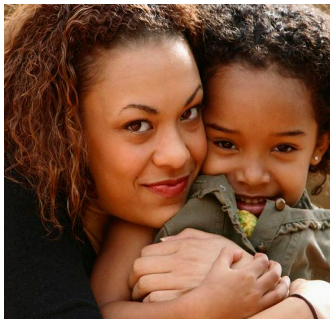


Sickle Cell *Disease Education*

INDIANA HEMOPHILIA & THROMBOSIS CENTER, INC.

Care of patients with sickle cell disease for primary care providers and emergency room personnel

Disclaimer: This handbook was developed by the Indiana Hemophilia and Thrombosis Center using critical review and analysis of available published scientific information. The guidelines were developed using the best available evidence. While the information and recommendations provided are believed to be true and accurate at the time of publication, the authors/IHTC have no legal responsibility for the contents and use of the information.

For issues related to a specific patient's care, medical care providers are advised to seek further required information from the 2014 NHLBI Evidence Based Management Guidelines or other sources of published data.

If you would like copies of handouts that are referenced within the handbook, please contact the IHTC directly.

Table of Contents

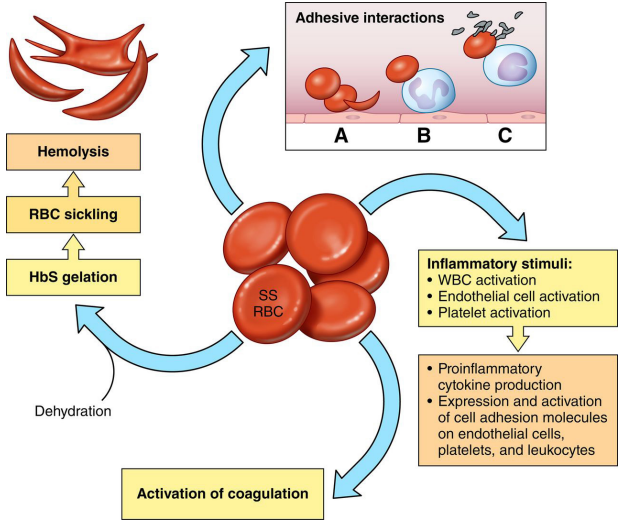
Background About Sickle Cell Disease and Making the Diagnosis

Sickle cell disease is the most common inherited hematologic disorder in the world, primarily affecting people of African, Mediterranean, East Indian or Latin American descent. Approximately 8% of the African-American population carries the sickle cell trait. Sickle cell disease affects about 1 in 500 African-Americans. An estimated 100,000 Americans are living with sickle cell disorders. An estimated 250,000 infants are born annually in sub-Saharan Africa with a sickling hemoglobinopathy.[1,2]

Sickle cell diseases are a group of inherited genetic disorders characterized by a predominance of hemoglobin S (HbS) which results in a chronic hemolytic anemia, increased susceptibility to infections, end-organ damage and episodes of vaso-occlusion causing both acute and chronic pain.

The sickle hemoglobinopathies include, but are not limited to:

- Sickle cell anemia (homozygous HbSS)
- Hemoglobin SC disease (HbSC)
- Hemoglobin SD disease (HbSD)
- Hemoglobin SO-Arab (HbSO-Arab)
- Sickle beta thalassemia syndromes (HbSβ^0 thalassemia which behaves like HbSS disease and HbSβ^+thalassemia, which is a mild form of sickle cell disease because of the presence of HbA)



Source: Telen MJ. Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease. Blood 2016;127(7):810-9. Reproduced with permission of AMERICAN SOCIETY OF HEMATOLOGY in the format Republish or display content in a Book via Copyright Clearance Center.

