- For episodes that last less than 2-3 hours: Drink extra fluids, take oral pain medicines, and have a warm bath
- Episodes longer than 4 hours:
    - Admit to a hospital — surgical drainage of the penis may be needed to avoid permanent damage.
    - Check Hgb and transfuse if patient otherwise meets criteria for transfusion

Other Complications – Osteonecrosis

The blockage of blood supply by sickle cells may result in the death of bone because of a lack of oxygen. This is called osteonecrosis or avascular necrosis. The most commonly affected sites are hip (femur or thigh bone) and shoulder (humerus or arm bone). Affected patients present with severe pain, limited joint movement, deformity, or limp.

This illustration shows avascular necrosis of the thigh bone in hip. Early diagnosis is important to minimize disability. Some patients with severe disease become dependent on wheelchairs to move around wheelchair, and others require hip replacement surgery.



Management

- Early diagnosis especially of hip osteonecrosis is important
- Pain medicines
- Patients with acute hip osteonecrosis should use crutches to restrict weight-bearing. This relieves pain and may slow the progression of the damage
- Refer to physiotherapy for exercises to strengthen the muscles around the bone and joint. This reduces pain and improves gait
- Patients with severe disease may require hip replacement surgery

Unit 5 Case Study / Quiz

5-1:	True (T) or False (F)?
	A 6-year-old girl who presents with inability to move her right arm and right leg but appears well and has Hgb of 9.1 g/dL should receive a blood transfusion right away.
5-2:	True (T) or False (F)?
	A 4-year-old boy with Hgb SS presenting to clinic for the first time has Hgb 5.9 g/dL and palpable spleen that is 5 cm below the rib margin. This is definitely acute spleen sequestration.
5-3:	True (T) or False (F)?
	A 12-year-old girl with SCD is hospitalized after cholecystectomy (removal of gallbladder). As recommended, she received a blood transfusion before surgery. If she develops fast breathing without fever on the day after surgery, the most likely explanation is internal bleeding at the surgical site.
5-4:	True (T) or False (F)?
	A 5-year-old girl with SCD who presents with 7 days of right arm pain and fever (39°C) has a positive rapid diagnostic test for malaria. In addition to antimalarial medicine, she should be treated with antibiotics that would cover bacteria that cause osteomyelitis (bone infection).
5-5:	True (T) or False (F)?
	High blood pressure and edema of both feet in a 12-year-old boy with SCD is most likely due to malnutrition.

UNIT 6:
BLOOD TRANSFUSION IN SCD

Most children with SCD always have mild to moderate anemia (typical hemoglobin is between 6.0 g/dL–9.0 g/dL). Despite this anemia, most children with SCD function normally because their bodies have had time to adjust to the anemia. Therefore, the finding of anemia alone or an uncomplicated pain crisis in a child with SCD is not a reason to transfuse blood. Furthermore, blood transfusions come with significant risks to the patient.

When should a SCD patient receive a blood transfusion?

- If Hgb is less than 4.0 g/dL (all patients)
- If Hgb 4.0 g/dL–7.0 g/dL, transfuse for
  - labored breathing, impaired consciousness, clinical dehydration, or heart failure
  - severe malaria parasitemia (greater than 10% of parasitized red cells)
  - ACS with labored breathing or oxygen saturation < 90% — aim for Hgb of ~ 9.0 g/dL
  - before surgery requiring general anesthesia that is expected to last longer than 30–60 minutes — aim for Hgb of ~ 10.0 g/dL
  - acute spleen or liver sequestration — aim for Hgb ~ 7.0 g/dL
- Regardless of Hgb level, transfuse for
  - new acute stroke (cerebrovascular accident)
  - patient with pain who develops failure of at least 2 organs - lungs, liver, kidneys, and brain are typical target organs

What blood is suitable to transfuse?

Only blood that meets the following criteria is suitable for transfusion

- Screened negative for infections that can be transmitted from transfusion. At a minimum, it should be negative for HIV, hepatitis B, hepatitis C, and syphilis
- Issued by the blood bank and certified to be compatible with the specific patient
- Patient's identifying information (name, date of birth, number, etc.) is accurately printed on the tag attached to the blood bag
- Blood bag has been out of the fridge for less than 2 hours, has no visible clots, does not appear black or purple, and is not leaking
- Today's date is before the expiry date stamped on the bag
- Blood is the correct ABO / Rhesus group. Whenever possible, blood transfused to patients with SCD should be matched for less common blood groups such as Kidd, Kell, Duffy, and Rhesus Cc /Ee in addition to routine ABO / Rhesus D. This is important to reduce the risk of reaction especially in those who are expected to receive multiple transfusions, or who have received many transfusions

How to administer blood transfusion?

- **Usual dose:** 10 ml/kg of packed red cells or 20 ml/kg of whole blood (if packed cells are unavailable). In general, 10 ml/kg of packed cells should raise Hgb by approximately 2.0 g/dL. To prevent further blood vessel blockage from too much blood, do not exceed Hgb of 11.0 g/dL in SCD patients
- **Duration:** Over 3 hours. Do not exceed 4ml/kg/hour for packed cells or 7 ml/kg/hour for whole blood. To prevent bacterial growth in contaminated blood units, blood that has not been transfused within 4 hours of removal from the blood bank refrigerator should be discarded
- **Monitoring:**
  - The first 15 minutes are critical for the onset of transfusion reactions. Record the patient's appearance, temperature, respiratory rate, pulse rate, and oxygen saturation (if available) **prior to** transfusion, **15 minutes after** the start of transfusion, **every hour** until the end of transfusion, **at the completion** of transfusion, then **every 4 hours for the following 24 hours**. Critically ill children require more frequent monitoring.
  - If respiratory rate or pulse rate rises, slow down the transfusion plus give furosemide — 1 mg/kg (maximum dose = 20 mg) especially if evidence of heart failure is present. Also, check oxygen saturation and give oxygen if needed
  - Document the start and stop times of transfusion, total volume given, and whether any reactions occurred
  - Regularly ensure that the transfusion is proceeding at the planned speed
- After transfusion is completed, wait a minimum of 15 minutes, and then recheck Hgb to decide if additional blood is needed

Acute transfusion reactions

Transfusion reactions may result from allergy/anaphylaxis, hemolytic and non-hemolytic transfusion reactions, bacteria, septic shock, and fluid overload.

Possible Symptoms and Signs (Clinical Presentation)

- fever (defined as temperature > 38^0C or rise of > 1^0C over baseline temperature)
- itchy rash
- increased heart rate
- throat swelling and wheezing
- fast breathing
- dark or red urine
- unexplained bleeding — may be the only sign of a major reaction in an unconscious child
- restlessness, confusion
- low blood pressure or collapse

- Back or flank pain

Management:

If any of these symptoms/signs occur, immediately do the following:

- Stop the transfusion
- Run normal saline through the line to keep it open
- Recheck blood product label against the patient to confirm that it is the correct unit
- Recheck patient's appearance and vital signs – temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation

If the only sign is an itchy rash that affects less than one-third of the body:

- Give antihistamine — e.g., chlorpheniramine: 0.1 mg/kg IM
- IF rash remains stable or improves, and no new symptoms develop, restart the transfusion at a slower rate for 30 minutes, then return to a normal rate after 30 minutes

If severe itchy rash affecting greater than one-third of the body, fever, increased pulse rate, or restlessness occurs:

- Give antihistamine — e.g., chlorpheniramine: 0.25 mg/kg IM
- Send blood sample in EDTA (purple) tube, urine sample, plus the bag of leftover blood to the blood bank for testing
- If patient worsens or does not improve within 5–10 minutes, immediately give adrenaline IM, and repeat every 5–10 minutes if needed. Adrenaline dose: Weight < 25 kg — 0.15 mg; Weight > 25 kg — 0.3 mg
- If patient improves, you may restart the transfusion with a different blood unit
- Use of a white blood cell filter reduces the risk of non-hemolytic reactions

If severe allergy symptoms such as throat swelling, stridor, wheezing, collapse, or hypotension occurs, this is anaphylaxis:

- Immediately give adrenaline IM and repeat every 5–10 minutes if needed. Adrenaline dose: Weight < 25 kg — 0.15 mg; Weight > 25 kg — 0.3 mg
- Give antihistamine — e.g., chlorpheniramine: 0.25 mg/kg IM
- Give albuterol inhaler or nebulizer if wheezing
- Give oxygen and maintain airway
- Send blood sample in EDTA (purple) tube, urine sample, plus the bag of leftover blood to the blood bank for testing

Other reactions such as fast heart rate, breathing difficulty, crepitations in lungs may indicate fluid overload (give furosemide: 1 mg/kg; maximum dose 20 mg); and antibiotics may be needed for bacterial infection

Other (delayed) complications of blood transfusions

Alloimmunization

Rarely, a transfusion reaction occurs 2–21 days after a transfusion with the result that the expected rise in hemoglobin does not occur. In other cases, a transfusion reaction occurs during a future transfusion. These complications are due to alloimmunization. Alloimmunization refers to the immune response that occurs when a person is exposed to foreign antigens causing antibodies to develop against a component of the transfused blood. It makes it difficult or impossible to find compatible blood for transfusion.

To reduce the risk of alloimmunization, blood transfused to patients with SCD should be matched for less common blood groups such as Kidd, Kell, Duffy, and Rhesus Cc /Ee in addition to routine ABO / Rhesus D grouping whenever possible. The blood bank should also screen for alloantibodies before every transfusion.

Iron overload

Iron overload occurs after about 1–2 years in patients who receive transfusions monthly. This is because there is no natural way for the body to get rid of iron that is contained in the blood. The excess iron accumulates in the liver, heart, kidney, and other body organs and eventually causes organ failure if not treated. Patients who receive ongoing or multiple transfusions should be routinely tested for iron overload. Treatment with medicines called iron chelators should be administered to those affected.

Infections

Viral, bacterial, protozoal, and other types of microbes may also be transmitted through transfusions. While infection from HIV and hepatitis viruses occur due to failure of screening, other infections that are not typically screened may also occur. Examples include viruses such as West Nile virus and parvovirus, plus other non-viral infections such as malaria, Chagas disease, and Leishmaniasis.

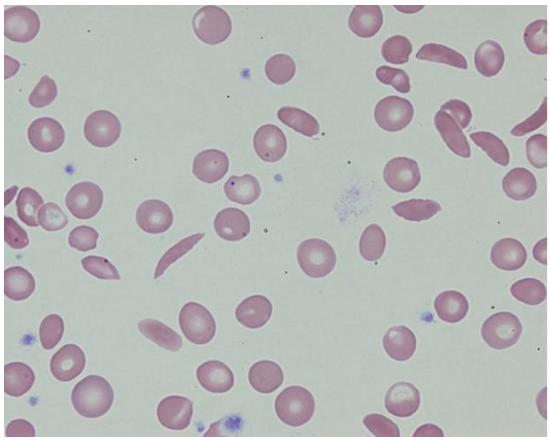
Unit 6 Case Study / Quiz

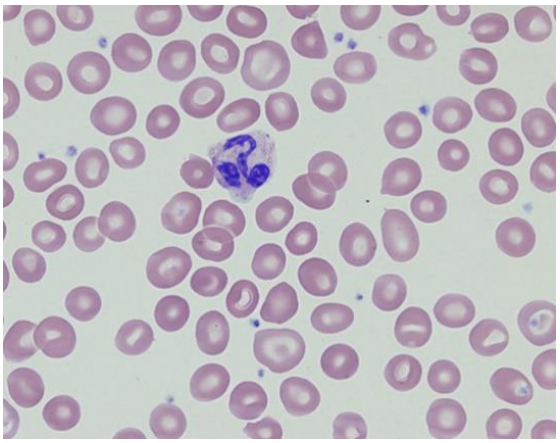
6-1:	**True (T) or False (F)?**
	A 10-year-old girl with SCD hospitalized 10 days ago for pain crisis is still in moderate pain. Hgb of 8.9 g/dL on admission is 7.7 g/dL today. She should be transfused to help resolve the pain.
6-2:	**True (T) or False (F)?**
	At a minimum, blood for transfusion to a SCD patient must be negative for West Nile virus and Zika virus.
6-3:	**True (T) or False (F)?**
	While giving a blood transfusion, the clinician should record patient's appearance, temperature, respiratory rate, and pulse rate prior to the transfusion, 15 minutes after start of transfusion, and then every hour until the end of transfusion.
6-4:	**True (T) or False (F)?**
	A 9-year-old boy with SCD has been receiving well-screened and compatible blood every month for the past 3 years to prevent a second stroke. He no longer experiences pain events and is not on any medicines. There is no need for concern about iron overload since he is doing well and has no complaints.

