SICKLE CELL DISEASE AND THALASSEMIA: A TRAINING MANUAL FOR HEALTH WORKERS

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List of abbreviations

ABG	arterial blood gas
ACS	acute chest syndrome
ARDS	acute respiratory distress syndrome
ATC	around the clock
CBC	complete blood count
CT	computed tomography
CVA	cerebrovascular accident
CXR	chest x-ray
DHTR	delayed hemolytic transfusion reaction
FIO_2	fraction of inspired oxygen
G-CSF	granulocyte colony stimulating factor
Hb	hemoglobin
HCT	hematocrit
HPLC	high performance liquid chromatography
HIV	Human Immunodeficiency virus
HTLV	Human T lymphotropic virus
IV	intravenous
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LFT	liver function test
MICU	medical intensive care unit
MRA	magnetic resonance angiogram
MRI	magnetic resonance imaging
NS	normal saline
NSAIDs	non-steroidal anti-inflammatory drugs
PNC	post-natal care
PRBC	packed red blood cells
PRN	as needed/when necessary
RBC	red blood cells
SCD	sickle cell disease
TB	total bilirubin
TCD	transcranial Doppler
TRV	tricuspid regurgitant jet velocity
TIA	transient ischemic attack
UTI	urinary tract infections
UA	urine analysis
WBC	white blood cells

CHAPTER 1: BACKGROUND

1.1. Sickle cell disease

Sickle cell disease (SCD) is an autosomal recessive genetic disease. It is inherited from affected parents. It is a group of disorders that affects hemoglobin, the molecule in red blood cells (RBCs) that delivers oxygen to cells throughout the body. Normal RBCs are biconcave disc-shaped and their average lifespan is about 120 days. The lifespan of RBCs in SCD patient is only about 10 to 20 days that causes anemia. Biconcave disc shape of RBCs changes to sickle shape under low oxygen tension, which becomes stiff & sticky and tends to block the blood flow in small capillaries in SCD patients.

Figure 1-1

1.2. Sickle cell disease (SCD): A public health issue in Nepal

Sickle Cell Disease (SCD) is usually believed to be associated with African ancestry and malaria-endemic areas. In Nepal, SCD is commonly found in the Mid-Western and Far-Western region in the Tharu Community. The common districts affected with SCD are Bardiya, Dang, Kailali, Banke, Kanchanpur, Nabalparasi, Rupandehi and Kapilvastu. In Surkhet, certain areas (Lati koili, Uttar Ganga and Jarbuta) inhabited by Tharus are also affected. Although SCD is common among Tharus of Mid-Western and Far-western region of Nepal, it can be found in Non-Tharu communities as well.

The burden of this disease led the Government of Nepal to create SCD improvised citizen fund. This fund provides compensations of one hundred thousand rupees for the SCD patients under the poverty line. These compensations are not given to the Sickle cell traits/carriers.

1.3. How do people get sickle cell disease (SCD) or trait?

- SCD is not contagious
- SCD is inherited in an autosomal recessive manner
- Sickle cell traits (A/S) are also known as sickle cell carriers
- Sickle cell patients can be homozygous (S/S) or heterozygous for Hb S with β-thalassaemia variants
- People with hemoglobin SS type of sickle cell disease inherit two hemoglobin S genes, each one from their father and mother

Section I: Sickle Cell Disease

- If both parents have the sickle cell trait, they have a one-in-four (25%) chance with each pregnancy of bearing a child with hemoglobin SS disease

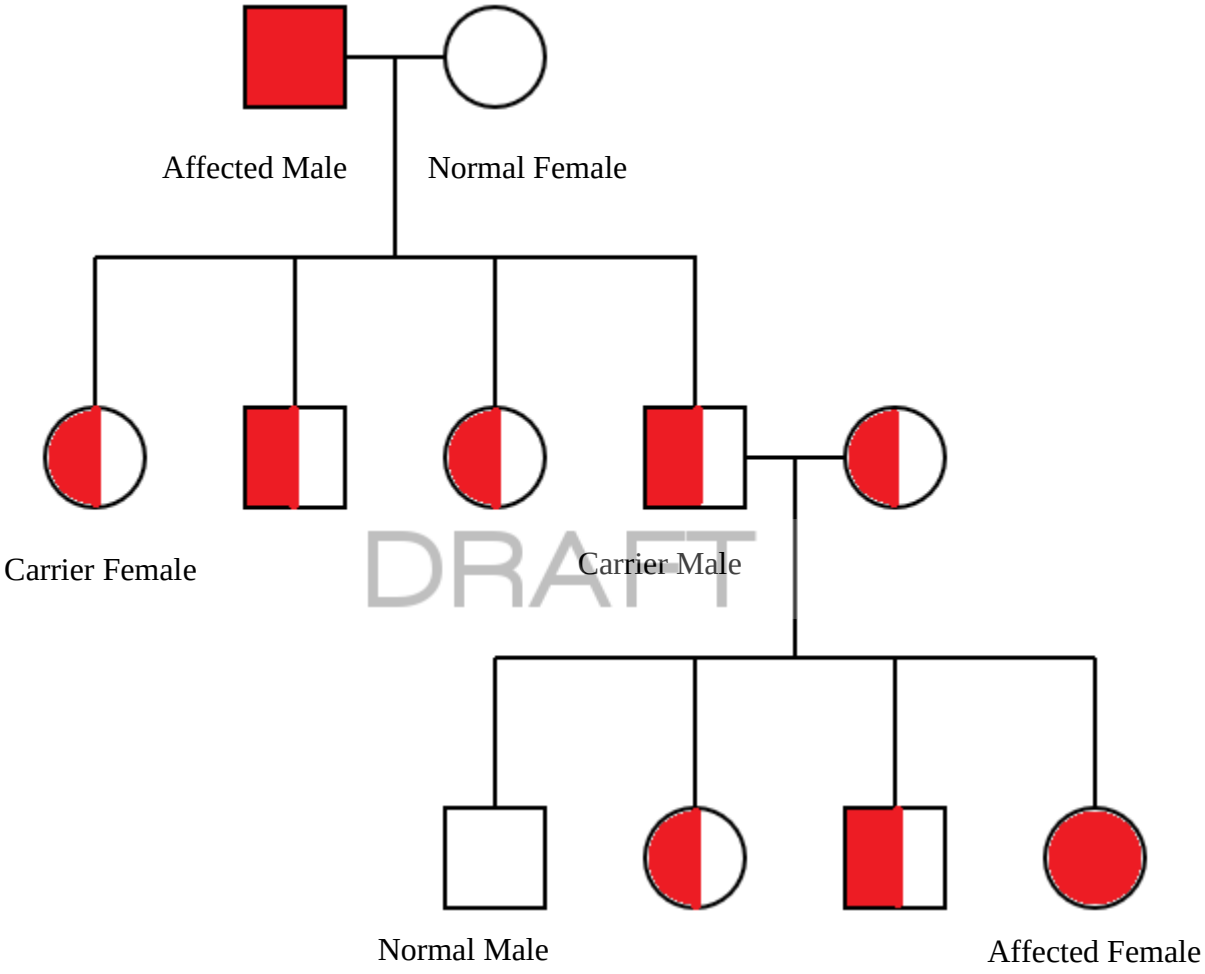

Figure 1-2. Inheritance of sickle cell disease

CHAPTER 2: DIAGNOSIS

2.1. Signs and symptoms of SCD

- Infants with spontaneous painful swelling of the hands and feet;
- Recurrent episodes of severe body pain with no other identified etiology;
- Unexplained anemia not related to iron deficiency;
- Sepsis, pneumonia and meningitis;
- Stroke (not common presentation in our population);
- Gallstone in young;
- Jaundice, pallor, severe anemia with splenic enlargement

2.2. Mimickers of SCD

In our population patient with SCD have been misdiagnosed with the following diseases, therefore in the Tharu community health workers should consider SCD before making these diagnoses.

