Management and Prognosis of Sickle Cell Disease

INTRODUCTION
Sickle cell disease is a group of disorders that affects hemoglobin ((the molecule in red blood cells that delivers oxygen to cells throughout the body)). People with this disorder have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent, shape. Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels, leading to local tissue hypoxia that accentuates the pathologic process.

Cardinal features of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4 to 6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly, and, in infants, pain and swelling of the hands and feet (eg, hand-and-foot syndrome or dactylitis).

Usual clinical signs and symptoms of SCD include chronic anemia; fever; pallor; arthralgia; sclera icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart; and hematuria.

Vaso-occlusive phenomena and hemolysis are the clinical hallmarks of sickle cell disease (SCD):

- **Vaso-occlusion** results in recurrent painful episodes (previously called sickle cell crisis) and a variety of serious organ system complications that can lead to life-long disabilities and even death.
- **Hemolysis** of red blood cells (RBC) causes chronic anemia and pigment gallstones.

**Acute complication of SCD:**

- fever and infection
- stroke
- acute chest syndrome: is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
- Priapism
- Acute episodes of pain can be precipitated by infection, dehydration, stresses, and sudden temperature changes. The most common type is vasoocclusive pain, which is manifested by pain over the involved areas without change in Hb.
- Aplastic crisis is characterized by acute decrease in Hb with decreased reticulocyte count manifested as fatigue, dyspnea, pallor, and tachycardia.
- Acute splenic sequestration: The trapping of sickled RBCs by the spleen leads to hypotension and shock, and can cause sudden death in young children.
Chronic complications include:

- pulmonary hypertension
- bone and joint destruction
- ocular problems
- cholelithiasis
- cardiovascular abnormalities
- depression
- hematuria and other renal complications
- Children experience delayed growth and sexual maturation

Goals of Treatment:

The goals are to reduce hospitalizations, complications, and mortality

Prevention of complications:

- **INFECTION PREVENTION:**

  Individuals with SCD are highly susceptible to bacterial and viral infections, largely due to functional asplenia that develops early in childhood.

  The two major measures for preventing infection in individuals with SCD are immunization for all patients, and prophylactic penicillin for all young children (eg, <5 years of age).

  A review of the patient’s immunizations should be performed at every medical contact to ensure that they are up to date, and parents of young children should confirm that prophylactic penicillin is being used appropriately.

  Parents of infants and children with SCD should also be instructed regarding early recognition of infection, which may present with isolated fever. A formal plan should be created for seeking medical attention for a predetermined elevated temperature (>38.5°C or >101.5°F).

  Adults should also have a clear plan for seeking medical attention for signs of infection. Fever should be considered a medical emergency requiring prompt medical attention, blood culture, and treatment with antibiotics.

  Immunizations are a cornerstone of infection prevention in SCD. Children with SCD should receive all routinely recommended childhood vaccines, including those against **Streptococcus pneumonia**, **seasonal influenza**, **Neisseria meningitides**, **hemophilic influenza 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.

  Vaccination has led to a decrease in the incidence of invasive pneumococcal disease in children with SCD. All children with SCD should be immunized with both PCV13 and PPSV23.

  The pneumococcal conjugate vaccine (PCV13 or, if not available, PCV7) can be administered as early as six weeks of age and elicits an effective immunologic response during the first two years of life. The pneumococcal polysaccharide vaccine (PPSV23) includes a greater number of serotypes but is not immunogenic in children younger than two years of age.
The pneumococcal conjugate vaccine (PCV13) is administered as four doses before 23 months of age on the same schedule as is routinely given to all children. The first three doses are administered at two, four, and six months of age. The first dose can be given as early as six weeks of age. A minimum of four weeks between the three doses is acceptable. The fourth dose should be given at 12 to 15 months of age but at least two months after the third dose. Children who had been fully immunized with PCV7 should receive a supplemental dose of PCV13.

The pneumococcal polysaccharide vaccine (PPSV23) is given as two doses: the first dose at 24 months of age (at least eight weeks after the last dose of PCV13). A second dose three to five years after the first dose of the pneumococcal polysaccharide vaccine also is recommended.