UNIT 7:
HYDROXYUREA

Hydroxyurea is the first medicine known to reduce the tendency of sickle cells to block blood flow. It is proven to reduce the frequency of pain events, including acute chest syndrome, and the need for blood transfusions or hospitalization. Additionally, it prolongs life and reduces the risk of malaria infection in children. These beneficial effects result mainly from hydroxyurea's ability to stimulate the production of fetal hemoglobin (Hgb F) and its tendency to decrease inflammation partly by reducing the total number of white blood cells.

These pictures show blood smears in the same patient before, and months after starting hydroxyurea treatment. The red cells in the second smear are larger (higher MCV), more numerous (higher Hgb level), and no sickle cells are seen.





Source: Texas Children's Hospital

While hydroxyurea is very useful when used appropriately, it may cause adverse effects. Therefore, it should only be prescribed according to the rules approved by the local health authorities and by clinicians who understand how to prescribe it, and how to monitor and prevent adverse effects. Of note, the CBC of children on hydroxyurea will often show a high MCV even in those who do not have a deficiency of folate or vitamin B12. An example of a CBC report from a child on hydroxyurea is below.

CBC W/Plat & Diff

	Ref Range & Units	
WBC	4.5 – 13.5 10^3/µL	5.75
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	4.1 – 5.1 10^6/µL	2.25 ˅
HGB	12.0 – 16.0 G/DL	8.0 ˅
HCT	36.0 – 45.0%	23.5 ˅
MCV	78.0 – 95.0 FL	104.4^
MCH	26.0 – 32.0 PG	35.6^
MCHC	32.0 – 36.0 G/DL	34.0
RDWCV	11.5 – 14.0 %	16.5^
RDWSD	38.5 – 49.0 FL	61.9^
Platelet	150 – 450 10^3/µL	292
MPV	6 – 10 FL	9.0
Differential Type		AUTO
Seg%	33 – 76%	57.2
Lymph%	15 – 55%	35.5
Mono%	0 – 4%	6.4^
EOS%	0 – 4%	0.2
Baso%	0 – 1%	0.5
IG%	0%	0.2^
ANC	1.8 – 8.0 10^3/µL	3.29
NRBC%	0%	3^
NRBC Absolute	10^3/µL	0.15
Reticulocyte Count		
Retic Percent	0.5 – 2.0%	8.7^
Retic Absolute	0.029 – 0.099 10^6/µL	0.195^

The following is a common approach to the use of hydroxyurea:

Which children with SCD can be treated with hydroxyurea?

In general, children diagnosed with SS or Sβ^0-thal type of SCD are eligible for treatment if they fall in one of the following categories:

- **Primary Treatment:** Subject to availability, hydroxyurea should be offered to all children with Hgb SS or Hgb Sβ^0-thal who are at least 9 months old regardless of clinical severity.
- **Secondary Treatment:** As a priority, hydroxyurea should be offered to children who have experienced any of the following complications.
  - Two or more pain events that lasted at least 4 hours and required treatment in a health care facility within the preceding 24 months
  - At least one definite acute chest syndrome event that required treatment in a health care facility within the preceding 24 months

- Stroke (cerebrovascular accident)
- High conditional (> 185 cm/sec) or abnormal (> 200 cm/sec) velocities on transcranial Doppler (TCD), especially since chronic transfusion is not available or practical

Prior to starting hydroxyurea

- Document a thorough history and physical examination. This must include diagnosis of Hgb SS or Hgb $S\beta^0$-thal, plus absence of other acute life-threatening illness such as severe malnutrition, tuberculosis, acute spleen sequestration, etc.
- Discuss the rationale and potential adverse effects of hydroxyurea plus requirement for regular monitoring with patient and family members
- Labs:
  - Complete blood count (CBC) and reticulocytes. Must meet the following criteria:
    - HGB > 5.9 g/dL;
    - Absolute reticulocyte count (ARC) over 100,000 /µL;
    - Absolute neutrophil count (ANC) over 1,000 /µL;
    - Platelet count (PLT) greater 100,000 /µL; and
    - Normal MCV (mean cell volume)

    These CBC with retic thresholds should not be regarded as permanent but as clues to further improve health before starting hydroxyurea. For example, a very low MCV suggests iron deficiency (that should be treated) or thalassemia trait (that does not require treatment). On the other hand, a high MCV may indicate B12 or folate deficiency. Carefully review diet and consult with a pediatrician or hematologist for review of blood smear for evidence of iron deficiency or thalassemia trait (low MCV); and vitamin B12 or folate deficiency (high MCV). Assessing the response to a trial of treatment with iron, folate, or B12 may help clarify the diagnosis.
  - Check liver function (ALT, direct/indirect bilirubin). ALT should be < 3x the upper limit of normal before starting hydroxyurea. Patients with extremely abnormal ALT values should be investigated to find a cause, then managed appropriately before starting hydroxyurea. In many patients, the abnormal ALT improves with time possibly due to resolution of virus- or medication-induced inflammation of the liver. Even patients with documented chronic hepatitis (e.g., hepatitis B or C) may be initially treated with a lower dose of hydroxyurea, followed by dose increases coupled with intensive monitoring of liver function.
  - Check serum creatinine (kidney function test). Patients with abnormal creatinine require a lower dose and more intensive monitoring.

Any exclusion based on the above laboratory criteria should not be regarded as permanent. Some patients who do not initially meet the above standards may qualify after appropriate clarification or treatment.

Dosing

- **Initial Dose:** Start at 20 mg/kg once daily by mouth. Patients on 'primary treatment' may continue on a fixed dose of 20 mg/kg with small dose adjustment once yearly if needed to account for growth. Adjustment for growth must not exceed 2.5 mg/kg/day. The dose may be averaged weekly if only 500 mg capsules are available. Thus, some children may receive uneven daily doses or skip medicine on some days.
- **Dose escalation:** A dose-escalation strategy for hydroxyurea is proven to be more effective in preventing complications of SCD compared to a fixed-dose strategy. However, dose escalation requires more intense monitoring for adverse effects. For this reason, only increase dose above 20 mg/kg IF resources for close laboratory monitoring are available. Dose escalation should be considered especially for patients with history of stroke or abnormal TCD (> 200 cm/sec), and for those with persistent severe or recurrent symptoms despite a fixed 20 mg/kg dose of hydroxyurea. Additionally, before every dose increase, the patient must meet ALL the following blood count criteria on at least 2 blood measurements done at least 1 month apart:
    - ARC > 100,000/μL;
    - ANC > 4,000/μL;
    - PLT > 100,000/μL; and
    - HGB > 6.5 g/dL

If the patient meets the criteria, increase hydroxyurea dose by 5 mg/kg every 2 months to a maximum of 35 mg/kg. Check adherence before every dose escalation. Monitor CBC and reticulocytes at 1 and 2 months after EVERY dose change. Refer patients on escalated dose strategy to a pediatrician or hematologist.

Clinical and laboratory evaluation during hydroxyurea treatment

- Document a thorough history and physical examination including weight, and interim clinical events such as pain events, surgery, hospitalization, transfusion, etc.
- Assess adherence by history and pill count and rate as good (> 70%), fair (30 – 70%), and poor (< 30%)
- Labs:
    - CBC and reticulocytes: At 1 and 2 months after treatment initiation. Then every 3 months. For patients on a dose-escalation regimen, this monitoring schedule should be repeated after EVERY dose escalation
    - Liver function tests (ALT, direct/indirect bilirubin) as needed based on clinical status
    - Kidney function test (creatinine) as needed based on clinical status

Modification or discontinuation of hydroxyurea treatment for hematological toxicity

Hydroxyurea causes bone marrow suppression. Therefore, the most common side effects of hydroxyurea are hematological in the form of low white blood count, low reticulocyte count with anemia, and low platelet count. Hematological toxicity is present if ANY one of the following is noted:

- ANC < 1,000/µL
- HGB < 4.0 g/dL with any ARC
- HGB < 6.0 g/dL **AND** ARC < 100,000/µL
- ARC < 80,000/µL **AND** HGB < 7.0 g/dL
- PLT < 80,000 /µL

All patients (either on fixed- or escalated-dose treatment with hydroxyurea) who develop hematological toxicity should be treated the same way. Do the following if hematological toxicity occurs:

- Discontinue hydroxyurea treatment
- Recheck CBC with reticulocytes every 2 weeks, then restart hydroxyurea once hematological recovery occurs (defined as blood counts that no longer meet the definition of hematological toxicity)
- If the blood counts recover within 2 weeks, restart at the previous dose
- Reduce hydroxyurea dose by 2.5 mg/kg if toxicity persists for more than 2 weeks or if there is a previous history of toxicity at the current dose within the preceding 3 months

Miscellaneous – including answers to common questions from patients about hydroxyurea

- Patients on antiretroviral drugs (didanosine or stavudine) for HIV concomitantly with hydroxyurea may develop pancreatitis, hepatotoxicity, or peripheral neuropathy. Avoid unless it is possible to closely monitor for these complications
- Other side effects that may occur due to hydroxyurea include nausea, vomiting, loss of appetite, constipation, weight gain, mouth sores, skin rash, or darkening of the skin and nail beds. These side effects are rare
- Non-hematological side effects are usually mild and most patients who experience them choose to continue hydroxyurea treatment because they feel healthier on hydroxyurea and experience fewer pain events. Similar to hematological toxicity, they resolve with discontinuation of the medicine
- Liver and kidney function tests should be monitored as clinically indicated. Pay special attention to those with abnormal liver or kidney function at initiation of hydroxyurea. Use a lower starting dose for patients with abnormal kidney function. Thoroughly investigate patients who develop significant liver or kidney dysfunction during treatment for potential etiologies other than hydroxyurea since these are more likely

- Even though hydroxyurea is listed as unsafe to use in pregnancy, many women who unintentionally became pregnant while taking hydroxyurea for SCD have delivered normal infants. Similarly, many men taking hydroxyurea have fathered normal babies.

Hydroxyurea is also used to treat cancer. Although some individuals who take hydroxyurea for cancer develop a second cancer, it is possible that the second cancer developed because these patients were already predisposed to cancer. There is no evidence that hydroxyurea causes cancer in patients with SCD. This conclusion is based on the fact that hydroxyurea has been safely used to treat SCD for more than 30 years. Hydroxyurea should **not** be discontinued for uncomplicated fever, pain, or hospitalization

Unit 7 Case Study / Quiz

7-1:	**True (T) or False (F)?**
	If available, hydroxyurea should be offered to all children over 9 months old who are diagnosed with SC or Sβ$^+$-thal forms of SCD regardless of clinical severity.
7-2:	**True (T) or False (F)?**
	A 3-year-old girl with Hgb SS has been receiving hydroxyurea (20 mg/kg) for 4 months. Today's complete blood count shows Hgb 8.9 g/dL, ARC 75,000/µL, PLT 189,000/µL, and ANC 1600 /µL. She should be instructed to continue hydroxyurea because there is no evidence of toxicity on today's CBC.
7-3:	**True (T) or False (F)?**
	A 4-year-old boy with Hgb SS has been receiving hydroxyurea (20 mg/kg) for 2 years and is doing very well. His nail beds appear dark in color. Today's complete blood count shows Hgb 9.2 g/dL and MCV 104.4 fL. He should be advised that the elevated MCV and darkened nail beds are most likely due to hydroxyurea.

APPENDIX I – QUIZZES WITH ANSWERS

QUIZ 1-1

True (T) or False (F)?

Normal hemoglobin level in children younger than 14 years varies according to whether patient is male or female?