- Viral hepatitis
- Rheumatic heart disease
- Arthritis
- Malaria
- Typhoid
- Kala-azar
- Sepsis
- Pneumonia and other chest infections
- Psychiatric disorders

Table 2-1. Clues for health workers to identify the organ/tissue involvement

Organ/Tissue	Problems
Brain	Headache
	Stroke
	Possible learning disability
Bones	Arm or leg pain
	Hip pain
	Back pain
Lungs	Productive cough
	Breathlessness
Kidney	Frequent urination
Spleen	Abdominal pain
Eyes	Yellow eyes
Penis	Priapism (painful unwanted erection)

2.3. Lab investigations for suspected SCD

- Complete blood count
- Reticulocyte count
- Peripheral blood smear
- Sickling test
- Serum ferritin (to rule out iron deficiency)
- HPLC/Capillary electrophoresis (Generally for all practical purpose HPLC/Capillary electrophoresis will detect Sickle cell disease and trait).
- If there is strong clinical suspicion and proper diagnosis cannot be made with HPLC because of recent blood transfusion or other reasons, the patient should be referred to tertiary Genetic/Molecular centre.

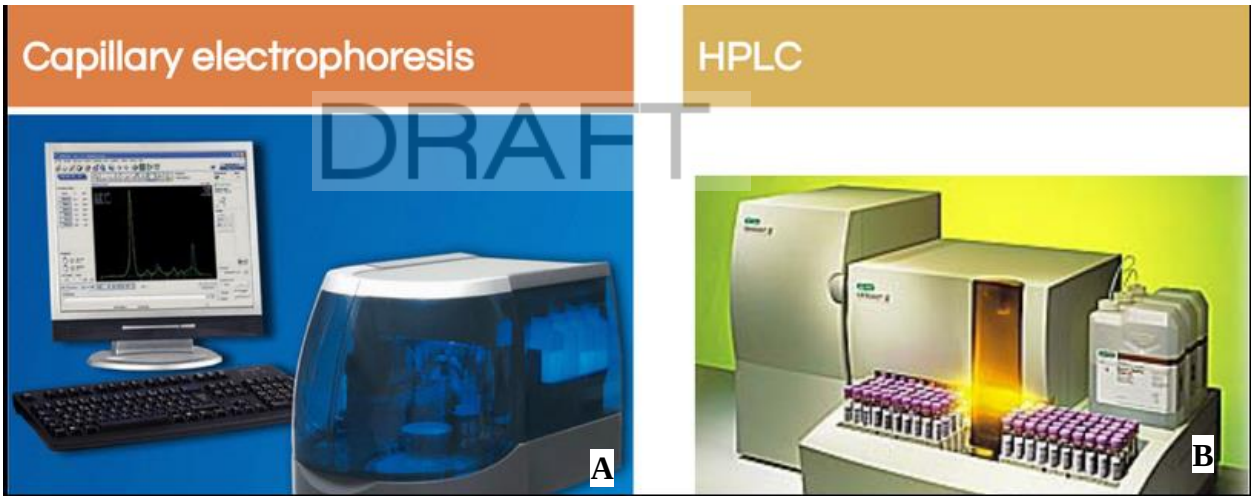

Figure 2-1. (A). Capillary electrophoresis and (B) ion exchange chromatography used for the diagnosis of hemoglobinopathies.

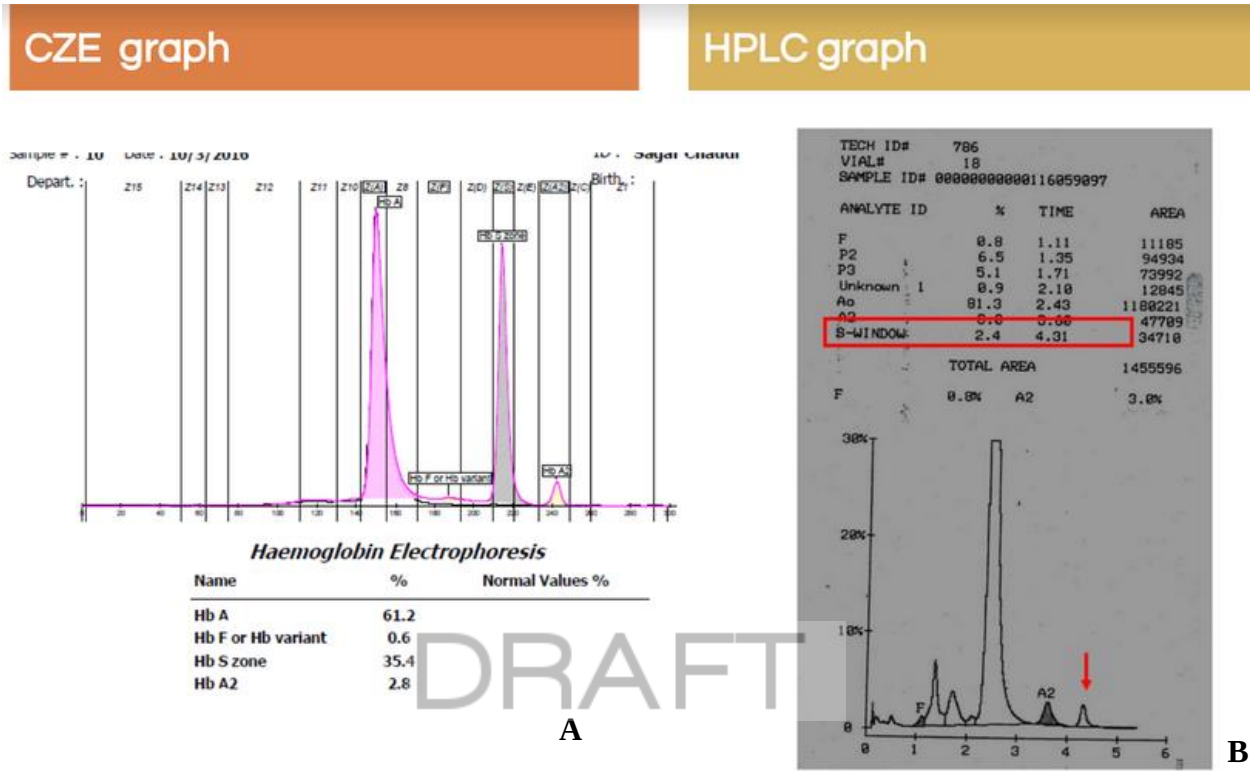

Figure 2-2. (A)Capillary zone electrophoresis graph showing HbA, HbF, HbS zone and HbA_2 quantification. (B) HPLC graph showing interpretation of normal and abnormal Hb in patients with hemoglobinopathies.

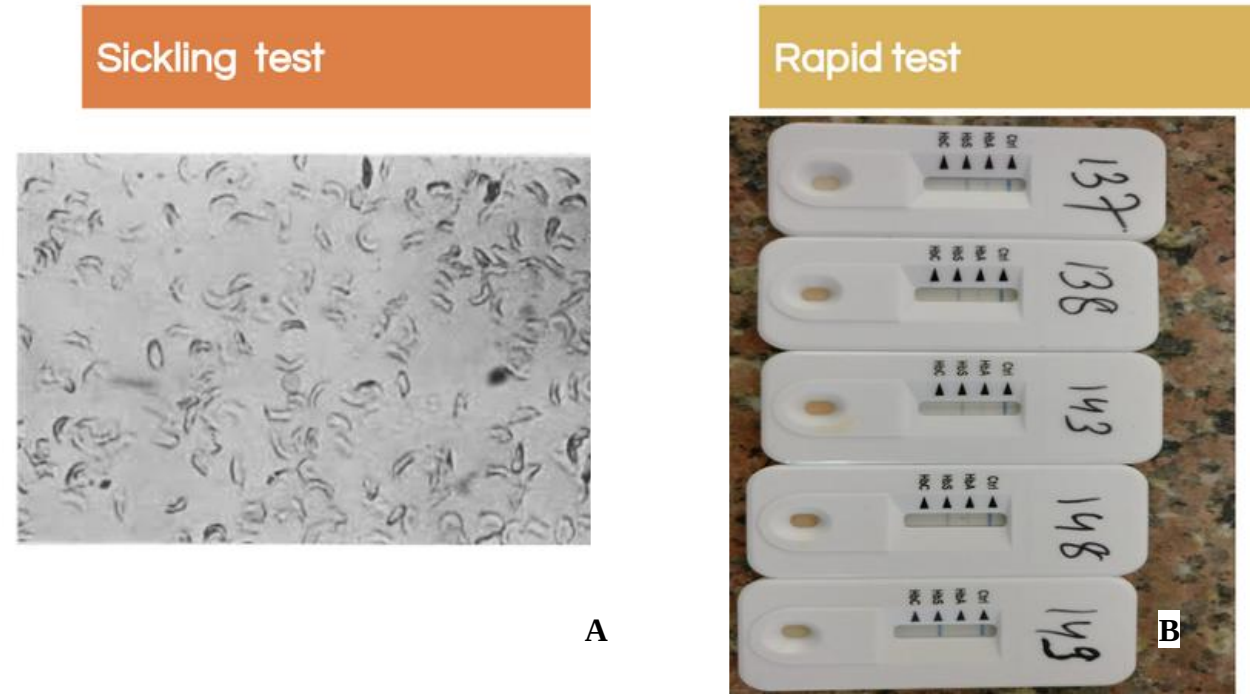

Figure 2-3. Sickling test (A) and rapid diagnostic test (B) used for the diagnosis of sickle cell disease