In patients younger than five years of age who did not receive the full complement of pneumococcal immunization based upon the above schedule, catch-up doses of vaccines should be given.

The timing and number of doses depend upon the number of total doses of the conjugate and/or polysaccharide vaccines that have been given by five years of age.

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. Standard influenza vaccination is also protective against the H1N1 strain of influenza.

A two-dose series of quadrivalent meningococcal conjugate vaccine (MCV4; Menactra or Menveo) may be given at least two months apart, starting between 2 and 10 years of age. A single booster dose of MCV4 is advised every five years thereafter. Children aged ≥10 years should receive the serogroup B meningococcal (MenB) vaccine.

Children with SCD should receive all standard childhood vaccinations, including those against hepatitis A and B; measles, mumps, and rubella; varicella; rotavirus; Haemophilus influenza; tetanus, diphtheria, and pertussis; and poliovirus in countries where it is still endemic.

Most of these vaccinations should be updated periodically during adulthood, inactivated virus vaccines are preferred.

**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 penicillin allergiesshould receive prophylactic erythromycin

Oral:(Infants and Children: 4 months to <3 years: 125 mg twice daily)

(Children 3 to 4 years: 250 mg twice daily)

**Prevention of Acute chest syndrome:**

Both hydroxyurea and chronic transfusion therapy decrease the frequency of acute painful vaso-occlusive episodes and acute chest syndrome.
**Hydroxyurea** is the only treatment that has been shown to decrease the incidence rate of ACS episodes.

Infants ≥6 months, Children, and Adolescents: Limited data available in infants and children <2 years: Initial: Oral: 20 mg/kg/dose once daily; monitor blood count every 2 weeks; may increase by 5 mg/kg/day every 8 weeks until mild myelosuppression is achieved or if painful crises occur (as long as myelosuppression acceptable); maximum daily dose: 35 mg/kg/day.

Chronic transfusion therapy is started when the response to hydroxyurea is inadequate.

Hydroxyurea titrated up to 30 mg/kg or an absolute neutrophil count of 2000/microL should be administered to all adults with a history of ACS regardless of genotype, unless contraindicated (ie, renal failure).

Hydroxyurea therapy should be considered for all adults with HbSS who are not on a chronic transfusion program based on data showing improved mortality with hydroxyurea use.

**Chronic transfusion therapy**: scheduled transfusion therapy has been performed to reduce the incidence of ACS episodes in adults with SCD.

initiate chronic transfusion therapy only in adults who have had two or more episodes of moderate to very severe ACS in the past 24 months despite maximal hydroxyurea therapy

**Hematopoietic cell transplantation**: while curative, is not part of standard practice for adults with SCD due to high toxicity associated with myeloablative regimens.

a non-myeloablative conditioning regimen in adults with SCD is well-tolerated, achieves stable, mixed donor-recipient chimerism, and improves clinical SCD parameters, including episodes of ACS.

**GENERAL PRINCIPLES AND GUIDELINES**

Individuals with SCD should be seen regularly by the clinician and treatment team as part of a comprehensive health care maintenance program, Routine office visits are used to educate the affected individual and family about SCD, infection prevention, pain management strategies, and anticipatory guidance for possible complications (eg, splenic sequestration, avascular necrosis of the femoral head, stroke and leg ulcers).

In addition, obtaining steady state laboratory values (eg, hemoglobin, reticulocyte count, white blood cell count, pulse oximetry readings) during routine visits will provide standards for comparison during clinical exacerbations, because these values are often abnormal at baseline.

Compared with patients with SCD (i.e. hemoglobin SS [Hb SS]), those with variant sickle cell syndromes (hemoglobin SC, sickle cell-beta thalassemia) may have reduced susceptibility to serious infections, depending on the disease severity. The risk of infection is proportional to disease severity due to the resulting effect on splenic function. Those with HbSC disease are less likely to develop invasive bacterial infection than those with HbSS. Because they maintain some splenic function during early childhood.
Among patients with sickle cell-beta thalassemia, severity of the disease varies with the production of hemoglobin A (HbA), and management varies accordingly:

• Patients with sickle cell-beta0 thalassemia (HbS-beta0 thalassemia) have a clinical course similar to patients with HbSS disease, with 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-beta+ thalassemia (HbS-beta+ thalassemia) produce variable amounts of HbA and in general have less severe SCD complications. In general, they are treated in a manner similar to those with HbSC.