Correct Answer: False

Although normal hemoglobin level generally varies according to age and gender (i.e., male versus female), the effect of gender does not manifest until puberty. In general, among all individuals who are 15 years or older, males have higher hemoglobin than females. Unlike gender, hemoglobin varies according to age in children. Healthy full-term newborns typically have high hemoglobin level greater than 14 g/dL. This quickly declines to about 11 g/dL at about 2 months of age. The WHO defines anemia as hemoglobin concentration less than 11.0 g/dL for children 6 months to 5 years old, hemoglobin less than 11.5 g/dL for those who are 5–11 years old, and hemoglobin less than 12.0 g/dL for children who are 12–14 years old.

In addition to age and gender, living in areas of high elevation above sea level raise the hemoglobin level of all residents. Consult published tables to determine how much to adjust hemoglobin level if you live in areas of high elevation of over 1,000 meters above sea level.

QUIZ 1-2

True (T) or False (F)?

While evaluating anemia with a complete blood count from an automated machine, the MCV is very important in suggesting the cause of the anemia.

Correct Answer: True

The MCV – i.e., average size of the red blood cells – is helpful to determine the cause of anemia. In general, MCV that is significantly greater than 90 fL in children suggests vitamin B12 or folate deficiency while a low MCV suggests iron deficiency or thalassemia. Since normal MCV value varies depending on age, the expected lower limit of MCV in children can be estimated by adding 70 to the child's age. For example, the MCV of a 6-year-old is low if it is lower than 76 fL. Most children with SCD have normal MCV. A reticulocyte count is usually combined with MCV to diagnose the cause of anemia. Reticulocytes are newly formed red blood cells released from the bone marrow to replace red cells that are destroyed by disease or through the normal process of replacing old red cells. In normal children, about 0.5%–2% of circulating red cells are reticulocytes. The number of these 'newborn red cells' (reticulocytes) in the blood is a useful indicator of production activity in the bone marrow where red blood cells are made. A reticulocyte count below 0.5% is typical of disorders where the production of red blood cells is reduced – e.g., infection, replacement of bone marrow by leukemia cells, and deficiency of iron, vitamin B12, or folate, etc. required to make red cells. On the other hand, blood loss or conditions characterized by fragile red blood cells such as SCD raise the reticulocyte count. Numerous bluish red blood cells (polychromasia) on a routine peripheral smear suggests a high reticulocyte count. To obtain an exact count, a special reticulocyte stain of the blood smear, or a reticulocyte-capable automated machine is needed.

QUIZ 1-3

True (T) or False (F)?

An African child who is noted to have anemia during a malaria illness is not likely to have other factors in addition to malaria to explain the anemia.

Correct Answer: False

Anemia in SSA children is usually due to multiple factors in the same child. In addition to malaria, micronutrient deficiencies (iron, vitamin B12, vitamin A, folate, etc.) due to malnutrition, intestinal helminths such as hookworm, HIV infection, schistosomiasis, and hemoglobinopathies such as SCD are important contributors.

Some recommended strategies to combat anemia include: 1) Late clamping of umbilical cord in term and preterm newborns; 2) controlling malaria in pregnant women and young children through prompt treatment of acute malaria and use of insecticide-treated nets, vector (mosquito) elimination with indoor spraying, etc.; 3) regularly deworming children; 4) Promoting a diet containing adequate amounts of micronutrients including iron, folate, etc., and administration of iron-containing micronutrient supplements; 6) teaching basic hygiene to reduce the risk of infection; and 7) routine screening of all newborns for SCD.

QUIZ 2-1

True (T) or False (F)?

Sickle cell disease only occurs in Africans or black people living outside Africa.

Correct Answer: False

Although SCD is more common in Africans (one in every 50–100 newborns in Africa has SCD) and those whose ancestors originated from Africa, the disease occurs in all racial groups. Any person can inherit SCD. SCD affects millions of people throughout the world. Outside Africa, SCD also occurs in India, Saudi Arabia, and in Mediterranean countries such as Greece, Italy, Spain, and Turkey. It also occurs in Caribbean countries such as Jamaica, Cuba, Bahamas etc., and in South, Central, and North American countries such as Brazil, Guatemala, Nicaragua, USA, etc. Because SCD may occur in people of all races, all babies in the USA are screened for SCD at birth.

QUIZ 2-2

True (T) or False (F)?

It is possible for a child to be born with sickle cell disease even if only one parent has sickle cell trait.

Correct Answer: True

SCD occurs when a child inherits at least one sickle hemoglobin (Hgb S) gene from one parent plus another abnormal beta-globin gene from the other parent. There are several types of SCD – depending on the specific abnormal beta-globin gene inherited with the Hgb S gene. The most common type of SCD is the Hgb SS form where an individual inherits the gene for Hgb S from both parents. In the less common types of SCD, the sickle cell gene from one parent is combined with another abnormal gene from the other parent. Examples of SCD types where the affected patient inherits sickle cell gene from only one parent include Hgb SC disease (Hgb S gene from one parent and Hgb C gene from the other parent), Hgb Sß^0-thal (Hgb S gene from one parent and beta-zero thalassemia gene from the other parent), and Hgb Sß$^+$-thal (Hgb S gene from one parent and beta-plus thalassemia gene from the other parent). In general, Hgb Sß^0-thal tends to be as severe as Hb SS, while Hgb Sß$^+$-thal and Hgb SC types are milder than Hgb SS or Hgb Sß^0-thal forms of SCD.

QUIZ 2-3

True (T) or False (F)?

While sickle cell trait (SCT or Hb AS) does not cause pain crisis, it may cause a mild anemia.

Correct Answer: False

Unlike individuals with SCD, people with SCT have normal hemoglobin and reticulocyte count. Sickle trait individuals are healthy because their RBC contain mostly Hgb A and therefore function normally to carry oxygen to body's tissues. Although people with SCT are healthy and do not have SCD, they can pass the sickle cell gene to their children. For this reason, it's important for everyone to know whether they have the SCT.

QUIZ 2-4

True (T) or False (F)?

Children with sickle cell trait (SCT or Hb AS) are less likely to die from malaria.

Correct Answer: True

The genetic change that causes SCD arose from areas of the world where malaria, a deadly disease, is very frequent. This genetic change persisted in the populations in these areas because it resulted in hemoglobin that protected those who carry it from malaria. While individuals with SCT or SCD may have malaria, children with SCT are less likely to die from malaria.

QUIZ 2-5

True (T) or False (F)?

Patients with SCD are expected to have a high reticulocyte count.

Correct Answer: True

Reticulocytes are newly formed red blood cells released from the bone marrow to replace red cells that are destroyed by disease or through the normal process of replacing old red blood cells. In normal children, about 0.5%–2% of circulating red cells are reticulocytes. The number of these 'newborn red cells' (reticulocytes) in the blood is a useful indicator of production activity in the bone marrow where red blood cells are made. Compared to normal red blood cells, sickle cells are sticky, stiff, and fragile. These fragile sickle cells break up easily and release their contents in the circulation. This results in a low number of RBC and hemoglobin (anemia), and yellow discoloration of eyes (jaundice) as these RBC contents accumulate in blood and stain the eyes. In addition to the anemia, a high reticulocyte count occurs in SCD from the abnormal breakdown of red blood cells and the bone marrow's attempt to correct the anemia by producing more red blood cells. Also, these stiff sickle cells block blood flow and cause damage to body organs due to reduced blood flow and oxygen supply. Examples of symptoms that occur due to poor supply of oxygen to body organs include pain (bones), stroke (brain), and difficulty with breathing (lungs). Similar damage to the spleen (an organ that is very important to protect the body against microorganisms such as bacteria, viruses, and parasites) results in a high risk of infection.

QUIZ 3-1

True (T) or False (F)?

Every child who is diagnosed with stroke should be tested for SCD.

Correct Answer: True

The risk of stroke in children with SCD is at least 333 times higher than the stroke risk of healthy children. In some children with SCD, stroke is the first presentation of the disease. Therefore, it is recommended to test all children with stroke for SCD, especially in places where screening of all newborns is not done. Ideally, all newborns should be screened for SCD to minimize morbidity and mortality. This is the practice in the USA and some regions in Europe. In addition to stroke, clinicians should readily test all children with enlarged spleen, need for blood transfusion after 3 months of age, unexplained bone pain, chronic anemia, or jaundice. It also makes sense to screen patients with severe infection, especially if due to S. pneumoniae or Salmonella, and the brothers or sisters of those already diagnosed with SCD.

QUIZ 3-2

True (T) or False (F)?

A child with anemia, jaundice, elevated reticulocyte count, plus obvious sickle cells on peripheral blood smear may or may not have SCD.

Correct Answer: False

A child with anemia, jaundice, elevated reticulocyte count, and sickle cells on a fresh blood smear definitely has SCD. Such children should be managed as SCD even if hemoglobin electrophoresis or another diagnostic tool is unavailable. While the finding of sickle cell forms on blood smear can help diagnose SCD in general, it cannot specify the type of SCD – i.e., if it is Hgb SS or Hgb SC, etc. Although the presence of sickle cells plus accompanying symptoms confirms SCD, some children with relatively mild forms of SCD such as Hgb SC or Hgb Sß$^{+}$-thal may not have sickle cells on a blood smear.

While hemoglobin electrophoresis or HPLC is an excellent test to diagnose SCD, the finding of sickle cells on a blood smear in a child with hemolytic anemia (low HGB with high reticulocyte count, jaundice, etc.) is also very specific for SCD and a diagnosis can be confidently made even in in the absence of hemoglobin electrophoresis or HPLC.

QUIZ 3-3

True (T) or False (F)?

Apart from jaundice, SCD does not affect the eyes.

Correct Answer: False

SCD may affect any body organ including brain, bones, spleen, kidney, liver, lungs, skin, eyes, and so on. Blindness or loss of vision can occur when sticky and stiff sickled red cells block the blood vessels that supply blood (and oxygen) to the eye including the retina. The retina is the layer of nerve cells that line the eye's back wall inside the eye. This layer of nerve cells is what senses light and sends messages to the brain so that a person can see. Individuals with SCD, especially those who are at least 10 years old, should visit an eye doctor every 1–2 years to look for damage to the retina so that damage to the retina can be treated early to prevent loss of vision.

QUIZ 3-4

True (T) or False (F)?

The first symptom of SCD in most young children is pain crisis involving hands or feet?

Correct Answer: True

Pain crisis that involves hands or feet of young children is called dactylitis or hand-foot syndrome. Dactylitis is the initial presentation of SCD in most children. As a form of pain crisis, dactylitis may be associated with fever and swelling and treatment should proceed as with other pain syndromes. However, bone infection (osteomyelitis) should be suspected if the fever is prominent or persistent. As with other pain syndromes, the patient should be started on an analgesic that matches the assessed pain severity. Thus, narcotics should be reserved for those who do not respond to simple measures such as rest, warm compresses, and oral paracetamol and ibuprofen.

QUIZ 4-1

True (T) or False (F)?

All children younger than five years with Hgb SC or Hgb Sß$^{+}$-thal types of SCD should be treated with twice daily penicillin V K?

Correct Answer: False

Although all children with SCD are prone to life-threatening infections due to S. pneumoniae, Salmonella, H. flu, E. coli, and S. aureus, this risk is highest in those who have Hgb SS and Hgb Sß^{0}-thal types of SCD. While twice daily penicillin is strongly recommended for all children younger than five years with Hgb SS and Hgb Sß^{0}-thal types of SCD, there is no evidence that penicillin is needed for other types of SCD. Therefore, only prescribe penicillin for young children with Hgb SC and Hgb Sß$^{+}$-thal who have had their spleen removed by surgery (splenectomy). To further reduce the risk of infections in children with all types of SCD, make sure that vaccinations are up to date. All children with SCD who never received the PCV13 (Prevnar) should be vaccinated. Children older than 6 years who never received PCV13 should get at least one dose of this vaccine. Additionally, parents of children with any type of SCD should be advised to promptly seek medical attention for any fever (defined as body temperature greater than 37.5°C). When these children present to hospital, they should be treated with antibiotics right away after appropriate tests including blood culture.

QUIZ 4-2

True (T) or False (F)?

Parents of young children with any type of SCD should be taught how to feel for the spleen.