2.4. Whom to test for SCD?

- People from Tharu community;
- People with signs and symptoms suggestive of SCD;
- Family members of the person with SCD or trait;
- Pregnant females of Tharu community and her husband (if not tested before); and
- Anyone who wants to get tested

2.5. Which age is appropriate for SCD screening?

- Sickle cell test can be offered to anyone from newborn to old age. The earlier the diagnosis is made the better is the prognosis.

2.6. Complications of sickle cell disease

- Acute vaso-occlusive crisis: Most common reason for hospital admission. Patients commonly present with multiple joint and bone pain.
- Acute chest syndrome: It is one of the leading cause of death in adults. Patients present with breathlessness and chest pain.
- Hemolytic crisis: Sudden onset of hemolysis characterized by a rapid fall in hemoglobin, increase unconjugated bilirubin and cola coloured urine.
- Splenic sequestration.
- Avascular necrosis of the bone.
- Sepsis: severe infection not responding to any common antibiotics.

CHAPTER 3: SCD MANAGEMENT

3.1. General considerations

- Sickle cell trait does not need treatment, however, risk of renal disease should be well explained to the patient.
- Treatment is not indicated in all patients diagnosed with SCD (homozygous).
- Treatment is based on clinical symptoms and hydroxyurea is indicated only in those patients with more than three pain crisis in a year.
- Sickle cell disease and trait need Genetic Counselling (premarital and preconception).
- Bone marrow transplant is the only cure for SCD.
- If there is a history of SCD in the siblings than parents should be referred to Geneticist for counselling and prenatal diagnosis is advice for the next pregnancy.

3.2. Where do SCD patients seek treatment?

- Most patients with SCD visit the traditional healers (Guruwa).
- Guruwa of the community should be made aware of the symptoms and complications of SCD, so that early referrals to the physicians can be made.

3.3. Must do things for SCD

- All individuals with SCD should receive age-appropriate vaccinations, including these against *Streptococcus pneumoniae*, Seasonal influenza, *Neisseria meningitides*, *Haemophilus influenzae* type B, and Hepatitis B.
- All individuals with SCD should begin antibiotic prophylaxis within the first three months of life.
- All individuals with SCD should begin antibiotic prophylaxis, prophylactic penicillin (or erythromycin if penicillin-allergic) until age five, rather than a shorter duration.
- Adults with SCD who are admitted to the hospital with an acute medical illness should receive thromboprophylaxis unless they have a contraindication.
- All individuals with SCD should receive folic acid supplementation.
- Replace Vitamin D and calcium, as needed, which are often deficient.
- For children with HbSS or HbS-β^0 thalassemia or other SCD syndromes with low baseline hemoglobin, transcranial Doppler ultrasound evaluation of cerebral blood flow be initiated at two years of age and performed annually until 16 years of age to screen for this complication.
- For children at increased risk of a first ischemic stroke based on two TCD velocity measurements ≥200 cm/sec within a one to two week period, chronic transfusion therapy should be initiated rather than no treatment.
- Children with any sign of cognitive dysfunction should be screened for silent infarcts using magnetic resonance imaging (MRI).

- Individuals with SCD are at risk for proliferative retinopathy. Retinal evaluation is begun at 10 years of age and continued routinely to detect early proliferative sickle retinopathy.
- Yearly echocardiogram to record the tricuspid regurgitant jet velocity.
- Pulmonary hypertension is typically suspected in SCD patients who have exertional dyspnea, oxygen desaturation, more severe hemolytic anemia, or elevated tricuspid regurgitant jet velocity (TRV >2.5 m/sec) on screening echocardiography.
- A routine urine analysis should be done in every visit and urgent nephrologist consultation should be done in case of proteinuria and microscopic hematuria.
- Creatinine more than 1mg/dl and hyperuricemia should be closely monitored and nephrologist consultation should be sought.
- Do not use granulocyte colony-stimulating factor (G-CSF) in individuals with SCD, due to the risk of multiorgan failure and death.
- Blood pressure screening should be done at every visit. Early treatment of systemic hypertension is critical because mild elevations in blood pressure are associated with an increased risk of overt stroke and silent cerebral infarct in individuals with SCD.

CHAPTER 4: MANAGEMENT OF COMPLICATIONS

4.1. Acute painful episode

4.1.1. Introduction

The acute painful episodes, also known as sickle cell crisis, is the hallmark clinical manifestation of sickle cell disease. The acute painful episode in sickle cell disease has been described as more severe than post-operative pain and as intense as the pain associated with cancer, worse than the pain associated with childbirth.

Pain episodes can begin as early as six months of age and typically last throughout life. In a series of children diagnosed with SCD at birth, one-third had experienced pain by the age of one year, two-thirds by the age of two years, and over 90 percent by the age of six.

The sites of pain can include the back, chest, extremities, and abdomen. In young children, dactylitis (acute pain in the hands or feet) may be the most common site of pain.

4.1.2. Assessment of acute painful episode

It is important to remember that all pain in patients with sickle cell disease is **NOT** sickle pain. It is necessary to always consider other possible etiologies.

At the time of the initial assessment of an acute painful episode, one should establish whether it is a **"Typical"** or **"Atypical"** episode. Most patients will be able to relate to whether the characteristics of the present pain episode are similar to previous ones. If it is noted that the present episode is "atypical", then this should alert one to the possibility of other etiologies for the pain.

During the initial assessment of the acute painful episode, it is also important to determine whether the present episode is **"Complicated"** or **"Uncomplicated".** Findings such as tachycardia, tachypnea, hypoxia, fever >38.5^{0}C, hypotension, neurological deficits, priapism, recurrent emesis, or acute joint swelling are indicative of a complicated episode.

4.1.3. Investigation

Initial work-up of an acute painful episode should include:

- CBC with reticulocyte count, serum chemistry, LDH, and LFTs.
- If the patient has any respiratory symptom, then a CXR should be obtained.
- Blood and urine cultures should be obtained if the patient is febrile or the WBC is above baseline.
- During the admission, one would follow at least daily CBC with reticulocyte count (may follow every other day if an uncomplicated episode). Other daily labs as clinically indicated.

4.1.4. Management of acute painful episode

It should be noted that the majority of pain episodes are managed at home. Therefore, aggressive regimens are recommended for the management of pain severe enough to require hospital admission. To reduce the risk of acute chest syndrome, one should encourage the use of incentive spirometry while awake and encourage ambulation as soon as possible.

4.1.4.1. Opioid analgesics/Around the clock (ATC) dosing

In around the clock (ATC) dosing, the opioid is administered IV or subcutaneously on a scheduled basis rather than PRN. The frequency of the scheduled dose is based on the effective half-life of the opioid. For example, the plasma half-life of morphine is approximately 2½ hours; therefore, it is scheduled every three hours. A PRN dose may be given--in addition to the scheduled dose--for breakthrough pain. As noted earlier if needed, a rescue dose of the IV opioids may be provided PRN for breakthrough pain at ¼ to ½ the scheduled dose. Limits should be set on the number of rescue doses that the patient uses before an adjustment is made in the scheduled dose.