**Treatment of complications:**

Several treatments are available for the complications of SCD, such as pain medications for vaso-occlusive events and antibiotics for infection.

A life-long cure for SCD is available only through hematopoietic stem cell transplantation. This treatment is primarily limited to children and adolescents, with use of a matched sibling donor and a myeloablative conditioning regimen.

• **INFECTION MANAGEMENT**

Infection is a frequent complication of SCD, and historically it has been the major cause of death in children.

Fever may be the first indication of a serious bacterial infection, and as such should be considered a medical emergency. Patients should seek prompt medical attention and be rapidly evaluated for a temperature >38.5°C.

The evaluation should include a brief history for localizing symptoms and an abbreviated physical examination focused on hemodynamic stability, signs of localized or generalized infection, splenic size, and evidence of stroke.

.Blood cultures and complete blood count with differential and reticulocyte count should be obtained.

Empiric parenteral antibiotics should be started as soon as possible, ideally within 60 minutes of triage. Evaluation for pneumonia is important; however, antibiotics should not be delayed while awaiting chest radiography.

Parenteral ceftriaxone as a single dose of 50 to 75 mg/kg, (maximum dose 2 g), the dose of which is increased (dose 75 to 100 mg/kg, maximum dose 2 g) in regions with a high prevalence of antibiotic resistant S. pneumoniae

In patients who are hemodynamically unstable or suspected to have meningitis, vancomycin is added (dose 15 mg/kg IV, maximum dose 1 g)

For patients who are allergic to cephalosporins, clindamycin can be used (dose of 10 mg/kg every six to eight hours; maximum daily dose 2.7 g for children; 4.8 g for adults).
Investigation of the infection source should be performed to ensure appropriate management of the infection.

A type and crossmatch is obtained if extreme pallor, severe pulmonary or neurologic symptoms, or significant acute increase in spleen size are present.

Patients who are more likely to have invasive bacterial infection should be hospitalized. We use the following criteria (one or more of the following) for inpatient admission:

1. Age <two years with hemoglobin SS (HbSS) or sickle cell-β0 thalassemia.
2. Temperature >40°C.
3. White cell count >30,000/microL or <5000/microL, Hemoglobin 2 grams/dL or more below the individual's steady state value.
4. Previous invasive bacterial infection, particularly with S. pneumoniae.
5. Indwelling central venous line.
6. Signs of systemic toxicity, meningitis, or hemodynamic instability.
7. Other complications of SCD (eg, acute chest syndrome, splenic sequestration) are present that would benefit from inpatient management.

In addition, other indications for hospitalization are treatment with either vancomycin or clindamycin (because of their shorter half-life); concern about inability to contact the family or ability to reliably return if the culture becomes positive or the patient's condition worsens; and the presence of other complications of SCD (eg, pain requiring parenteral opioids) that require inpatient management.

Inpatient management includes initiation of hemodynamic monitoring, oxygen saturation monitoring, supportive care (if needed), continuation of empiric antibiotic therapy, venous thromboembolism prophylaxis (age dependent), and readjustment of antibiotics when culture results are available.

- **LEG ULCERS**

The clinical characteristics and natural history of skin ulcers in individuals with SCD differ from those seen in individuals with other hemolytic anemias. Severe pain at the wound site is disproportionately greater in SCD than in other populations.

The best approach to leg ulcers is prevention, which includes attention to properly fitting shoes and immediate treatment for early signs of skin injury.

If a patient develops a leg ulcer, we routinely use lower extremity Doppler to evaluate for deep vein thrombosis (DVT). Leg ulcers in patients with SCD are associated with a DVT, likely due to lower extremity edema.