Correct Answer: True

Parents of young children with any type of SCD should be taught how to check for pallor and to feel for the spleen because acute spleen sequestration (ASS) is a common cause of death in children. Early diagnosis of ASS saves lives. It is particularly important to teach parents of those who have had least one episode of ASS since this condition often recurs. All parents should be told to immediately seek medical attention if sudden spleen enlargement occurs, especially if it accompanied by skin pallor.

QUIZ 4-3

True (T) or False (F)?

While it is possible to prevent infections and treat SCD symptoms as they occur, there is currently no way to directly modify SCD or to permanently cure the disease.

Correct Answer: False

In addition to preventing infections (antibiotics, vaccines, etc.), and managing symptoms such as pain crisis as they occur, there are treatment options to directly modify SCD itself. These options include hydroxyurea, ongoing blood transfusions, and stem cell transplantation. Clinicians typically consider the risks and benefits of these options to decide the best option for an individual patient. In general, hydroxyurea is the usual first choice after these risks and benefits are considered. A stem cell transplant (also called bone marrow transplant) is currently the only permanent cure for SCD. A transplant works best if there is a well-matched person to donate normal bone marrow cells. It is likely that in the future, research will discover new ways for an affected patient who does not have a well-matched donor to be permanently cured. Although transplant is successful in a high percentage of cases, 5%–10% (1 in 10-20) of patients who undergo transplant do not survive. Therefore, transplant is usually reserved for SCD patients with severe complications.

QUIZ 4-4

True (T) or False (F)?

It is possible for the individual whose CBC /reticulocyte count and hemoglobin electrophoresis are shown to have a child with SCD in the future?

CBC W/Plat & Diff

	Ref Range & Units	
WBC	5.0 – 14.5 10^3/µL	12.8
RBC	4.1 – 5.1 10^6/ µL	5.12
HGB	12.0 – 16.0 G/DL	11.1 v
HCT	36.0 – 45.0 %	33.3 v
MCV	78.0 – 95.0 FL	65.1 v
MCH	26.0 – 32.0 PG	21.7v
MCHC	32.0 – 36.0 G/DL	33.3
RDWCV	11.5 – 15.0 %	13.8
Platelet	150 – 450 10^3/µL	291
MPV	6 – 10 FL	8.6
Differential Type		AUTO
Seg%	33 – 71 %	48.6
Lymph%	15 – 55 %	43.8
Mono%	0 – 4%	4.9
EOS%	0 – 3%	2.7
Baso%	0 – 1%	0.9
ANC	1.8 – 8.0 10^3/µL	6.2
Reticulocyte Count		
Retic Percent	0.5 – 2.0%	0.9
Retic Absolute	0.029 – 0.099 10^6/µL	0.046
Hemoglobin Electrophoresis		
Hemoglobin A	90 – 100%	90.8
Hemoglobin A2	<4%	6.3^
Hemoglobin F	0 – 3%	2.9
Hemoglobin S	%	0.0
Hemoglobin C	%	0.0
Hemoglobin Other	%	0.0

Correct Answer: True

This individual's CBC/reticulocytes and hemoglobin electrophoresis do not show sickle cell trait (SCT or Hgb AS). Instead they show beta thalassemia trait. Individuals with beta thalassemia trait typically have mild anemia with normal reticulocyte count, very small red blood cells (low MCV), absence of Hb S, plus elevated Hb A2 or Hb F on hemoglobin electrophoresis. Because severe iron deficiency also causes anemia and low MCV, iron deficiency should be excluded in patients suspected to have beta thalassemia trait. Although this individual does not have sickle cell trait, they could have a baby with SCD in the future if their partner has SCT. If this individual marries someone with SCT, in each pregnancy, the couple has a 25% chance of each of the following outcomes: Hgb AA (normal), Hgb AS (sickle cell trait), Hgb Aß-thal (beta thalassemia trait), and Hgb Sß-thal (sickle-beta thalassemia disease).

The following table summarizes typical results of CBC / reticulocytes, sickle solubility test, and Hgb electrophoresis in SCT, beta-thalassemia trait, and common types of SCD:

	Sickle cell trait	Beta-thal trait	Hgb SS	Hgb $Sß^0$-thal	Hgb $Sß^+$-thal	Hgb SC
HGB (ref range 11.0–16.0 g/dL)	12.8	10.5	7.5	7.5	10.1	9.8
MCV (ref range 72–95 fL)	80	55	80	55	55	65
Reticulocyte (ref range 0.5–2.0 %)	1	1	12	12	4	4
Hgb A (ref range 90–100 %)	59	89	0	0	13	0
Hgb A2 (ref range < 4 %)	2	6	2	6	6	3
Hgb F (ref range 0–3 %)	2	5	8	8	8	2
Hgb S (%)	37	0	90	86	73	50
Hgb C (%)	0	0	0	0	0	45
Sickle solubility Test	Positive	Negative	Positive	Positive	Positive	Positive

Note the following points:

1. Sickle cell trait (Hgb AS) does not cause anemia or elevated reticulocytes
2. Beta thalassemia trait, Hgb $Sß^0$-thal disease, and Hgb $Sß^+$-thal disease are associated with low MCV and elevated Hgb A2
3. Although patients with beta thalassemia trait may have mild anemia, unlike Hgb $Sß^+$-thal type of SCD, beta thalassemia trait individuals are healthy and have a normal reticulocyte count
4. Although patients with Hgb $Sß^+$-thal have Hgb A and Hgb S, they differ from those with SCT in having more Hgb S compared to Hgb A (i.e., Hgb S > Hgb A) on hemoglobin electrophoresis (in SCT, Hgb A is > Hgb S).

QUIZ 5-1

True (T) or False (F)?

A 6-year-old girl who presents with inability to move her right arm and right leg but appears well and has Hgb of 9.1 g/dL should receive a blood transfusion right away.

Correct Answer: True

Painless weakness on one side of the body suggests acute overt stroke – a complication that results from blockage of blood supply to the brain and occurs in up to 5%–10% of children with SCD. In addition to weakness or paralysis, stroke may also cause abnormalities with speech, vision loss, loss of consciousness, or convulsions depending on the part of the brain that's affected. Children with suspected stroke should be admitted to closely monitor breathing, heart rate, blood pressure, oxygen saturation, and level of consciousness. If available, MRI scan or CT scan of the brain should be used to confirm brain damage. Blood transfusion should be given early to limit the degree of brain damage. Although an exchange blood transfusion (using a special machine to replace most of the patient's sickle red cells with normal blood) is preferred in SCD patients with stroke, a regular transfusion should be done if exchange transfusion is not possible. Due to a very high risk of a second or third stroke over time, long-term treatment with blood transfusions or hydroxyurea is required. For children who have never experienced stroke, transcranial Doppler (TCD) ultrasound every 6–12 months is useful in predicting those who are most likely to have a stroke so that preventive treatment can be given. TCD is not helpful to diagnose a stroke after it has occurred.

QUIZ 5-2

True (T) or False (F)?

A 4-year-old boy with Hgb SS presenting to clinic for the first time has HGB 5.9 g/dL and palpable spleen that is 5 cm below the rib margin. This is definitely acute spleen sequestration.

Correct Answer: False

Though this may be acute spleen sequestration (ASS), we cannot say for sure since this child is presenting to clinic for the first time and we do not know his usual Hgb or how long his spleen has been enlarged. Acute spleen sequestration (ASS) is usually defined by a drop from baseline Hgb of 2 g/dL or more plus an acute enlargement of the spleen. In addition to ASS, aplastic crisis due to infection such as parvovirus B19 can cause acute severe anemia in SCD. Though ASS or aplastic crisis may cause severe anemia, they can be differentiated based on the observed reticulocyte count – reticulocyte count is abnormally low in aplastic anemia but significantly elevated in ASS. Regarding the management of this particular child who is in clinic for the first time, the clinician must decide whether or not to refer him for a blood transfusion. To decide, it would help to know if he appears ill, has tachycardia (fast heart rate), or low blood pressure. The presence of any of these would be a reason to arrange a blood transfusion right away.

QUIZ 5-3

True (T) or False (F)?

A 12-year-old girl with SCD is hospitalized after cholecystectomy (removal of gallbladder). As recommended, she received a blood transfusion before surgery. If she develops fast breathing without fever on the day after surgery, the most likely explanation is internal bleeding at the surgical site.

Correct Answer: False

This child most likely has post-operative acute chest syndrome (ACS). Though many children come to hospital with ACS, it also commonly develops during hospitalization for pain crisis, surgery, or other complication. While blood transfusion before surgery reduces the risk of SCD complications such as ACS, it doesn't work in every case. ACS presents with cough, fever, fast breathing, chest indrawing, or chest pain plus new infiltrate on chest X-ray – symptoms that are like pneumonia. Since ACS is a risk for all children admitted for pain or surgery, breathing exercises using an incentive spirometer, or balloons, pinwheels, or bubbles should be done. Antibiotics to treat ACS should cover the common bacteria that cause lung infection in patients with SCD. These include S. pneumoniae, H. flu, and atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae. Atypical bacteria require macrolide antibiotics such as azithromycin, clarithromycin, erythromycin, etc. Children with ACS and labored breathing should be transfused.

QUIZ 5-4

True (T) or False (F)?

A 5-year-old girl with SCD who presents with 7 days of right arm pain and fever (39°C) has a positive rapid diagnostic test for malaria. In addition to antimalarial medicine, she should be treated with antibiotics that would cover bacteria that cause osteomyelitis (bone infection).

Correct Answer: True

Since children with SCD are highly prone to bacterial infections, all children with SCD and fever should be assumed to have a life-threatening bacterial infection and treated accordingly even if malaria is also present. Bone damage from blockage of blood flow predisposes to infection of the bone (osteomyelitis) and joint (septic arthritis). The most common bacteria associated with these bone and joint infections are Staphylococcus aureus and Salmonella. Since delayed or improper treatment of osteomyelitis may result in permanent deformity, admit all patients with suspected osteomyelitis, and administer intravenous antibiotics after culture of blood, joint fluid, or bone is done. To prevent deformity, patients should be treated with antibiotics for many weeks. Keep in mind that the very common pain crisis of SCD is sometimes associated with mild fever but this must not lessen your vigilance for osteomyelitis, especially in those with persistent fever. While many pain crises can be treated at home with hydration, rest, and oral paracetamol or ibuprofen, stronger analgesics such as narcotics (codeine, morphine, hydromorphone, etc.) plus hospitalization is needed for those with severe pain. Clinicians should look out for symptoms such as significant fever or shortness of breath that may indicate complications such as osteomyelitis and acute chest syndrome.

QUIZ 5-5

True (T) or False (F)?

High blood pressure and edema of both feet in a 12-year-old boy with SCD is most likely due to malnutrition.

Correct Answer: False

Severe acute malnutrition (SAM) causes edema but not hypertension. Promptly check for the possibility of kidney disease in this child. SCD affects the kidney in 10%–30% of older children and adults, and if left untreated, it may result in kidney failure. Routinely monitor blood pressure in children and pay attention to the dose of medicines such as ibuprofen, diclofenac, gentamicin, etc. that may affect kidney function. Also routinely monitor serum creatinine and check urine for protein in patients over 10 years. This should be repeated every 1–2 years. Refer patients with protein in the urine or high serum creatinine to pediatrician or kidney specialist.

QUIZ 6-1

True (T) or False (F)?

A 10-year-old girl with SCD hospitalized 10 days ago for pain crisis is still in moderate pain. Hgb of 8.9 g/dL on admission is 7.7 g/dL today. She should be transfused to help resolve the pain.

Correct Answer: False

Most children with SCD have mild to moderate anemia at all times (typical Hgb is 6 g/dL–9 g/dL). Despite this anemia, most children with SCD function, grow and develop normally because their bodies have had time to adjust to the anemia since it is chronic. An uncomplicated pain crisis in a child with SCD is not a reason to transfuse blood. Furthermore, blood transfusions come with significant risks to the patient. However, SCD patients being treated for a pain crisis should be transfused under certain circumstances. These circumstances include 1) fast breathing, chest indrawing or other signs of acute chest syndrome, 2) Hgb drops by 2–3 g/dL lower than baseline and sudden liver or spleen enlargement is noted, or 3) Hgb drops by 2–3 g/dL lower than baseline but this drop is not accompanied by a rise in the reticulocyte count, especially if the patient has a fast heart rate.