Once the painful episode has abated, one can attempt to taper off the IV opioids and subsequently convert to oral analgesics in anticipation of discharge home.

4.1.4.2. Non-opioid analgesics

Non-opioid analgesics such as acetaminophen or NSAIDs may be used in the treatment of acute painful episodes. These may be used alone which is usually during a minor painful episode at home, or in conjunction with opioids for synergy and opioid-sparing effect.

Patients with SCD are already at risk for renal complications because of their disease, therefore NSAIDs should be used cautiously.

Acetaminophen can also be used in conjunction with opioids for synergy and opioid-sparing effect. This should also be used cautiously given that many of the PO opioids already have acetaminophen and one needs to be very cautious about associated hepatotoxicity.

The patient should be encouraged for incentive spirometry and studies has shown it will prevent acute chest syndrome and

4.1.4.3. Fluid management and supportive care

Hydration is an integral part of the management of the acute painful episode. Oral fluids should be given if there is no IV access and the patient is not nauseated. IV hydration with ½ NS or normal saline is preferred. Input and output charting should be done every 6 hourly to avoid fluid overload. In patients with an oxygen saturation <95% on room air, oxygen should be administered. Blood should not be transfused unless there are other indications for transfusion.

4.2. Acute chest syndrome

4.2.1. Introduction

Acute chest syndrome (ACS) is one of the leading causes of death of adult sickle cell patients. Patients with ACS have the potential to rapidly progress to respiratory failure with an ARDS picture. Given the potential for rapid deterioration, patients with ACS need to be diagnosed in a timely manner with appropriate and effective management instituted immediately.

4.2.2. Diagnosis

ACS is diagnosed when there is a **NEW** pulmonary infiltrate consistent with consolidation involving at least one lung segment on CXR or CT scan with at least one or more of the following NEW symptoms: fever > 38.5^0C, chest pain, cough, sputum production, wheezing, or hypoxia. CBC may reveal an increase in the WBC above baseline and worsening anemia as reflected by a drop-in hemoglobin.

However, Clinicians should maintain a high index of suspicion of ACS in patients who have chest symptoms and signs, especially if hypoxic, even in the presence of a normal chest x-ray.

4.2.3. Management

Once the criteria for the diagnosis of acute chest syndrome (ACS) are met, then one should proceed with close monitoring and prompt institution of appropriate treatment.

4.2.4. Institute the following treatment

- Continuous pulse oximetry;
- Serial/Daily ABGs;
- Serial/Daily CXR until improvement noted;
- Serial/Daily CBC and reticulocyte count; and
- Pre/post-transfusion hemoglobin electrophoresis.

4.2.5. Monitor the following

- IV hydration with ½ NS no more than 1½ of daily maintenance.
- Antibiotics consisting of cephalosporin/macrolide or fluoroquinolone.
- Supplemental O_2 to maintain pulse ox >95%. If noted to have increasing O_2 demands with FIO_2 (fraction of inspired oxygen) needs greater than 40% then consider the transfer to MICU.
- Adequate pain control while avoiding oversedation.
- Bronchodilator therapy in those with evidence of reactive airway disease.
- Incentive spirometer.
- Transfusions: A type and cross should be sent immediately once ACS is suspected. RBC transfusions whether simple or exchange can be lifesaving in the treatment of ACS, as they may prevent its progression to acute respiratory failure. Simple transfusion of 1-2 units or PRBCs can be given to raise the hemoglobin level (NOT to exceed Hb level of 10 g/dl) as this will increase the oxygen-carrying capacity. Exchange transfusions, on the other hand, can be used to remove sickle cells and replace them with normal red cells. The goal of exchange transfusion is to reduce the Hemoglobin S level <30% with a total hemoglobin level of ~10 g/dl. The choice to proceed with simple versus exchange transfusion is based on the patient's clinical status, availability of units of PRBCs, and hemoglobin level.

If a patient with ACS is noted to be unstable/deteriorating as indicated by low O_2 saturation despite aggressive vent support, serial deterioration in O_2 saturation with increasing O_2 demands, and unstable vitals such as persistent tachypnea then one should proceed with immediate rapid exchange transfusion.

4.3. Acute neurological events

4.3.1. Introduction

Central nervous system involvement in sickle cell disease is common. Cerebrovascular accidents are common complications seen in both children and adults with SCD. The type of stroke varies

with age; ischemic strokes are more common in the pediatric population while hemorrhagic strokes are more common in adults.

4.3.2. Diagnosis/Management

Any of the following signs or symptoms noted in a patient with sickle cell disease should raise one's suspicion of an acutely evolving neurological event:

- Headache
- Syncopal episode
- Change in the level of consciousness
- Motor or sensory deficit
- Change in vision, or
- New onset seizures

The concern for an acute neurological event is further raised if, in addition to the aforementioned sign/symptoms, the patient has a prior history of a neurological event as repeat strokes whether ischemic or hemorrhagic are common.

An adult patient with sickle cell disease with signs/symptoms suggestive of an acute CVA should have an immediate general assessment including evaluation of ABCs and vital signs. A CT of the brain without contrast should be obtained STAT which will subsequently determine the course that will need to be followed.

4.3.3. Hemorrhagic stroke

As noted earlier a hemorrhagic stroke is more common than ischemic stroke in the adult sickle cell population. These include subarachnoid, intraparenchymal, or interventricular hemorrhage. Patients with intracranial hemorrhage commonly present with a severe headache, nausea/vomiting, and change in mental status. If the CT of the brain reveals hemorrhage, then neurosurgery needs to be consulted immediately. Neurosurgery is consulted as patients with intracranial hemorrhage will likely need angiography to identify the source of bleed. The angiography should be preceded by an exchange transfusion with goal Hb S <30% and total Hb of ~10g/d. Subsequent surgical intervention is to be determined by neurosurgery.

4.3.4. Ischemic stroke

Ischemic strokes although less frequent than the hemorrhagic type may still occur in the adult sickle cell population. A non-contrast CT of the brain is less likely to reveal an acute/evolving ischemic stroke. If the non-enhanced CT does reveal an ischemic stroke (which is possible particularly if the ischemia has been ongoing for several hours), then one may give the patient aspirin 325 mg and subsequently proceed with an exchange transfusion (goal, as noted, is Hb S<30% with total Hb level of ~10g/dl). If the non-contrast CT is negative (no bleed or ischemia noted), then one may still give ASA 325 mg and subsequently proceed with obtaining the MRI/MRA. If the MRI is positive for an ischemic stroke, then one would proceed with exchange transfusions immediately with the previous noted goals for Hb S reduction and total hemoglobin.

4.3.5. Transient ischemic attack (TIA)

If the imaging studies are negative and the clinical suspicion is high for a TIA, then one would still consider proceeding with an immediate exchange transfusion with the noted goal for HbS

reduction and total hemoglobin. If the clinical suspicion for TIA is low, then one can subsequently just observe the patient.

4.3.6. Aneurysm and Moyamoya

Even though the imaging studies may not reveal an acute/evolving stroke, the MRA may still identify a vascular lesion such as an aneurysm (not uncommon for a patient to have multiple aneurysms). Injury to the endothelium by the sickle cells and the high viscosity associated with SCD likely promotes the formation of aneurysms. If aneurysms are noted, then neurosurgery should be consulted for evaluation and possible intervention such as clipping or coiling. The MRA may also reveal moyamoya which are collateral circulations formed as a result of large vessel stenosis. Patients with moyamoya are at risk for recurrent strokes, both hemorrhagic and ischemic. Neurosurgery should again be consulted in this situation for evaluation and possible intervention.

4.4. Fever/Infection

4.4.1. Introduction

Both pediatric and adult SCD patients have increased susceptibility to infection mainly as a result of their afunctional spleen. Children with SCD have an increased risk for overwhelming sepsis with *Streptococcus pneumoniae*, the most common cause of death in the sickle cell pediatric population. The mortality due to *Streptococcus pneumoniae* sepsis has been significantly decreased in the sickle cell pediatric population because of pneumococcal vaccination and PNC prophylaxis.

Adults with SCD have an immune system that has matured such that they are less susceptible to the overwhelming sepsis seen in the pediatric population. Despite this, they are still more prone to infection as compared with normal adults. Therefore, any fever in adults with SCD requires an aggressive approach.