In addition, since pulmonary hypertension is associated with the development of lower extremity ulcers, we evaluate for pulmonary hypertension with a transthoracic Doppler echocardiography and obtain a complete blood count (CBC), lactate dehydrogenase (LDH) level, and serum chemistries.

Management of large skin ulcers requires a multidisciplinary team. Although many systemic and local therapies have been examined, the mainstays of therapy are wound care, compression, and SCD-based therapy with hydroxyurea or chronic blood transfusion.
Components of management may include the following:

- Immediate attention to the pain: Many providers use systemic opioids. Topical opioids also have been examined and found to relieve pain and facilitate healing. Topical opioids also decrease local fluid extravasation.

- Local edema must be minimized with rest, lower extremity elevation, and compression bandages. In some cases diuresis is also appropriate.

- Bedrest, though difficult to comply with, is essential for healing of large and/or recalcitrant ulcers.

- Therapeutic debridement is important in order to remove fibrotic tissue and stimulate healing.

Initially refer the patient to a wound care specialist for debridement, dressing changes and, if necessary, topical antibiotics. Wet to dry dressings and Duoderm hydrocolloid dressings may also facilitate healing.

- Infections require treatment, but antibiotics are often not helpful and should be used appropriately.

- Repeated blood transfusion therapy accelerates wound healing and is often a core therapy.

  {Alternatively, hydroxyurea may be beneficial, even though hydroxyurea-related skin ulcers have been reported. Patients can be managed initially with hydroxyurea and transitioned to chronic transfusion, or treated with chronic transfusion initially, depending on other comorbidities and patient factors.}

- Grafts may be necessary, but they have a very high failure rate and should be used conservatively.

In addition to the specific therapies listed above, many patients with SCD and skin ulcers have multiple other problems that impair wound healing, including malnutrition, vitamin D and nutritional deficiencies, pulmonary hypertension, and depression. These confounding factors also need to be addressed.

There are multiple therapies that may be beneficial but remain unproven, including Apligraf (a skin equivalent), topical sodium nitrite 2% cream, RGD peptide dressings, and topical Timolol. We do not routinely use these therapies, but rely on pain relief, bedrest, transfusion therapy, local wound care, and when necessary, consultation with chronic ulcer programs.

Acute chest syndrome management:

- **Adequate and immediate pain control**
  Pain control with parenteral opioids typically delivered by patient-controlled analgesia is necessary during ACS episodes in adults.
  Careful monitoring is necessary to avoid over-sedation, which can lead to depressed respiratory rate, poor inspiration, hypoxemia, and worsening vaso-occlusion and AC

- **Fluid management to prevent hypovolemia**
The typical regimen is 1.5 times maintenance fluids of D5 in one-half normal saline for the first 24 to 48 hours. Fluid balance should be monitored frequently to avoid fluid overload and pulmonary edema, which can worsen the ACS process.

- **Supplementary oxygen and incentive spirometry**
  standard practice includes ongoing use of incentive spirometry when a patient is admitted to the hospital and develops ACS.

  Incentive spirometry should be encouraged with 10 maximal breaths every two hours while awake to prevent ACS during vaso-occlusive pain episodes.

  Oxygen needs to be delivered to adults with ACS who have low oxygen saturation (SaO2) or low oxygen partial pressure (PaO2).

  For moderate to severe episodes involving >1 lobe and with an oxygen requirement ≥4 liters nasal cannula to maintain PaO2 >70 mmHg (approximately corresponding to an oxygen saturation of 92 percent).

- **Bronchodilator**
  Despite the lack of high quality evidence, bronchodilators are commonly used.

  Potentially, bronchodilators are more effective during an ACS episode in adults with asthma. Use of bronchodilators should also be considered in the setting of progressive respiratory distress occurring in ACS.

- **Blood transfusion**
  IS the mainstay of acute treatment is transfusion therapy, Mild episodes require no transfusion, moderate episodes require simple or exchange transfusion, and severe episodes mild or developing ACS with simple transfusion should increase the hemoglobin up to 10 g/dL.