QUIZ 6-2

True (T) or False (F)?

At a minimum, blood for transfusion to a SCD patient must be negative for West Nile virus and Zika virus.

Correct Answer: False

According to the WHO, the only infections that MUST be screened for are HIV, hepatitis B, hepatitis C, and syphilis. However, the USA and some other high-income countries also routinely test for other infectious agents including West Nile and Zika viruses. Although transfusion can be very beneficial in managing SCD, it carries several risks including some that are life-threatening. For this reason, transfusions should only be given when appropriate. In addition to infections that may be acquired through improperly screened blood, incompatibility of major blood groups between donor and patient that may occur when blood is not properly labeled may cause death. For these reasons, always check to make sure that blood to be transfused has not expired and is certified by an approved blood bank to be compatible with the specific patient as confirmed by the patient's identifying information such as name, date of birth, number, etc. printed on the tag attached to the blood bag. Additionally, always confirm that the blood is the correct ABO / Rhesus group. Whenever possible, blood transfused to patients with SCD should be matched for less common blood groups such as Kidd, Kell, Duffy, and Rhesus Cc /Ee in addition to routine ABO / Rhesus D. This is important to reduce the risk of reaction in those who are expected to receive multiple transfusions, or with a history of multiple transfusions.

QUIZ 6-3

True (T) or False (F)?

For a blood transfusion, the clinician should record patient's appearance, temperature, respiratory rate, and pulse rate prior to the transfusion, 15 minutes after start of transfusion, and then every hour until the end of transfusion.

Correct Answer: True

The first 15 minutes of any transfusion are critical for the onset of transfusion reactions. Transfusion should be stopped immediately if any of the following symptoms occur: fever (defined as temperature > 38^0C or rise of > 1^0C over baseline temperature), rash, increased heart rate, throat swelling, fast breathing, dark urine, unexplained bleeding, restlessness, low blood pressure, and back pain. Occasionally, the same blood unit may be restarted at a slower rate if a reaction is mild such as a skin rash that goes away after treatment with an antihistamine such as chlorpheniramine. For moderate or severe reactions, do not restart the blood unit. Consult the blood bank or a hematologist to investigate the reaction. For the blood bank investigation of the reaction, send a blood sample in a purple (EDTA) tube and a urine sample from the patient, plus the bag of leftover blood for testing. If the reaction is severe, therapies such as IM adrenaline for anaphylactic shock or albuterol inhaler (for wheezing) should be given.

QUIZ 6-4

True (T) or False (F)?

A 9-year-old boy with SCD has been receiving well screened and compatible blood every month for the past 3 years to prevent a second stroke. He no longer experiences pain events and is not on any medicines. There is no need for concern about iron overload since he is doing well and has no complaints.

Correct Answer: False

Ongoing monthly transfusion, often used to prevent stroke in children with abnormal transcranial Doppler (TCD), or to prevent a second stroke in those who have experienced a stroke can also reduce the frequency of other SCD complications such as pain events, acute chest syndrome, etc. Although this strategy is effective to prevent complications, it is not suitable for most patients due to the short- and long-term risks of blood transfusions. While careful screening and matching of blood can reduce risks of infection and incompatibility, the problem of iron overload remains. Monthly blood transfusions result in iron overload after 12–20 transfusions in most patients and, unless special medications are used to eliminate iron, the iron gets deposited in the organs. The organs most commonly affected are liver and heart with resulting liver disease and heart failure. Unfortunately, most patients do not have any symptoms due to iron deposition until it's too late. To prevent disease due to iron overload, special medicines called 'iron chelators' must be given to help the body eliminate excess iron. Without these medicines, ongoing blood transfusions should not be done.

QUIZ 7-1

True (T) or False (F)?

If available, hydroxyurea should be offered to all children over 9 months old who are diagnosed with SC or Sβ^+-thal forms of SCD regardless of clinical severity.

Correct Answer: False

Hydroxyurea is an oral medicine that is proven to reduce the frequency of pain events, including acute chest syndrome and the need for blood transfusions in children with Hgb SS or Hgb Sβ^0-thal. Its effectiveness in other types of SCD is not as clear. If available, it should be offered to all children over 9 months old who have **SS or** Sβ^0-thal forms of SCD regardless of clinical severity. To be effective, hydroxyurea should be administered indefinitely with regular monitoring of blood counts. In situations where the technology to define the specific type of SCD is unavailable, it helps to know that Hgb SS is the most common type of SCD worldwide, and even in regions such as West Africa where Hgb SC comprise 20%–40% of patients with SCD, most children with significant hemolytic anemia whose Hgb level is lower than 9 g/dL plus sickle cells on smear very likely have Hgb SS or Hgb Sβ^0-thal. On average, patients with Hgb SC and Hgb Sβ^+-thal have higher average HGB level and may not have sickle cells on a blood smear — i.e., in general, Hgb SC and Hgb Sβ^+-thal types are milder than Hgb SS and Hgb Sβ^0-thal.

QUIZ 7-2

True (T) or False (F)?

A 3-year-old girl with Hgb SS has been receiving hydroxyurea (20 mg/kg) for 4 months. Today's complete blood count shows Hgb 8.9 g/dL, ARC 75,000/µL, PLT 189,000/µL, and ANC 1600 /µL. She should be instructed to continue hydroxyurea because there is no evidence of toxicity on today's CBC.

Correct Answer: True

While hydroxyurea is very useful when used appropriately, it may cause adverse effects. Therefore, it should only be prescribed according to the rules approved by the local health authorities and by clinicians who understand how to prescribe it, and how to monitor and prevent adverse effects. The most common adverse effects of hydroxyurea are hematological in the form of low white blood count, low reticulocyte count with anemia, or low platelet count. Hematological toxicity is present if ANY one of the following is noted: ANC < 1,000 /µL; Hgb < 4.0 g/dL with any ARC; Hgb < 6.0 g/dL **AND** ARC < 100,000/µL; ARC < 80,000/µL **AND** Hgb < 7.0 g/dL; or PLT < 80,000 /µL. Of note, although her ARC is less than 80,000/µL, her Hgb is greater than 7.0 g/dL. Therefore, she does not have evidence of hematological toxicity. Hydroxyurea should be temporarily discontinued in patients who develop hematological toxicity and the clinician should recheck CBC with reticulocytes every 2 weeks, then restart hydroxyurea once hematological recovery occurs (defined as blood counts that no longer meet the definition of hematological toxicity).

QUIZ 7-3

True (T) or False (F)?

A 4-year-old boy with Hgb SS has been receiving hydroxyurea (20 mg/kg) for 2 years and is doing very well. His nail beds appear dark in color. Today's complete blood count shows Hgb 9.2 g/dL and MCV 104.4 fL. He should be advised that the elevated MCV and darkened nail beds are most likely due to hydroxyurea.

Correct Answer: True

Elevation of MCV is typical in children being treated with hydroxyurea. This MCV elevation usually goes along with clinical benefit. In addition to MCV, Hgb level, and fetal hemoglobin level also rise, while white blood count including ANC, platelet count, and reticulocyte count decrease. To be effective, hydroxyurea should be administered indefinitely with regular monitoring of blood counts. In addition to effects on complete blood count, many children on hydroxyurea notice mild hyperpigmentation (darkening) of skin and nail beds.

APPENDIX II – CASE STUDIES

Case Study 1: 20-month-old with hand swelling

A 20-month-old female presents to you in a remote community clinic with painful swelling of both hands of 3 days duration.

Source: TCH Global HOPE

There is no history of fever. She was born after a normal pregnancy and has been healthy except for malaria at 11 months of age that resulted in a blood transfusion. Two brothers who are 3 years and 6 years old are healthy.

On evaluation, she does not have any danger signs – i.e., not lethargic, or unconscious, no convulsions, not vomiting, and she's able to drink.

Vital signs: Temperature 37.1^{0}C, HR 100, RR 20, Oxygen saturation – 99% on air.

Physical Exam: She appears comfortable in her mother's arms and cries only when you try to touch her hands. Moderate pallor and jaundice are present. Spleen is palpable ~ 4 cm below the left costal margin.

For each of the following statements about this child, write (T) if true, and (F) if false

A. ( ) Check hemoglobin level using a point-of-care device (or complete blood count with reticulocytes if available)

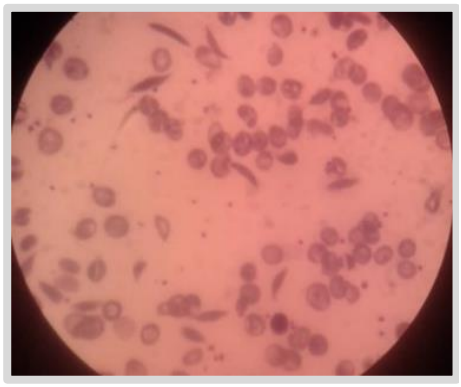
B. ( ) Send a blood test for sickle cell disease (SCD) such as blood smear or hemoglobin electrophoresis, etc. depending on what is available

C. ( ) Prescribe oral morphine for pain to take every 4–6 hours for pain at home

D. ( ) Prescribe oral antibiotics to treat the hand infection

E. ( ) Instruct family to gently wrap her hands in cold packs to reduce swelling and inflammation

You draw blood for a complete blood count with reticulocytes, and a blood smear to review under a microscope (results are shown below). Hemoglobin electrophoresis or HPLC is not available in this remote community clinic.



Source: TCH Global HOPE

Complete Blood Count

	Ref Range & Units	
WBC	5.0 – 14.510^3/ µL	16.89
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	3.7 – 5.3 10^6/ µL	2.51
HGB	10.5 – 14.0 G/DL	7.6
HCT	33.0 – 39.0 %	19.3
MCV	76.0 – 90.0 FL	76.9
MCH	23.0 – 31.0 PG	25.5
MCHC	30.0 – 34.0 G/DL	33.2
RDWCV	11.5 – 16.0 %	28.4
RDWSD	38.5 – 49.0 FL	77.6
Platelet	150 – 450 10^3/ µL	301
Differential		
Seg%	37 – 71 %	22.5
Band%	0 – 1.0 %	2.1
Lymph%	17 – 67 %	66.1
Mono%	0 – 5 %	7.8
EOS%	0 – 3 %	0.9
Baso%	0 – 1 %	0.6
ANC	1.5 – 8.0 10^3/ µL	4.16
NRBC%	0 %	7
NRBC Absolute	10^3/ µL	1.18
Reticulocyte Count		
RETIC PERCENT	0.6 – 1.9 %	14.5
Retic Absolute	0.029 – 0.099 10^6/ µL	0.364

For each of the following statements about this patient including results of these tests, write (T) if true, and (F) if false

F. ( ) She should be discharged home on oral ibuprofen or paracetamol and asked to return the next day for another assessment

G. ( ) At this point, we do not know for sure that this patient has SCD. Hemoglobin electrophoresis or another definitive test is needed before we can be certain that this patient has SCD.

H. ( ) She should be transfused immediately for acute spleen sequestration since she has low hemoglobin and an enlarged spleen

I. ( ) The patient's healthy brothers should be screened for SCD as soon as possible

J. ( ) Her anemia may be due to aplastic crisis of SCD

[A-true; B-true; C-false; D-false; E-false, F-true; G-false; H-false; I-true; J-false]

Discussion

This patient's clinical presentation and laboratory tests are typical of dactylitis due to SCD. Dactylitis is the initial presentation of SCD in many children. As a form of pain crisis, dactylitis may be associated with fever and swelling and treatment should proceed as with other pain syndromes. However, bone infection (osteomyelitis) should be suspected if the fever is prominent or persistent. As with other pain syndromes, the patient should be started on an analgesic that matches the assessed pain severity. Thus, narcotics should be reserved for those who do not respond to simple measures such as rest, warm compresses, and oral paracetamol or ibuprofen. While warm compresses may relieve pain due to SCD, do not use cold or ice packs because these may worsen pain.

While hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) is an excellent test to diagnose SCD, the finding of sickle cells on a blood smear in a child with hemolytic anemia (low HGB with high reticulocytes, jaundice, etc.) is also very specific for SCD. In this patient, a diagnosis can be confidently made even in the absence of hemoglobin electrophoresis or HPLC. Ideally, all newborns should be screened for SCD to minimize morbidity and mortality. Where universal newborn screening is impractical, clinicians should readily test young children with enlarged spleen, need for blood transfusion, stroke, or with unexplained bone pain, anemia, or jaundice. It also makes sense to screen the brothers or sisters of those already diagnosed with SCD. Although the finding of sickle cells on the blood smear of a symptomatic child with hemolytic anemia is specific for SCD in general, this diagnostic method cannot reliably define the type of SCD – i.e., SS, SC, Sß^0-thalassemia, etc.

Hydroxyurea is an effective oral medicine for SCD. If available, it should be offered to all children over 9 months old who have Hgb SS or Hgb Sß^0-thal forms of SCD regardless of clinical severity. In situations where technology to define the specific type of SCD is unavailable, it helps to know that Hgb SS is the most common type of SCD worldwide, and even in regions such as West Africa where Hgb SC comprise 20%–40% of patients with SCD, most children with significant hemolytic anemia whose HGB level is lower than 9.0 g/dL plus sickle cells on smear very likely have SS or Sbeta^0 thalassemia type of SCD. This is because on average, Hgb SC and Hgb Sß$^+$-thal types of SCD tend to higher average HGB levels and may not have sickle cells on a blood smear.

Acute spleen sequestration (ASS) is usually defined by a drop from baseline HGB of 2.0 g/dL or more plus an acute enlargement of the spleen. It is not possible to know for sure if this child's presentation is due to ASS because we do not know her baseline HGB or whether she has an enlarged spleen all the time. However, her normal heart and respiratory rates do not suggest need for a blood transfusion. She does not have aplastic crisis because this complication is defined by anemia and an abnormally low reticulocyte count.

Case Study 2: Young adult with sickle cell trait

The older brother of one of your SCD patients approaches you for advice. He has sickle cell trait (SCT), is planning to marry in 8 months, and is curious about his chance of having a baby with SCD. Regarding his wife-to-be, nobody in her family (parents, brothers, sisters, grandparents, uncles, aunts, cousins, nephews, nieces) has sickle cell disease.

For each of the following statements about this couple, write (T) if true, and (F) if false

A. ( ) Sickle solubility test on the wife-to-be is sufficient to properly assess the risk of SCD for this couple's children

B. ( ) Complete blood count with reticulocytes on the wife-to-be is sufficient to properly assess the risk of SCD for this couple's children

C. ( ) There is no chance of SCD in this couple's children since there is no history of SCD in the any of the immediate or extended family members of the wife-to-be

D. ( ) Since husband-to-be has sickle cell trait, we already know that this couple has a 25% chance of having a child with SCD in each pregnancy

E. ( ) To properly assess the risk of SCD for this couple's children, complete blood count with reticulocytes plus hemoglobin electrophoresis should be completed on the wife-to-be

Two months later, the man returns with the results of complete blood count with reticulocytes, hemoglobin electrophoresis, and a picture of the sickle solubility test performed on the wife-to-be for you to review.

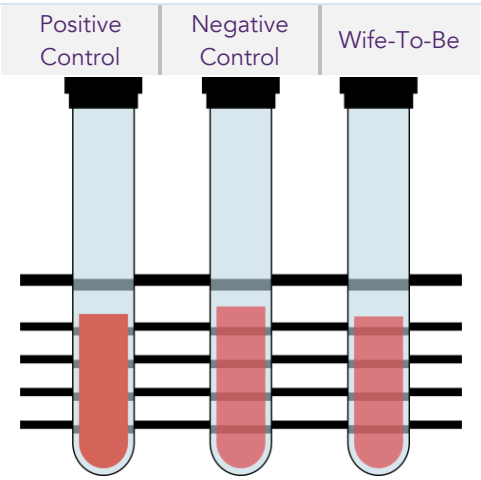
Complete Blood Count

	Ref Range & Units	
WBC	5.0 – 14.5 10^3/ µL	12.8
RBC	4.1 – 5.1 10^6/ µL	5.12
HGB	12.0 – 15.3 G/DL	11.1
HCT	36.0 – 45.9 %	33.3
MCV	80.0 – 90.0 FL	65.1
MCH	25.0 – 30.0 PG	21.7
MCHC	32.0 – 36.0 G/DL	33.3
RDW	11.5 – 15.0 %	13.8
Platelet	150 – 450 10^3/ µL	291
MPV	6 – 10 FL	8.6
Differential		
Seg%	37 – 71%	48.6
Lymph%	17 – 67 %	43.8
Mono%	0 – 5%	4.9
EOS%	0 – 3%	2.7
ANC	1.5 – 8.0 10^3/ µL	6.2
Reticulocyte Count		
RETIC PERCENT	0.6 – 1.9 %	0.9
Retic Absolute	0.029 – 0.099 10^6/ µL	0.046

Hemoglobin Electrophoresis

	Ref Range & Units	
Hemoglobin A	90 – 100%	90.8
Hemoglobin A2	<4.0 %	6.3
Hemoglobin F	0 – 3%	2.9
Hemoglobin S	%	0.0
Hemoglobin C	%	0.0

Sickle Solubility Test



Michael Stencel, 2020

For each of the following statements about this couple including results of these laboratory tests, write (T) if true, and (F) if false

F. ( ) There is a risk of SCD in this couple's children because the man has SCT and his wife-to-be has anemia

G. ( ) There is a 25% chance in each pregnancy of a child with SCD in this couple. On average, the type of the SCD that may result will definitely be milder than Hgb SS type of SCD since only one parent has SCT

H. ( ) There is no chance of SCD in this couple's children since the husband-to-be has SCT but the wife-to-be does not have SCT

I. ( ) There is a 25% chance in each pregnancy of a child with SCD in this couple. The SCD that results may be as severe as Hgb SS type of SCD even though only one parent has SCT

[A-false; B-false; C-false; D-false; E-true, F-false; G-false; H-false; I-true]

Discussion

Sickle cell trait (SCT or Hgb AS) does not cause anemia or elevated reticulocytes. Additionally, individuals with SCT have a positive sickle solubility test, and on hemoglobin electrophoresis, have both Hb A and Hb S. While the sickle solubility test is also positive in all types of SCD, patients with SCD also have anemia or elevated reticulocytes unlike those with SCT. Whereas Hb A and Hb S is also found in patients with Hgb Sß$^{+}$-thal type of SCD, this condition differs from SCT in having more Hgb S compared to Hgb A on hemoglobin electrophoresis (in SCT, the amount of Hgb A always more than Hgb S).

The complete blood count with reticulocytes and hemoglobin profile on the wife-to-be indicate beta thalassemia trait. Individuals with beta thalassemia trait typically have mild anemia with normal reticulocyte count, very small red blood cells (low MCV), absence of Hb S, plus elevated Hb A2 or Hb F on hemoglobin electrophoresis. Because severe iron deficiency also causes anemia and low MCV, iron deficiency should be excluded in patients suspected to have beta thalassemia trait.

SCD occurs when a child inherits at least one sickle hemoglobin (Hgb S) gene from one parent PLUS another abnormal beta-globin gene from the other parent. There are several types of SCD – depending on the specific abnormal beta-globin gene inherited with the Hgb S gene. The most common type of SCD is the Hgb SS form where an individual inherits the gene for Hgb S from both parents. In each pregnancy, the couple in this case example has a 25% chance of each of the following outcomes: Hgb AA (normal), Hgb AS (sickle cell trait), beta thalassemia trait, and Hgb S-thalassemia disease. Based on the information available at this stage, it is not possible to accurately predict the type of Hgb Sß-thalassemia their child may have — i.e., whether Hgb Sß^{0}-thal or Hgb Sß$^{+}$-thal. On average, Hgb Sß^{0}-thal is comparable to Hgb SS in terms of severity. In contrast, Hgb Sß$^{+}$-thal tends to be milder than Hgb SS.

The following table summarizes typical results of CBC / reticulocytes, sickle solubility test, and Hgb electrophoresis in SCT, beta-thalassemia trait, and common types of SCD.

	Sickle cell trait	Beta-thal trait	Hgb SS	Hgb Sß^0-thal	Hgb Sß$^+$-thal	Hgb SC
HGB (ref range 11.0 – 16.0 g/dL)	12.8	10.5	7.5	7.5	10.1	9.8
MCV (ref range 72 – 95 fL)	80	55	80	55	55	65
Reticulocyte (ref range 0.5 – 2.0 %)	1	1	12	12	4	4
Hgb A (ref range 90 – 100 %)	59	89	0	0	13	0
Hgb A2 (ref range < 4 %)	2	6	2	6	6	3
Hgb F (ref range 0 – 3 %)	2	5	8	8	8	2
Hgb S (%)	37	0	90	86	73	50
Hgb C (%)	0	0	0	0	0	45
Sickle solubility Test	Positive	Negative	Positive	Positive	Positive	Positive

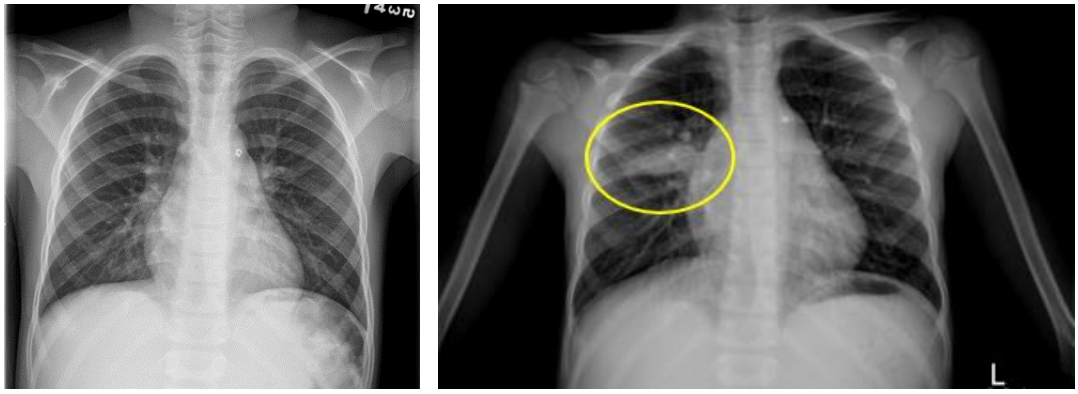
Note the following points:

1. Sickle cell trait (Hgb AS) does not cause anemia or elevated reticulocytes
2. Beta thalassemia trait and sickle-thalassemia types of SCD (Hgb Sß^0-thal and Hgb Sß$^+$-thal) are associated with low MCV and elevated Hgb A2
3. Although patients with beta thalassemia trait may have mild anemia, unlike Hgb Sß$^+$-thal type of SCD, beta thalassemia trait individuals are healthy and have a normal reticulocyte
4. Although patients with Hgb Sß$^+$-thal have Hgb A and Hgb S, they differ from those with SCT in having more Hgb S compared to Hgb A on hemoglobin electrophoresis (in SCT, Hgb A is > Hgb S).

Case Study 3: Boy with weakness of right arm and leg

A 5-year-old male diagnosed with SCD (Hgb SS type) is admitted for severe pain in chest and right arm (faces pain scale score = 8). Patient's only routine medicine at home is folic acid once daily by mouth. The pain was treated with oral ibuprofen and morphine. Due to severe chest pain, a chest radiograph was done on the first day of hospital admission. Complete blood count with reticulocytes was also done.

A chest radiograph was repeated after 3 days due to worsening pain, new fever, fast breathing, and chest indrawing. This radiograph showed a new infiltrate (highlighted below).