4.4.2. Management

Acute painful episodes themselves may cause low-grade fever with the temperature usually $<38.5^0$C, but fever over 38.5^0C is more likely to be from an infectious etiology. Workup should include CBC, reticulocyte count, CXR, UA, and blood culture. A lumbar puncture may be considered if the clinical presentation suggests the possibility of meningitis. Given the increased susceptibility of SCD patients to infection, there should be a low threshold for initiating empiric antibiotics in those presenting with fever. The clinical presentation and findings on CBC, chest x-ray, urine analysis determine the need and type of empiric antibiotics.

4.4.3. Common infections in adult SCD patients

Pneumonia: one of the most common etiologies of acute chest syndrome. If this is suspected as by CXR finding, then one should initiate ceftriaxone plus a macrolide or a fluoroquinolone antibiotic. Ensure that there is atypical coverage since Mycoplasma and Chlamydia have been identified as the most common infectious agents resulting in acute chest syndrome.

Urinary tract infection: recurrent UTIs are common particularly with *E. Coli* as the most common pathogen. Patients with SCD usually should be treated as having a complicated UTI. Antibiotics are chosen based on their sensitivities.

Osteomyelitis: often occurs at the sites of necrotic bone. Although Salmonella occurs more often in SCD patients, *Staphylococcus aureus* remains the most common cause of infection overall. MRI is the preferred imaging study. Bone biopsy remains the gold standard for diagnosis. Therapy is 2-6 weeks of parenteral antibiotics (choice of antibiotics based on isolated pathogen and susceptibilities).

Cholecystitis: Cholelithiasis is common as a result ongoing hemolysis with the formation of pigmented stones and acute cholecystitis may be subsequently noted. Empiric broad-spectrum antibiotic with piperacillin plus tazobactam or combination therapy with a fluoroquinolone and metronidazole may be warranted prior to definitive surgical intervention.

4.5. SCD: Infection prophylaxis

4.5.1. Immunizations

Immunizations are a cornerstone of infection prevention in SCD. Children with SCD should receive all routinely recommended childhood vaccines, including those against *Streptococcus pneumoniae*, seasonal influenza, *Neisseria meningitidis*, *Haemophilus influenzae* type B, and Hepatitis B virus. When feasible, antibiotic prophylaxis of individuals with SCD who are household contacts of persons with these infections may be indicated.

Influenza: Annual seasonal influenza vaccination is recommended for all individuals with SCD. Vaccination should be administered annually at the start of the flu season, beginning at six months of age. Individuals with SCD should receive that inactivated vaccine rather than the live-attenuated vaccine because of the increased risk of severe or complicated infection. Standard influenza vaccination is also protective against the H1N1 strain of influenza.

4.5.2. Prophylactic penicillin

Prophylactic penicillin should be given to all individuals with SCD at least until age five. The dose from age three months to three years is 125 mg penicillin V orally twice daily, and at age three years this should be increased to 250 mg twice daily until the age of five.

Patients with sickle cell-β^0 thalassemia (HbS-β^0 thalassemia) have a clinical course similar to patients with HbSS disease, with the development of functional asplenia early in childhood and a similar risk of invasive bacterial infection. As a result, their infection prevention strategy should be the same as those with HbSS, including immunizations, prophylactic penicillin, and empiric antibiotic therapy when they are febrile.

Patients with sickle cell-β^+ thalassemia (HbS-beta$^+$ thalassemia) produce variable amounts of HbA and in general have less severe SCD complications, although limited data are available regarding their risk of infection. In general, they are treated in a manner similar to those with HbSC.

4.5.3. Prophylactic antibiotics

Empiric broad-spectrum antibiotic with piperacillin plus tazobactam or combined therapy with fluoroquinolone and metronidazole may be warranted prior to definitive surgical intervention.

4.6. Aplastic crisis

Given the significantly short lifespan of the RBC in sickle cell disease (~10 days in sickle cell anemia), any temporary suppression of the bone marrow may result in a rapid decline in hemoglobin levels. Any infection may result in bone marrow suppression, but the principal cause of transient red cell aplasia in sickle cell patients is Parvovirus B19. CBC will reveal a hemoglobin that is significantly below the baseline. The mean hemoglobin at the time of presentation is noted to be ~4g/dl. Reticulocytes are <1% or an absolute count <10,000. Treatment consists of simple transfusion until the bone marrow recovers. Recovery is noted when there is evidence of red cell production as determined by an increase in the reticulocyte count. On may consider treatment with IVIG which may potentially shorten the course of infection.

Other complications associated with infection with parvovirus B19 in SCD patient beside the aplastic crisis are noted to be a nephrotic syndrome, stroke, acute chest syndrome, and hepatic or splenic sequestration.

4.6.1. Acute sequestration crisis

During a sequestration crisis, the sickled erythrocytes can become acutely entrapped in the spleen, liver, or lung with an acute drop in the Hb/HCT.

4.6.1.1. Acute splenic sequestration

Splenic sequestration is a life-threatening complication usually seen in the pediatric population of Hb SS patients between the ages of 3 months and 5 years. Rarely does one see acute splenic sequestration in Hb SS patients over the age of five as the spleen has usually auto infarcted by that age. In adults SCD patients it is more common to see acute splenic sequestration in Hb SC and sickle/β-thal (+) patients. These patients frequently actually have an enlarged spleen; therefore, during vaso-occlusive episodes, they have the potential for sequestration. During splenic sequestration, the Hb is usually noted to drop by more than two grams accompanied by increased reticulocytosis. The mortality rate is as high as 10 to 15 percentage, and patients often die before transfusions can be given. Splenic sequestration has been reported to occur in as many as 30 percentages of young children with SCD and to be the presenting symptom in up to 20% of patients. Simple transfusions can be given in order to maintain hemoglobin levels. In this case, one has to be careful with reverse sequestration as the entrapped RBCs may return to circulation and increase the viscosity. To decrease the likelihood of hyperviscosity syndrome occurring after a simple blood transfusion, transfuse the individual with approximately 50 percent of what we would commonly transfuse. **If more than one episode of sequestration is noted, then a splenectomy should be considered.**

4.6.1.2. Acute hepatic sequestration

This is an uncommon complication usually seen in Hb SS patients. During a vaso-occlusive episode, sickled erythrocytes become entrapped in the hepatic sinusoids. The Hb/HCT is noted to

drop significantly below baseline accompanied by increased reticulocytosis and hepatic size. Also, a dramatic rise in bilirubin may be noted with the majority being conjugated.

The alkaline phosphatase levels may rise but the transaminases usually are not significantly elevated. Treatment consists of either simple or exchange transfusion. Again, one has to be cautious with the transfusions given the potential for reverse hepatic sequestration as entrapped RBCs return to the circulation increases the potential for hyperviscosity.

4.7. Priapism

This is the least common clinical manifestation seen in Nepal in sickle cell disease. Priapism is a persistent, painful, and unwanted erection that occurs without sexual stimulation. This a common complication of sickle cell disease with the majority of male sickle cell anemia patients noted to have had at least one episode by the age of twenty. In sickle cell disease priapism results from the failure of venous outflow (therefore it is a low-flow state) involving the corpus cavernosum. The corpus spongiusum is spared.

The episode of priapism is either noted to be stuttering which spontaneously resolves within three hours (usually only last several minutes), or prolonged, lasting more than three hours. Prolonged priapism is a medical emergency as it may result in loss of functionality. The risk of impotence is significantly increased if priapism lasts longer than 24 hours. The goal of the treatment is to relieve the pain, achieve detumescence, and maintain functionality.

When patients initially present with priapism, they should be immediately started on IV fluids preferably NS and their pain controlled. The priapism may be associated with an acute sickle painful episode. Pain associated with the priapism, whether accompanied by a painful episode or not, will likely require treatment with IV opioids. If detumescence is not achieved with conservative treatment and has been prolonged and ongoing for 4-6 hours, then urology should be consulted for possible penile aspiration. If the priapism recurs despite urological evaluation/treatment, then exchange transfusion may be indicated at the time. The goal of exchange transfusion is to reduce the Hemoglobin S less than 30%. If priapism persists despite above-noted interventions, then a shunting procedure may be considered. The aforementioned procedure is the last resort and if possible should be avoided.