  Exchange transfusion performed by automated erythrocytapheresis allows for the rapid transfusion of large amounts of blood (eg, 6 to 8 units of packed red blood cells for a typical adult), effectively decreasing hemoglobin S percentage while avoiding the hyperviscosity that may occur when hemoglobin levels are raised above 11 g/dL.

  The preferred modality of exchange transfusion is erythrocytapheresis to achieve a hemoglobin S percentage <30 percent, and we target an end-hemoglobin of 10 g/dL.

- **Antibiotics**
  The most common organisms are atypical bacteria (Chlamydia and Mycoplasma) along with Streptococcus pneumonia and Haemophilus influenzae, and therefore a third generation cephalosporin along with a macrolide, or a fourth generation fluoroquinolone are typical regimes.

  As an example, we administer cefotaxime 1 to 2 grams IV every eight hours plus azithromycin 500 mg orally or IV once daily for seven days or moxifloxacin 400 mg orally or IV for seven days.
Ceftriaxone should be used with caution as drug-induced immune hemolysis has been associated with ceftriaxone in children with SCD.

Bronchoscopy: Due to the invasiveness of bronchoscopy, this procedure is reserved for atypical cases or cases refractory to conventional therapy.

- **Glucocorticoids**
  
The use of glucocorticoids is not standard practice for the management of ACS in adults with SCD since the phenomenon of rebound vaso-occlusion after a course of steroids has been confirmed.

- **Venous thromboembolism (VTE) prophylaxis**
  
  All adult patients with ACS should receive VTE prophylaxis with low molecular weight heparin, unfractionated heparin, or fondaparinux.

  In contrast, we do not use routine thromboprophylaxis for VTE in hospitalized children with SCD (ie, those less than 21 years).

  **Prophylaxis may be done with one of the following:**

  - One of the low molecular weight (LMW) heparins (eg, enoxaparin; dalteparin, tinzaparin); with the dose based on the agent and indication.
  - Low dose unfractionated heparin (eg, 5000 units SQ three times a day).
  - Fondaparinux (eg, 2.5 mg SQ daily).

- **PAIN MANAGEMENT:**
  
  Acute vaso-occlusive pain episodes are one of the most frequent reasons for individuals with SCD to seek medical attention, and chronic pain affects a large number of these individuals.

  There are a number of issues related to the treatment of SCD pain that differ from other acute and chronic pain syndromes. These include common misperceptions about the severity of pain, the need for opioid analgesia for the majority of patients, the need to evaluate for SCD complications associated with pain (eg, avascular necrosis of the hip), and the avoidance of certain medications such as meperidine and ketorolac.

  Blood transfusion is not used for uncomplicated pain episodes in the absence of other complications.

**Splenic and hepatic sequestration:**

Splenic sequestration is a potentially life-threatening complication of SCD that requires admission to the hospital for maintenance of hemodynamic stability.

**Splenic sequestration in SCD is characterized by the following four features:**

  - Splenic enlargement, often tender.
  - A drop in hemoglobin concentration of at least 2 g/dL.
Thrombocytopenia.

Reticulocytosis.

Splenic sequestration is commonly observed in infants and children, including those as young as two months of age. Less commonly, acute splenic sequestration episodes may occur in adolescents and adults, particularly those with SCD-SC.

The primary concern in the event of a splenic sequestration episode is hypovolemic shock resulting from a disproportionate amount of the intravascular blood volume being sequestered in the spleen because of ensnared red and white blood cells. Hence, management should be directed at maintaining the individual in a euvoelemic state.

The optimal management of an acute splenic sequestration episode in adults is based on the following principles:

- A high index of suspicion when an individual presents with a sudden drop in hemoglobin, thrombocytopenia, reticulocytosis, and an enlarged spleen.

- Assessment of volume status and immediate intravenous fluid resuscitation if needed, with the goal of maintaining the individual in a euvoelemic state. This may require administration of isotonic solution.

When the individual is hypovolemic and is symptomatic from anemia, a simple blood transfusion therapy should be considered. However, caution should be used when transfusing the individual, as the blood trapped in the spleen is still available to re-enter the circulation.