Source: Texas Children's Hospital

For each of the following statements about this child's admission for pain, write (T) if true, and (F) if false

A. ( ) This child does not have acute chest syndrome since the chest radiograph was normal on admission

B. ( ) He should be started on hydroxyurea soon since it is proven to reduce the frequency of pain events

C. ( ) Amoxicillin alone is sufficient - similar to treatment of children with pneumonia

D. ( ) Since he has fast breathing and chest indrawing, patient should receive a simple blood transfusion regardless of the hemoglobin level

E. ( ) Breathing exercises with incentive spirometry, or blowing balloons, should be started from hospital day # 3 when he developed fast breathing and chest indrawing

Patient improved with treatment and was discharged home on oral antibiotics after 5 days in hospital. He returns to clinic one week after discharge home — i.e., about 2 weeks from date of admission. Family reports that the chest and right arm pain improved steadily after discharge, then completely resolved about 5 days ago. He played without any discomfort throughout yesterday but woke up today unable to move his right leg and right arm as before. This weakness is not associated with pain, jaundice, headache, or vomiting.

On evaluation, he does not have any danger signs – i.e., not lethargic, or unconscious, no convulsions, not vomiting, and he's able to drink.

Vital signs: Temperature 37.1^{0}C, HR 100, RR 20, Oxygen saturation – 99% on air.

Physical Exam: He appears comfortable in dad's arms but is unable to fully move his right arm and leg when instructed to do so. Moderate pallor and jaundice are present. Spleen is not palpable

Which of the following elements of history and examination are important to correctly determine the cause of this patient's right-sided weakness? For each, write (T) if true, and (F) if false

F. ( ) History of trauma such as a fall while playing

G. ( ) Did he complete the antibiotics prescribed at time of discharge?

H. ( ) X-rays of the right arm and right leg

I. ( ) Presence of an enlarged liver

J. ( ) Examination of his face when he smiles

For each of the following statements about the next steps in managing this child, write (T) if true, and (F) if false

K. ( ) Refer the patient to the physiotherapist (physical therapist) immediately for further management

L. ( ) Check complete blood count with reticulocytes

M. ( ) Admit patient for a blood transfusion right away

N. ( ) Transcranial Doppler (TCD) should be performed immediately if available

O. ( ) Monitor patient's breathing, heart rate, blood pressure, and oxygen saturation closely

[A-false; B-true; C-false; D-false; E-false, F-false; G-false; H-false; I-false; J-true, K-false; L-true; M-true; N-false; O-true]

Discussion

Pain is a common symptom in patients with SCD and though many episodes can be treated at home with hydration, rest, and oral paracetamol or ibuprofen, stronger analgesics such as narcotics (codeine, morphine, hydromorphone, etc.) plus hospitalization as needed for those with severe pain. Clinicians should watch out for symptoms such as significant fever or shortness of breath that may indicate complications such as osteomyelitis and acute chest syndrome.

Though children may come to the hospital with acute chest syndrome (ACS), it also commonly develops after several days in children admitted for a pain crisis or other complication. This child developed ACS during hospitalization. ACS presents with cough, fever, fast breathing, chest indrawing, or chest pain PLUS a new infiltrate on chest X-ray – symptoms that are like pneumonia. Since ACS is a risk for all children admitted for pain or surgery, breathing exercises using an incentive spirometer, or balloons, pinwheels, or bubbles should be started without delay — i.e., on the first day of hospitalization. Antibiotics to treat ACS should cover the common bacteria that cause lung infection in patients with SCD. In addition to amoxicillin (or ceftriaxone or amoxicillin-clavulanate), SCD patients with ACS should receive macrolide antibiotics such as azithromycin, clarithromycin, or erythromycin, etc. to cover atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae. Hydroxyurea is proven to reduce the risk of pain events including acute chest syndrome. It should be prescribed to patients with Hgb SS or Hgb Sβ^0-thal who have a history of ACS.

Blood transfusion is usually reserved for patients with ACS associated with labored breathing or oxygen saturation < 90%, and whose hemoglobin is lower than Hgb of 7.0 g/dL. To prevent further blood vessel blockage from too much blood, do not exceed Hgb of 11 g/dL after transfusion. Therefore, a simple transfusion is usually not possible in SCD patients with a high baseline Hgb level. In situations where a SCD patient with a high baseline Hgb level requires a transfusion, a manual or automated exchange transfusion must be done.

Painless weakness on one side of the body suggests acute overt stroke – a complication that results from blockage of blood supply to the brain. The inability to move muscles that control smiling on one side of the face indicates facial nerve paralysis and may accompany paralysis of arms and legs in patients with stroke. Unlike overt strokes that may cause obvious symptoms such as limb weakness, abnormalities with speech, vision, loss of consciousness, or convulsions depending on the part of the brain that's affected, so-called silent stroke cause subtle symptoms such as problems with attention, impulse control, judgement, and learning difficulty. Silent strokes are usually only detectable on brain MRI and may affect up to 30% of children with SCD.

Completion of antibiotics for ACS and whether liver enlargement is present are not important factors in the diagnosis of stroke. Trauma is unlikely and plain x-rays of the limbs are not likely to be helpful because the patient does not report pain.

Children with suspected stroke should be admitted to closely monitor breathing, heart rate, blood pressure, oxygen saturation, and level of consciousness. While transcranial Doppler (TCD) ultrasound every 6–12 months is useful in predicting children, who are most likely to have a stroke so that preventive treatment can be given, TCD is not helpful to diagnose a stroke after it has occurred. Unlike TCD, MRI scan or CT scan of the brain should be used to confirm brain damage. Early blood transfusion limits brain damage. Although an exchange blood transfusion (either manually or using a special machine to replace most of the patient's sickle red cells with normal blood) is preferred in SCD patients with stroke, a regular transfusion should be done if an exchange transfusion is not possible. Due to a very high risk of a second or third stroke over time, long-term treatment with blood transfusions or hydroxyurea is required.

Case Study 4: New patient with SCD

A 7-year-old female who was recently diagnosed with SCD (Hgb SS type) in a peripheral hospital is in the SCD clinic for a routine checkup for the first time. She has no complaints. Her history is significant for a total of 4 pain events so far, the first one at 8 months of age. Two of the pain events resulted in hospitalization. Additionally, she was transfused at 2 years of age due to malaria. None of her 3 brothers or parents have a history of anemia or SCD. A review of her vaccine record showed evidence of vaccination against diphtheria, tetanus, pertussis (DTP), Hepatitis B, and Haemophilus influenza. However, she was not vaccinated against S. pneumoniae because PCV13 (Prevnar13) was not routinely available until one year ago.

Vital signs: Temperature 37.1^{0}C, HR 100, RR 20, Oxygen saturation – 99% on air. Weight – 24 kg

On examination, she is well developed and not in any distress. Moderate pallor and very mild jaundice are present. The liver or spleen is not palpable.

You draw blood for complete blood count and reticulocytes.

Complete Blood Count

	Ref Range & Units	
WBC	5.0 - 14.5 10^3/µL	12.36
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	3.7 - 5.3 10^6/µL	3.24
HGB	11.5 - 14.5 G/DL	8.3
HCT	33.0 - 40 %	23.8
MCV	76.0 - 90.0 FL	73.5
MCH	25.0 - 30.0 PG	25.6
MCHC	32.0 - 36.0 G/DL	34.9
RDWCV	11.5 - 15.0 %	19.0
RDWSD	38.5 - 49.0 FL	50.6
Platelet	150 - 450 10^3/µL	414
MPV	6 - 10 FL	9.0
Differential		
Seg%	37 - 71 %	55.2
Band%	0-1.0 %	0
Lymph%	17 - 67 %	33.5
Mono%	0-5 %	8.7
EOS%	0 - 3 %	1.5
Baso%	0 - 1 %	0.6
ANC	1.5 - 8.0 10^3/µL	6.81
NRBC%	0 %	1
NRBC Absolute	10^3/µL	0.07
Reticulocyte Count		
RETIC PERCENT	0.6 - 1.9 %	8.9
Retic Absolute	0.029 - 0.099 10^6/µL	0.288

For each of the following statements regarding the management of this child when your colleague saw him 6 months earlier, write (T) if true, and (F) if false

A. ( ) Start penicillin v k – 250 mg twice daily by mouth

B. ( ) Administer typhoid vaccine

C. ( ) Schedule transcranial Doppler ultrasound

D. ( ) Administer PCV13 (pneumococcal conjugate vaccine)

E. ( ) Check liver and kidney function tests and if normal, prescribe hydroxyurea – 1000 mg daily

She returns to clinic for routine evaluation about 6 months after she started hydroxyurea treatment. CBC with reticulocytes done one month and again at two months after starting hydroxyurea treatment were fine. You request full blood count and reticulocytes today to monitor her (result is below).

Complete Blood Count

	Ref Range & Units	
WBC	5.0-14.5 10^3/µL	7.01
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	3.7 - 5.3 10^6/µL	2.47
HGB	11.5 - 15.5 G/DL	9.9
HCT	33.0 - 39.0 %	26.9
MCV	76.0 - 90.0 FL	108.9
MCH	23.0 - 31.0 PG	40.1
MCHC	30.0 - 34.0 G/DL	36.8
RDWCV	11.5 - 16.0%	16.4
RDWSD	38.5 - 49.0 FL	65.5
Platelet	150 - 450 10^3/µL	335
MPV	6 - 10 FL	9.2
Differential		
Seg%	37 - 71 %	12.1
Band%	0 - 1.0%	1.0
Lymph%	17 - 67 %	75.6
Mono%	0 - 5%	7.3
EOS%	0 - 3%	3.3
Baso%	0 - 1%	0.7
ANC	1.5 - 8.0 10^3/µL	0.92
NRBC%	0%	1
NRBC Absolute	10^3/µL	0.07
Reticulocyte Count		
RETIC PERCENT	0.6 - 1.9 %	7.6
Retic Absolute	0.029 - 0.099 10^6/µL	0.187

For each of the following statements regarding today's visit (6 months after starting hydroxyurea), write (T) if true, and (F) if false

F. ( ) Remind family that hydroxyurea should be continued indefinitely with periodic dose adjustments

G. ( ) Evaluate for Vitamin B12 or folate deficiency to explain elevated MCV of 108.9 fL

H. ( ) Remind family that body temperature > 38.3^{0}C should always be managed promptly with antibiotics

I. ( ) Discontinue hydroxyurea for now and recheck CBC with reticulocytes in 2 weeks

J. ( ) Reduce the current dose of hydroxyurea and recheck CBC with reticulocytes in 1 month

[A-false; B-false; C-true; D-true; E-false, F-true; G-false; H-true; I-true; J-false]

Discussion

Children with SCD are highly prone to life-threatening infections due to S. pneumoniae. To reduce this risk, administer penicillin prophylaxis to all children younger than 5 years with Hgb SS and Hgb Sß^0-thal types of SCD, and make sure that vaccinations are up to date. All children with SCD who never received the PCV13 (Prevnar) should be vaccinated. Children older than 6 years should be given at least one dose of this vaccine. While pneumococcal, H. flu, and meningococcal vaccines are specifically recommended for children with SCD, the typhoid vaccine is not routinely used in this condition. Patients with fever (defined as body temperature greater than 37.5^{0}C) should be promptly treated with antibiotics after appropriate tests including blood culture. Additionally, to find those most likely to develop a stroke, children between 2-16 years with SS and SBeta^0 types of SCD should be screened at least once yearly with transcranial Doppler (TCD) ultrasound.

Hydroxyurea is the first medicine that is proven to reduce the frequency of pain events, including acute chest syndrome and the need for blood transfusions or hospitalization. Additionally, it prolongs life and reduces the risk of malaria infection in children. To be effective, hydroxyurea should be administered indefinitely with frequent monitoring of blood counts. The usual starting dose of hydroxyurea in children is approximately 20 mg per kilogram. Elevation of MCV is typical in children being treated with hydroxyurea. This MCV elevation usually goes along with clinical benefit. In addition to MCV, HGB concentration, and fetal hemoglobin (Hb F) level also rises, while white blood count including ANC, platelet count, and reticulocyte count decrease.

While hydroxyurea is very useful when used appropriately, it may cause adverse effects. Therefore, it should only be prescribed according to the rules approved by the local health authorities and by clinicians who understand how to prescribe it, and how to monitor and prevent adverse effects. The most common side effects of hydroxyurea are hematological in the form of low white blood count, low reticulocyte count with anemia, and low platelet count. Hematological toxicity is present if ANY one of the following is noted: ANC < 1,000 /µL; HGB < 4.0 g/dL with any ARC; HGB < 6.0 g/dL **AND** ARC < 100,000/µL; ARC < 80,000/µL **AND** HGB < 7.0 g/dL; or PLT < 80,000 /µL. This patient has hematological toxicity based on an ANC of 920 /µL.