4.8. Avascular necrosis of bone

Avascular necrosis of bone, also called osteonecrosis, ischemic necrosis, or aseptic necrosis, results from infarction of bone trabeculae. The femoral and humeral heads may be affected. The femoral heads more commonly undergo progressive joint destruction as a result of chronic weight bearing. The changes are best detected by magnetic resonance imaging (MRI). Orthopedic consultation should be sought as early as possible.

4.9. Retinopathy

SCD can cause retinopathy from retinal artery occlusion and ischemia, with associated proliferative retinopathy, vitreal hemorrhage, and retinal detachment. These changes may be observed in older children and adolescents and tend to progress throughout adulthood. Unlike other complications, which tend to occur with greater frequency in individuals with homozygous HbSS

or sickle-β^0 thalassemia, proliferative retinopathy is more common in hemoglobin SC disease than in other SCD genotypes. Management may involve laser photocoagulation, similar to that used in other forms of proliferative retinopathy in other settings such as diabetes. The role of antiangiogenic therapy, hydroxyurea, and chronic transfusion in preventing or treating SCD-associated retinopathy remain to be established.

4.10. Use of hydroxyurea in sickle cell disease

Hydroxyurea reduces vaso-occlusive events such as pain episodes and acute chest syndrome (ACS) in people with sickle cell disease (SCD). For infants <9 months with HbSS or sickle β^0 thalassemias who are symptomatic (e.g. dactylitis, acute pain episodes) hydroxyurea is indicated. Hydroxyurea is also indicated for infants ≥9 months, children, and adolescents who have HbSS or sickle beta^0 thalassemia of any clinical severity.

For adults with HbSS or sickle β^0 thalassemia who have severe symptoms (>3 painful episodes in a year; >3 episodes of ACS in two years), hydroxyurea should be started.

Initial hydroxyurea dose of 15 mg/kg daily in infants <1 year, 20 mg/kg daily in children, and 15 to 20 mg/kg daily in adults; the daily dose may be rounded to the nearest 2.5 mg/kg. Those with creatinine clearance <60 mL/min dose should be reduced by half. Treatment is continued indefinitely in those for whom it is effective. The use of hydroxyurea in adults with less severe symptoms and in individuals with other SCD genotypes such as HbSC disease or sickle β^+ thalassemia is individualized.

CHAPTER 5: TRANSFUSION IN SICKLE CELL DISEASE

5.1. Introduction

Red blood cell transfusion plays an integral part in the management of sickle cell disease. PRBC transfusions are indicated in various clinical scenarios in SCD both in the acute and none acute settings. In many cases transfusions are lifesaving. This does not mean that PRBC transfusions in SCD are a panacea. There are various serious complications related to transfusion therapy, therefore there needs to be a thoughtful approach prior to proceeding with any transfusions.

5.2. Special considerations

Special considerations for the blood that is to be transfused to sickle cell patients are the following:

- Sickle negative: this means that blood from sickle cell trait patients should not be transfused to SCD patients since this will confound the hemoglobin electrophoresis results.
- Leukocyte depleted: this can decrease the risk of alloimmunization. Also decreases the likelihood of febrile non-hemolytic transfusion reactions and transmission of CMV.
- Phenotypically matched: by matching for minor antigens the risk of alloimmunization is reduced.

Depending on the clinical scenario, patients may be either simple or exchanged transfused. Exchange transfusion offers the benefit of actually removing the sickle cells and replacing them with normal red blood cells without increasing the viscosity. Depending on the hemoglobin level, one may be limited in how aggressive the patient can be simple transfused given possibility of hyperviscosity at higher hematocrits (transfusing above a Hct of 30 should be avoided). The other advantage of exchange transfusion besides the ones already noted is the fact that it limits the iron overload associated with the transfusions. So, why not exchange everybody?

As with any intervention, an exchange transfusion also has its downside. The disadvantages associated with an exchange transfusion are the likely need for placing a large bore central venous catheter, need for several units of PRBCs which means an increased chance for alloimmunization, and last but not least the cost.

5.3. Indications for transfusion whether simple or exchange in sickle cell patients

5.3.1. Episodic simple transfusions

Severe acute anemia as seen with hyper-hemolysis (non-immune mediated), infection (any infection may result in suppression of the bone marrow as may be evident by a low reticulocyte count.

- Acute splenic sequestration
- Aplastic crisis
- Pre-operatively: the goal of hemoglobin is ~10g/dl prior go going to the OR.

- Acute chest syndrome: Simple transfusions are acceptable in patients who are stable with low hematocrit (should not exceed hct of 30).

5.3.2. Episodic exchange transfusion

- Acute chest syndrome
- Stroke
- Acute multi-organ failure

5.3.3. Chronic transfusions

- Primary and secondary stroke prevention.

The studies to justify chronic transfusion have been done mainly in the pediatric population and have been extrapolated to adults. Once the hemoglobin S has been reduced to 30% with an exchange transfusion, then this fraction may be maintained with simple transfusion of 1-2 units every 3-4 weeks.

5.4. Complications of transfusion therapy

5.4.1. Alloimmunization

This is one of the major complications of transfusion therapy in SCD patients where they form antibodies to the antigens in the transfused blood. Usually, many alloantibodies are present, which make it rather difficult in finding compatible blood. It has been noted that anywhere from ~5 to 50% of sickle cell patients will develop alloantibodies after several transfusions. The risk of alloimmunization has been estimated as ~3% per unit of PRBCs transfused. The high rates of alloimmunization in sickle cell patients have been attributed to the fact that the blood that they receive is likely from people of different ethnic/racial background who have a different antigenic frequency. The risk of alloimmunization can be reduced by transfusing only leukopoor, phenotype-matched RBCs.

5.4.2. Delayed hemolytic transfusion reaction (DHTR)

This usually occurs 5-14 days following the transfusion as a result of primary or an anamnestic immune response in a previously alloimmunized patient. This may result in immune hyper-hemolysis where not only the transfused blood may be hemolyzed but also autologous peripheral destruction may be noted (bystander hemolysis). During the episode of DHTR, the LDH and TB will rise significantly above baseline, and the direct antibody test (DAT) will be positive if the cohort of cells has not been destroyed. In sickle cell patients, the hemoglobin fractionation will likely reveal a Hb A level of 0% as all of the transfused blood will have been hemolyzed. In this case, further transfusions should be avoided as they will exacerbate the situation. In addition to avoiding transfusions, the patient can be placed on corticosteroids (usually 1 mg/kg of prednisone should suffice). The patient may also be given erythropoietin injection to maintain/increase hemoglobin level. IVIG has also been used in this case.

5.4.3. Iron overload

Each unit of blood has approximately 250 mg of elemental iron. The body does not readily excrete iron; hence it will accumulate with multiple transfusions of PRBCs. The accumulated iron may subsequently result in organ dysfunction usually involving heart, liver, and endocrine organs. In Africans and African-Americans, ferritin levels may not correlate well with the actual tissue stores. The MRI of the liver may be a more accurate estimation of iron stores/overload. The gold standard is a liver biopsy. Treatment of iron overload in sickle cell patient is problematic given that phlebotomy is not usually an option. The use of iron chelators such as deferoxamine or deferasirox should be encouraged.

5.4.4. Infection

Viral infections such as hepatitis B and C, HIV, and HTLV type I and II may be transmitted with transfusion of PRBCs. According to the American Red Cross, the risk of transmission of HIV is noted to be ~1 in 2.1 million transfusions. Hepatitis B transmission is ~1 in 200,000 transfusions. The risk of Hepatitis C, on the other hand, is ~1 in 2 million transfusions.