Accordingly, following such transfusion the individual's hemoglobin may rise acutely to levels that result in hyperviscosity syndrome.

To decrease the likelihood of hyperviscosity syndrome occurring after a simple blood transfusion; we typically transfuse the individual with approximately 50 percent of what we would commonly transfuse. Thus, instead of transfusing the adult individual with two units of blood, we transfuse a single unit of blood or calculate (and deliver) the amount of blood needed to get the individual back to their baseline level and re-evaluate the clinical status after transfusion.

The natural history of splenic sequestration in infants and toddlers with SCD is well documented, with a reasonable proportion having a second event within 12 months of the first event. In adults with SCD we would manage them in similar way.

- Future management should include education about self-palpation of the spleen and instructions on what to do in the event of an enlarging spleen.

- After consideration of risks and benefits, there should be a discussion of the potential removal of the spleen in a non-acute setting.
• Institution of regular blood transfusion therapy to prevent subsequent episodes of acute splenic episodes is not indicated and has not proven to be of benefit.

**NUTRITION**

It’s recommended to use the following nutritional supplement in SCD patients:

• Folic acid is given to all individuals in an oral dose of 1 mg daily.

{However, some clinicians may reasonably omit folic acid supplementation for patients who have sufficient dietary intake, especially in settings where grains and cereals are routinely supplemented}.

• We use a daily multivitamin without iron for all of our patients.

{This replaces some of the vitamins and micronutrients commonly reported to be deficient in these individuals, including zinc, vitamin D, vitamin E, vitamin C, vitamin A, magnesium, selenium, carotenoids, and flavonoids. Excessive iron stores and oxidative injury may contribute to the depletion of antioxidant vitamin}.

• We screen all infants with SCD for risk factors for iron deficiency, including those not receiving transfusions, during the first two years of life. We also use laboratory screening at one year of age.

{All children with SCD who have evidence of iron deficiency anemia should be treated because iron deficiency has a negative effect on neurodevelopment}.

• Non-transfused young women with risk factors for iron deficiency or those who practice breast feeding also should undergo screening and treatment. In patients with iron deficiency, it is important to establish the cause.

• For individuals found to be vitamin D deficient, additional supplementation with oral vitamin D and calcium is appropriate.

{Vitamin D deficiency is under-recognized and undertreated in the SCD population; this deficiency may contribute to osteopenia and osteoporosis}.

**ROUTINE EVALUATIONS AND TREATMENTS:**

We screen for the following:

• **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.
In children ≤16 years of age with hemoglobin SS or hemoglobin S-beta thalassemia that produces no hemoglobin A, referred to as S beta thalassemia zero, cerebral blood flow should be evaluated by transcranial Doppler (TCD) annually, because children at risk for strokes can be identified with this technique and the incidence of stroke can be reduced by the use of regular blood transfusion therapy aimed at maintaining the maximum hemoglobin S level at less than 30 percent.

We also screen individuals with any sign of cognitive/neurologic dysfunction (eg, poor school performance, headaches, concerns expressed by family members) for silent infarcts using magnetic resonance imaging (MRI).

In contrast, children with hemoglobin S beta+ thalassemia and hemoglobin SC disease do not require TCD screening. TCD measurements are lower in adults with SCD compared with children so we do not recommend TCD screening in individuals >16 years of age.

Optimal intervals for TCD measurements have not been formally evaluated, but TCD measurements should be started at two years of age and performed annually.

Retinal evaluation is begun at 10 years of age and continued routinely to detect early proliferative sickle retinopathy.

Asthma is common in children with SCD. We perform a baseline pulmonary evaluation that includes at least assessment of severe recurrent wheezing, shortness of breath with exercise, or persistent cough as part of routine review of systems with ongoing health maintenance visits.

We also perform spirometry in asymptomatic children in intervals of one to two years, starting when they are able to perform the spirometry and continuing until adulthood. For individuals with a positive history or abnormal spirometry results, we perform spirometry at least annually, and more frequently if respiratory symptoms change.