Hydroxyurea should be temporarily discontinued in patients who develop hematological toxicity, recheck CBC with reticulocytes every 2 weeks, then restart hydroxyurea once hematological recovery occurs (defined as blood counts that no longer meet the definition of hematological toxicity).

APPENDIX III – ESSENTIAL SKILLS

To give the best possible care to children with sickle cell disease, you should also master the following skills:

1. Check for General Danger Signs:

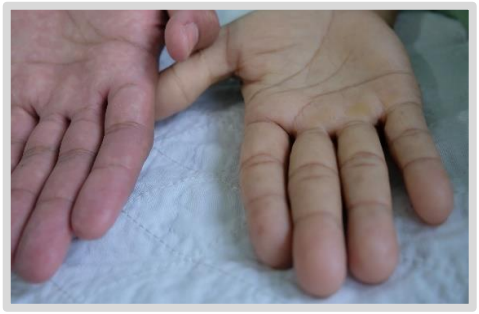
It involves asking and looking.

ASK	LOOK
■ Is child able to drink or breastfeed?	■ Is the child lethargic or unconscious?
■ Does child vomit everything?	■ Is the child convulsing now
■ Has child had convulsions?	

If yes to any of the above, a danger sign is present. Immediately admit patient or refer patient to a higher level of care

2. Check for Pallor:

- Look at the skin of the child's palm to see if it is unusually pale
- Compare the color of the child's palm with your own palm and with the palms of other children.
- If the palm is pale, there is pallor, and if it is very pale or looks white, the child has severe palmar pallor.
- Most children affected by SCD have pallor at baseline (i.e., all the time). Monitor to see if it is worse than usual.

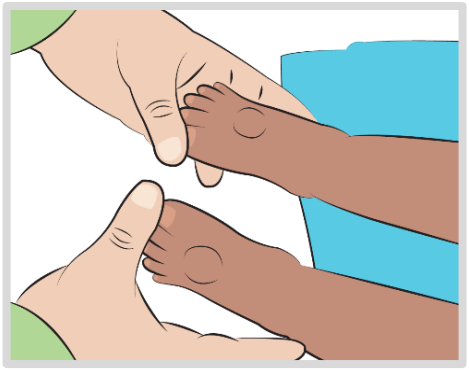


- When pallor is noted, measure the hemoglobin level, or test for SCD if SCD status is not yet known

3. Monitor Growth and Check for Malnutrition:

Children with SCD are at risk for growth delay and malnutrition. Malnourished children with SCD have an even higher risk of complications compared to those who are not malnourished. To monitor growth plus assess and classify malnutrition if needed, you should be able to do the following:

- Assess edema —To assess edema, use your thumbs to push the top of both feet for at least 3 seconds to see if dents remain after you remove your thumbs as shown in the drawing.



Michael Stencel, 2020

- Plot weight-for-age; height (or length)-for-age; weight-for-height (or length); and BMI-for-age on the appropriate WHO growth chart to determine the Z-score. Use length for children younger than 2 years, and height for those who are older than 2 years. Note that there are different WHO growth charts for boys and girls, and for different age ranges.
- Weight-for-age, and height (or length)-for-age should be plotted during every routine well-child visit so that an individual child's growth track can be compared to the averages of healthy children. Although weight-for age and height-for-age are easiest to plot, if there is concern for malnutrition, specifically review weight-for-height (or length) in children younger than 5 years to determine the Z-score; or body mass index (BMI)-for-age to determine the Z-score in those older than 5 years. BMI is a calculation using a person's height and weight. Use a calculator to determine BMI as follows:

  BMI = weight (kg) / height (cm) / height (cm) x 10,000

  To plot weight-for-age, height (or length)-for-age, weight-for-height (or length), or BMI-for-age, use a ruler to find the point where the paired measurements intersect on the appropriate growth chart and mark that point with a pen. Then look to see the position of this point relative to the curved lines that represent the averages of other children
- Measure mid-upper arm circumference (MUAC) in children 6 – 59 months old. Do not use MUAC in children younger than 6 months.

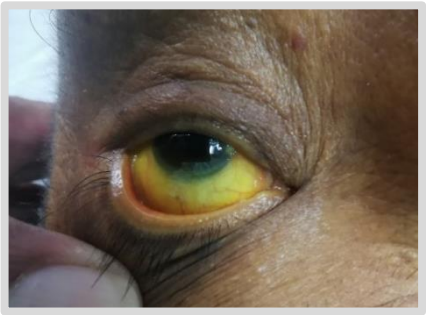
Severe acute malnutrition (SAM) is defined by the presence of ANY one of the following:

0-6 months old	6-59 months old	Older than 5 years
■ Weight-for-length **Z-score < -3** ■ Bilateral pitting edema	■ Weight-for-length (or height) **Z-score < -3** ■ MUAC **< 115 mm** ■ Bilateral pitting edema	■ BMI-for-age **Z-score < -3**

Moderate acute malnutrition (MAM) is described by the presence of ANY one of the following:

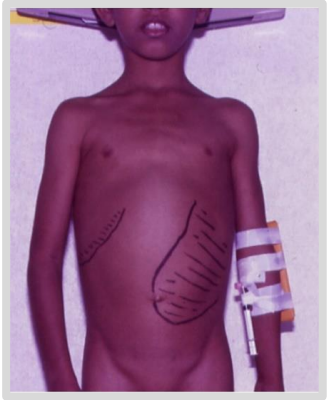
0-6 months old	6-59 months old	Older than 5 years
■ Weight to length **Z-score between -3 and -2**	■ Weight-for-length (or height) **Z-score between -3 and -2** MUAC **between 115 to 124 mm**	■ BMI-for-age **Z-score between -3 and -2**

4. Check for Jaundice



- Yellow coloration of the white part of the eye implies jaundice. Asking child to look down while you hold head steady may expose more of the white part of eye
- SCD children usually have jaundice due to the breakdown of red cells that is part of the disease. Search for an additional reason for jaundice if it is accompanied by dark urine or pale stools PLUS abdominal pain. This may indicate liver or gallstone disease. Also, finding of significant bilirubin on urine analysis suggests liver or gallstone disease as an explanation for the jaundice

5. Palpate spleen



By Al-Salem AH - ISRN Dermatology (2010) doi: 10.5402/2011/864257

- Spleen is normally located behind the ribs in the left upper abdomen.
- Spleen usually enlarges towards the right lower part of abdomen
- Start palpation in the right lower abdomen so you do not miss a very big spleen
- Stand on the right side of patient lying flat, with your fingers together place your hand flat on the abdomen, then feel abdomen using a light dipping motion toward left upper part
- Note lowest point of spleen, then measure from the edge of the lowest rib at the nipple line

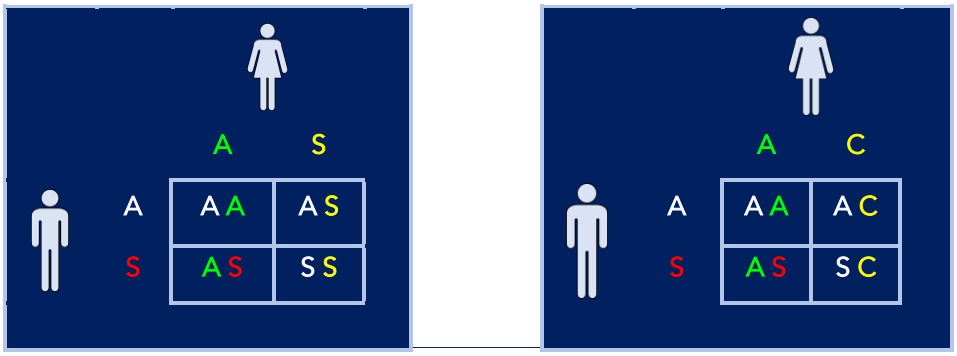
6. Recognize signs of respiratory distress such as fast breathing, chest indrawing, and nasal flaring

- Fast breathing: Using a watch with a second hand, count breaths (number of times the chest moves up and down) for 60 seconds. A full 60 seconds is needed as changes can occur in the respiratory pattern and rate. Normal respiratory rate varies according to a child's age. This table shows the rate that defines fast breathing in each age group
- Chest indrawing: Observe the lower chest wall to see if it pulls inwards when the child breaths in
- Nasal flaring: Observe to see if nostrils widen each time the child breaths in

Age	Respiratory Rate
2 - 12 months	> 50 / minute
1 - 5 years	> 40 / minute
5-12 years	> 30 / minute
Over 12 years	> 20/minute

7. Calculate probability of offspring with SCD if given the sickle cell/thalassemia status of a couple

- Draw and use a Punnett square to determine probabilities of having children with SCD when given the sickle cell status of parents. You should know that the Punnett square shows the probabilities in EACH pregnancy. Two examples are below – each member of the first couple has sickle cell trait. In the second couple, one member has sickle cell trait and the other has Hgb C trait.



8. Know how the absolute neutrophil count (ANC) and absolute reticulocyte count (ARC) is derived. Most CBC/retic machines automatically calculate the ANC and ARC.

- ANC = WBC (thousand/μL) x total neutrophils% (segmented neutrophil% + bands%) where WBC is white blood cell count. The normal range for the ANC = 1.5 to 8.0 x 10^3/μL (thousands per μL).
- ARC = RBC (million/μL) x Reticulocyte% where RBC is red blood cell count.

On the CBC report, thousands per μL is usually shown as 10^3/μL (or 10^3/μL), and millions per μL shown as 10^6/μL (or 10^6/μL). The normal range of ARC is 29 – 99 x 10^3/μL (thousands per μL), or 0.029 – 0.099 x 10^6/μL (millions per μL).

This picture shows example of ARC (green) and ANC (red) calculation from a CBC/retic report

Complete Blood Count		
	Ref Range & Units	
WBC	5.0 - 14.5 10^3/µL	12.36
Comment: WBC ADJUSTED FOR NUCLEATED RBCS		
RBC	3.7 - 5.3 10^6/µL	3.24
HGB	11.5 -14.5 G/DL	8.3
HCT	33.0 - 40 %	23.8
MCV	76.0 - 90.0 FL	73.5
MCH	25.0 - 30.0 PG	25.6
MCHC	32.0 - 36.0 G/DL	34.9
RDWCV	11.5 - 15.0 %	19.0
RDWSD	38.5 - 49.0 FL	50.6
Platelet	150 - 450 10^3/µL	414
MPV	6 - 10 FL	9.0
Differential		
Seg%	37 - 71 %	51.8
Band%	0-1.0 %	3.4
Lymph%	17 - 67 %	33.5
Mono%	0 - 5 %	8.7
EOS%	0 - 3 %	1.5
Baso%	0 - 1 %	0.6
ANC	1.5 - 8.0 10^3/µL	6.82
NRBC%	0 %	1
NRBC Absolute	10^3/µL	0.07
Reticulocyte Count		
RETIC PERCENT	0.6-1.9 %	8.9
Retic Absolute	0.029 - 0.099 10^6/µL	0.288

Example calculation of the ANC:
WBC: 12.36 x 10^3/µL
Segs: 51.8% of the WBC;
Bands: 3.4% of the WBC
Neutrophils (segs + bands): 55.2% of the WBC
ANC: 55.2% x 12.36 = 6.82 x 10^3/µL
Normal range: 1.5 to 8.0 x 10^3/µL

Example calculation of the ARC:
RBC: 3.24 x 10^6/µL
Retic percent: 8.9% of the RBC
ARC: 8.9% x 3.24 = 0.288 x 10^6/µL
or 288 x 10^3/µL
Normal range: 0.029 to 0.099 x 10^6/µL,
or 29 to 99 x 10^3/µL

9. Use a faces pain scale to assess pain severity

- Explain to patient that each face represents a person who has no pain (face 0), some pain (face 2), a little more pain (face 4) all the way to the worst pain imaginable (face 10 or 11). You don't have to be crying to have this worst pain.
- Which of these faces best represents the pain you are experiencing?