CHAPTER 6: SICKLE CELL DISEASE AND PREGNANCY

6.1. Effects of SCD in pregnancy

- Infertility
- Repeated abortion
- Pre-term delivery
- Intra-uterine growth retardation (IUGR)

6.2. Maternal mortality management of sickle cell disease during pregnancy

- The management of painful vaso-occlusive episodes is the same as that in non-pregnant women, except nonsteroidal anti-inflammatory drugs (NSAIDs) are generally avoided after 30 weeks of gestation because of an increased risk of premature narrowing or closure of the ductus arteriosus.
- Opioids are the mainstay of therapy in pregnant and non-pregnant women.
- There are no medical contraindications to vaginal delivery in SCD.
- In the absence of maternal or fetal complications, awaiting spontaneous labor is reasonable.
- Given the increased risk of preeclampsia administer low-dose aspirin from the beginning of the second trimester to 5 to 10 days before the expected date of delivery as long as aspirin is not contraindicated.
- Patients with SCD (hemoglobin SS) should be transfused to keep Hb above 9 gm/dL in third trimester.
- In high-risk patients with chronic organ dysfunction or significant history of acute chest syndrome and painful events initiate transfusion early in pregnancy.
- In patients with mild hemoglobin variants or a benign clinical history, prophylactic transfusions are not utilized.
- In chronically ill patients with high baseline hemoglobin levels, exchange transfusions are indicated to maintain the hemoglobin A level greater than 30 to 50%.

POINTS TO REMEMBER

➢ Sickle cell trait

- People with sickle cell trait do not develop SCD.
- The mere presence of Hb S in the HPLC should not be considered as SCD.
- The Hb electrophoresis in Patients with sickle cell trait will have Hb S less than Hb A.
- Sickle cell trait is not a disease and should not be treated with hydroxyurea.
- Sickle cell trait is commonly present in the Tharu community of Nepal.
- Sickle cell trait originated many years ago in areas of the world where malaria was present.
- People with sickle cell trait rarely have medical problems.

➢ Sickle cell disease

- Comprehensive care includes early diagnosis, preventive measures, treatment of complications and ongoing patient education.
- Most of our sickle cell patients don't manifest severe symptoms like those mentioned in Western textbooks.
- Many people with sickle cell disease live long without experiencing acute or severe symptoms
- Very few patients need a risky procedure like bone marrow transplantation to get rid of SCD and its complication.
- With adequate medical care and hydroxyurea, most patients are able to carry out their daily activities.
- Individuals with SCD can pursue a variety of professions.
- Patient with SCD can undergo any form of major surgery under the vigilance of specialist.

CHAPTER 7: THALASSEMIA: INTRODUCTION

7.1. Thalassemia Syndromes

Thalassemia syndromes are inherited disorders characterized by reduced synthesis of the hemoglobin. Hemoglobin is an iron-containing oxygen transport metalloprotein (metal-iron and protein-globin) in the red blood cells. More than 95% of normal adult hemoglobin is of HbA which consists of 2 α chains and 2 β chains. Depending upon the type of missing globin chain, it can be α-thalassemia, β-thalassemia or less common thalassemia E, thalassemia delta etc.

7.1.1. α-thalassemia

α-thalassemia is characterized by the reduced or absent production of α- globin chains. It has two clinically significant forms: hemoglobin Bart hydrops fetalis (Hb Bart) syndrome, caused by deletion of all four α-globin genes; and hemoglobin H (HbH) disease, most frequently caused by deletion of three α-globin genes. Other two carrier forms are α-thalassemia trait [caused by loss of 2 α-globin genes either *in cis* (--/αα, α^0 carrier) or *in trans* (-α/-α)] and α-thalassemia silent carrier [caused by loss of 1 α-globin gene (-α/αα, α^+ carrier)].

7.1.2. β-thalassemia

β-thalassemia is the most common type of thalassemia in Nepal. Beta thalassemia is clinically divided into:

7.1.3. β-thalassemia major

severe, transfusion-dependent due to the mutation in both beta globin chains. It should be suspected in an infant or child younger than two years of age with severe microcytic anemia, mild jaundice and hepatosplenomegaly.

7.1.4. β-thalassemia intermedia

It should be suspected in individuals who present at a later age with similar but milder clinical findings. Individuals with thalassemia intermedia do not require regular treatment with blood transfusion.

7.1.5. β-thalassemia minor or trait

Asymptomatic with mild to absent anemia. They have one mutated β-globin with a normal β-globin chain.

Note: Low hemoglobin level causes anemia. In contrast to iron deficiency anemia, thalassemia syndromes are characterized by anemia due to lack of globin production.

7.2. Thalassemia syndromes: A public health issue in Nepal

The thalassemia is the commonest monogenic disease in human. They occur at a high gene frequency throughout the Mediterranean populations, Middle East, Indian subcontinent. In Nepal, 225 patients of thalassemia (majority-β thalassemia major) are registered in Nepal Thalassemia Society and 51 more patients came to contact but many are expected to go unreported and many die undiagnosed, untreated or improperly treated. According to the data of Nepal Thalassemia

Society, most of the patients are from the Terai region and the Tharu community. Beside these communities, it is seen in Chetri/Brahman, Newar, Rai, Tamang and other ethnic groups of Nepal as well.

Thus, there is an urgent need for quality healthcare for Thalassemia patient in every part of Nepal. Medical doctors need to recognize Hb disorders as a significant threat to public health.

7.3. How do people get thalassemia major or Trait?

- Thalassemia syndromes are not contagious.
- It is inherited in an autosomal recessive manner.
- Thalassemia traits are also known as thalassemia carriers
- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

CHAPTER 8: DIAGNOSIS OF THALASSEMIA

8.1. Signs and symptoms of β-thalassemia major

Affected infants are well at birth. Anemia usually develops during the first few months of life and becomes progressively more severe. Infants fail to thrive and may have feeding problems, bouts of fever, diarrhea, and other gastrointestinal symptoms. Patients with inadequate transfusion and chelation develop the following features:

- Fatigue, exercise intolerance, pallor, jaundice, gallstone
- Stunted growth
- Mongoloid appearance of the face due to bossing of skull and overgrowth of maxillary regions
- Hepatosplenomegaly
- Increased skin pigmentation
- Lack of secondary sexual characteristics
- Thrombocytopenia, leukopenia due to hypersplenism
- Prone to infections

8.2. Lab investigation for suspected thalassemia (pathology)

- Complete blood count
- Reticulocyte count
- Peripheral blood smear
- Serum ferritin (to rule out iron deficiency)
- HPLC/ Capillary electrophoresis
- Common single α-globin-gene deletions (α+-genotype)
- The 3.7-kb deletion (-α3.7) deletion
- The 4.2-kb deletion (-α4) deletion

➢ If there is strong clinical suspicion and proper diagnosis cannot be made with HPLC because of recent blood transfusion or other reasons, the patient should be referred to tertiary Genetic/ Molecular center.

8.3. Whom to test for thalassemia?

- People with signs and symptoms suggestive of thalassemia major.
- Family members of persons with thalassemia major, intermediate and minor.
- Any patients with microcytic hypochromic anemia after ruling out iron deficiency.
- Carrier females and their husband (or vice versa) before conception.
- Anyone who wants to get tested.

8.4. Which age is appropriate for Thalassemia?

Thalassemia can be offered to anyone from newborn to old age. The earlier the diagnosis is made the better.

CHAPTER 9: MANAGEMENT

9.1. Hypertransfusion

Thalassemia international federation (TIF) has given following guidelines for transfusion which is applicable for us as well.

9.1.1. Whom to transfuse?

- Confirmed diagnosis of thalassaemia.
- Laboratory criteria:
  - Hemoglobin level (Hb) <7 g/dl on 2 occasions, >2 weeks apart (excluding all other contributory causes such as infections), OR
- Clinical criteria irrespective of hemoglobin level:
  - Hemoglobin >7 g/dl with any of the following:
    - Facial changes
    - Poor growth
    - Fractures
    - Clinically significant extramedullary haematopoiesis

Ideally, patients with thalassaemia major should receive leukoreduced packed red blood cell but this is usually not available so packed red cells or if packed red cells is not available whole blood can be transfused.

The target pre-transfusion hemoglobin is in the range of 9.5 to 10.5 g/dL. The post-transfusion hemoglobin should be approximately 12 to 13 and no higher than 15 g/dL. The timing and dose of RBC transfusions can be titrated for the individual patient. Typically, a dose of 8 to 10 mL of RBCs per kg every two to three weeks will maintain the desired hemoglobin levels but in adults, it is easier to order a certain number of units rather than a volume of blood.