For individuals with evidence of respiratory symptoms, but no obstruction on pulmonary function testing, we may also measure lung volumes.

we take a thorough history of respiratory symptoms in all patients

For symptomatic patients, we have a low threshold for evaluation of pulmonary hypertension risk. It is important to note that symptoms of Pulmonary hypertension are variable; patients may report chronic dyspnea, chest pain, presyncope, or exercise intolerance; or they may gradually limit activities without recognizing specific symptoms.

It is also important to note that children presenting with acute or chronic respiratory symptoms should be evaluated for more common conditions, such as asthma and acute chest syndrome, in addition to evaluation for pulmonary hypertension.
• Priapism in Boys and men with SCD should be educated about priapism and asked questions about the presence of priapism; this is usually not volunteered because of the sensitivity of the issue.

• Identifying renal disease is important because individuals with sickle cell disease hyperexcrete creatinine, which may mask renal impairment.

Pre-conception counseling and screening for red blood cell alloantibodies is provided to individuals of childbearing age who are planning a pregnancy. Referral of a partner of unknown SCD status for hemoglobinopathy screening is appropriate prior to conception.

• Evaluation for leg ulcers and education concerning their prevention are important, particularly in areas with warm climates.

• We assess contributors to bone health including calcium intake, vitamin D status, and bone density at 12 years of age, and perform a screening physical exam for avascular necrosis. We repeat vitamin D screening annually and bone density testing every one to three years.

• We measure height and weight in children and adolescents, and weight in adults, because children with SCD may show delayed growth trajectories. If children have decreased growth trajectories, we evaluate nutritional and environmental factors as potential contributors. Growth disturbances are common in sickle cell disease and have multiple etiologies that can be corrected.

Correction of nutritional deficiencies may be beneficial, particularly zinc, which is associated with improved linear growth and weight gain. An increased metabolic rate resulting in elevated resting energy expenditure and increased caloric requirements is common and may be improved by caloric intake or decreasing energy expenditures. Transfusion therapy or hydroxyurea decreases metabolic rate and improves growth.

Finally, monitoring growth and weight velocity may uncover growth hormone disturbances, which are responsive to growth hormone replacement.

These routine evaluations and treatments should be tailored for individual patients when co-morbidities are present (eg, chronic renal insufficiency, interstitial lung disease).

**Commonly used agents for prevention and treatment of complications:**

The use of hydroxyurea is a mainstay in the overall management of individuals with SCD, since it reduces the incidence of acute painful episodes and hospitalization rates, and prolongs survival.

Pharmaceutical-grade L-glutamine is an oral medication approved in 2017 to reduce acute complications in children >5 years and adults with SCD. The mechanism is unknown but is thought to involve an antioxidant effect. While hydroxyurea is first
line therapy, L-glutamine could provide benefit in patients treated with hydroxyurea with a suboptimal response or those not treated with hydroxyurea due to intolerance or lack of perceived benefit.

Hematopoietic cell transplantation (HCT) is the only available curative option in individuals with SCD, and a discussion of the risks and benefits of HCT should be offered to all individuals with SCD.

Blood transfusions are used to treat and prevent complications of SCD, including preparation for surgery; treatment of symptomatic anemia, acute stroke, multiorgan failure, and acute chest syndrome; and prevention of stroke, acute chest syndrome, and recurrent priapism.

- AVOIDANCE OF G-CSF

The use of granulocyte colony-stimulating factor (G-CSF) in individuals with SCD and variant sickle cell syndromes (eg, HbSC, HbS-beta+ thalassemia) has been associated with sickle cell crisis and multiorgan failure.

G-CSF may also play a role in the acute chest syndrome and the complications associated with it. So do not use G-CSF administration in individuals with SCD or variant sickle cell syndromes.

However, there may be a rare case in which the potential benefits of G-CSF therapy outweigh the risks (eg, treatment of chemotherapy-induced fever with sepsis), and the judicious use of G-CSF may be justified.

In contrast to those with sickle cell syndromes, individuals with sickle cell trait may receive G-CSF.

References:

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