9.2. Iron overload-iron chelating agents

Indications of iron chelating agents:

- After the serum ferritin exceeds 1000 ng/mL (1000 mcg/L).
- After transfusion of approximately 20 to 25 units of RBCs.

If available, T2* MRI of liver and heart can be done to assess tissue iron deposition which also guides for iron chelation therapy.

- Three iron chelating agents are available but none are registered in DDA though it has permitted the import of deferasirox and deferiprone in Nepal.

Table 9-1. Iron chelating agents

Name	Deferoxamine	deferasirox	deferiprone
Dose (mg/kg/d)	30-60 5-7 x/week	20-40 once daily	75-100 in 3 divided doses
Route	SC, IM, IV injection	Oral- dispersed tablet give as a suspension in water preferably before a meal	Oral- tablet or liquid
Age group	> 2 years	> 2 years	> 6 years
Side effects	Ocular, auditory, bone growth retardation local reactions, allergy	Gastrointestinal, increased creatinine, increased hepatic enzymes	Gastrointestinal, arthralgia, agranulocytosis/ neutropenia
Monitoring	Audiometry Eyes Kidney function	Creatinine –monthly, more often on starting or dose escalation Urine protein Liver function	-Absolute neutrophil count (ANC) before starting & weekly: (hold if ANC is < 1.5 x 10^9/ L) -hold if fever develops -Symptoms of arthropathy -Liver function
Trade name		Defrijet	Kelfer
Cost (discounted price)		500 mg tablet-Rs. 55.56 250 mg tablet-Rs. 33.34	Box containing 50 capsules of 500 mg- Rs. 530 Box containing 50 capsules of 250 mg- Rs. 277

9.3. Splenectomy

Indications for splenectomy:

- A dramatic increase in transfusion requirement (eg, doubling of transfusion requirement over the course of one year).
- Hypersplenism leading to other cytopenias (leukopenia [eg, absolute neutrophil count below 1000/microL], thrombocytopenia with a platelet count <10,000/microL).
- Symptomatic splenomegaly (eg, abdominal discomfort, early satiety.
- Splenic infarction or splenic vein thrombosis.

Splenectomy should be avoided in children <5 years of age because of a considerably greater risk of fulminant post-splenectomy sepsis.

9.4. Vaccination

Following vaccinations are recommended before splenectomy. The patient should be vaccinated at least 2 weeks prior to splenectomy. These vaccines can be given at the same time in different syringes at different sites. Patients who underwent splenectomy without being given pneumococcal vaccine may still benefit from vaccination post-splenectomy.

a. Pneumoccocal conjugate (PCV13: Prevnar)
b. Pneumococal polysaccharide (PPSV23: Pneumovax)
c. Meningococcal conjugate
d. Haemophilus influenza b conjugate

9.5. Prophylaxis

Penicillin prophylaxis can be used according to the given flow chart to prevent infection after splenectomy.

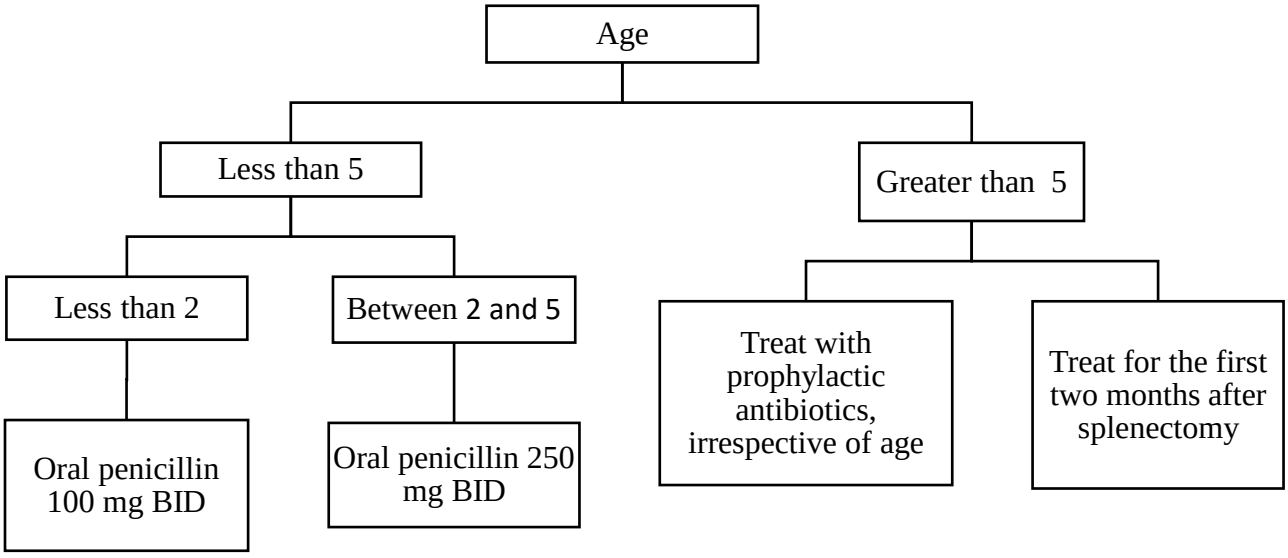

Figure 9-1: Penicillin prophylaxis in thalassemia

9.6. Routine evaluation, monitoring and prevention of complications

- **Anemia**
  - Complete blood count (CBC) -monthly.
- **Iron stores**
  - Serum ferritin two to three times per year.
- **Cardiac status**
  - Cardiac magnetic resonance imaging (MRI) and myocardial T2* MRI can be used to assess cardiac function and myocardial iron deposition if available.

- **Liver**
  - Liver function tests and hepatitis serologies two to four times per year.
- **Bone health**
  - The patient should be encouraged for physical exercise, adequate intake of calcium, vitamin D, and to avoid smoking. .Bone health assessment if bony abnormality (referral to an endocrinologist is advisable).
- **Endocrine status**
  - Thyroid function and glucose at the time of diagnosis and periodically thereafter.
  - Refer to an endocrinologist for delayed puberty and growth retardation.

9.7. Allogeneic bone marrow transplant (BMT)

Allogeneic BMT is the potential curative therapy for patients with thalassemia major.

9.8. Prevention (genetics)

Carrier testing for individuals at risk (including family members, gamete donors, and members of at-risk ethnic groups) is possible. Once both *HBB* pathogenic variants have been identified in a couple at risk, prenatal testing and preimplantation genetic diagnosis are possible. Thus, thalassemia can be prevented in the next generation.

NEPAL THALASSEMIA SOCIETY

Nepal Thalassemia Society is a nonprofit organization. It was registered as an NGO in Kathmandu by some parents and guardians of thalassemia patients in 2060 B.S. Due to difficulty accessing transfusion service, NTS started its own blood transfusion service in 2067 B.S.

It has two main objectives:

- Arrange/provide comprehensive treatment, prolong life and inspire each patient to be competitive in their life;
- Make people aware of thalassemia, raise public awareness and stop the birth of thalassemia.

NTS is a member of Social Welfare Council of Nepal and also voting member of Thalassemia International Federation (TIF) Cyprus from the beginning of the society. Now, its clinic (Thalassemia Daycare Center) is running with help of 3 doctors (including a clinical hematologist, volunteer), experience retired nurse and a BMLT lab technologist where it provides free blood, blood transfusion service and doctor consultation. Besides, it has two other senior doctors who are supporting from outside clinic. There are 225 registered patients where 135 patients are regularly receiving treatment from the center. In an individual basis, some extra poor patients are getting free iron chelation.

FURTHER READING

- National Guideline for Sickle Cell Disease and Thalassaemia Management, 2074 (Ministry of Health, Department of Health Service, Epidemiology and Disease Control Division, Teku, Kathmandu).
- A handbook on Sickle Cell Disease (Sickle Cell Institute Chhattisgarh, Raipur, India)
- Ghosh K, Colah R, Manglani M, Choudhry VP, Verma I, Madan N, Saxena R, Jain D, Marwaha N, Das R, Mohanty D. Guidelines for screening, diagnosis and management of hemoglobinopathies. Indian journal of human genetics. 2014 Apr;20(2):101.
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