Previous Image Caption:

The sickle red blood cell is a source of multiple pathophysiologic pathways. Red cells with predominantly HbS become rapidly dehydrated, which increases the propensity of HbS to polymerize when deoxygenated. Pharmacologic reagents that prevent dehydration may therefore also reduce HbS polymerization and hemolysis. Altered lipid sidedness (phosphatidylserine exposure) may play a role in sickle red blood cell adhesion and also promote activation of coagulation. Oxidative damage of red cell membrane proteins likely contributes to altered cell elasticity. Abnormal adhesive properties lead to sickle red blood cell adhesion to endothelial cells (A), sickle red blood cell adhesion to neutrophils (B), and adhesive interactions that result in heterocellular aggregate formation involving sickle red blood cell, monocytes, and platelets (C). Abnormal intracellular signaling increases the activation state of red cell adhesion molecules, and increased adhesive interactions then lead to abnormally active cell-cell signaling, which leads to activation of both other blood cells and endothelial cells. Both sickle red blood cell and hypoxia/reperfusion also lead to activation of inflammatory pathways involving both mononuclear and polymorphonuclear leukocytes. Platelet activation also contributes to inflammatory pathways as well as activation of coagulation.[3,4]

Complications of sickle hemoglobinopathies result from the inability of the rigid, sickled cells to pass through the microvasculature. The changes occurring in the red blood cells lead to hypoxia of the tissues and potential or actual tissue damage. Most commonly, this is manifested clinically as the onset of the acute sickle cell painful vaso-occlusive episode.

Macrovascular occlusion may also occur, such as in the cerebral arteries (stroke), usually in children with HbSS or HbSβ^0thalassemia. Ischemic stroke can affect adults and children with other genotypes, though to a significantly lesser degree.[5]

Other complications of sickle cell disease include splenic infarction, splenic sequestration, and increased risk of infection. Adults have progressive end-organ damage, particularly of the lungs and kidneys, and there are increased risks when women with sickle hemoglobinopathies become pregnant.

All of the manifestations associated with sickle cell anemia (HbSS) or HbSβ^0thalassemia can occur in HbSC and HbSβ^+thalassemia. Patients with HbSC disease and HSβ^+thalassemia tend to have a milder clinical course, with the exception that sickle retinopathy and avascular necrosis of the hip are more common in those groups.[6]

Patients with sickle cell disease and their families must cope with the impact of recurrent and unpredictable pain episodes, chronic pain, chronic anemia and easy fatigue which cause absenteeism from school and work, hospitalizations, and increase likelihood of early death. The prognosis is uncertain and complications are variable and often not easy to objectively measure (as in vaso-occlusive pain). Complications are often inadequately managed due to attitudes among health care workers and their unfamiliarity with the disease.

Appropriate management begins with definitive diagnosis by hemoglobin electrophoresis. Treatment requires a multi-disciplinary approach with adequate therapy for pain, infections, and other acute complications, as well as attention to psychosocial and spiritual needs.

Making the Diagnosis – Newborn Screening Results and Beyond

A patient is considered to have a sickle hemoglobinopathy if HbS is the predominant hemoglobin produced.

Sickle cell trait is not considered a disease because people with sickle trait make more HbA than HbS (typically in a 60% HbA, 40% HbS distribution). The HbS gene is inherited from one parent and the HbA gene is inherited from the other resulting in the carrier state (AS).

Sickle hemoglobinopathies include inheritance of the gene for HbS from one parent and one of the following:

1. A gene for HbS from the other parent resulting in (HbSS)
2. A gene for another abnormal hemoglobin from the other parent resulting in (HbSC, HbSD Punjab, HbSO-Arab, HbS Leopore, or HbSE)
3. A gene that limits HbA production from the other parent resulting in (HbSβ^+thalassemia or HbSβ^0thalassemia). In HbSβ^+thalassemia there is some production of HbA, and in HbSβ^0thalassemia there is no HbA production

All of these conditions are accompanied by health problems.[7]

Table 1. Newborn Screen Results for Common Hemoglobinopathies

Newborn Screening Result	Interpretation
F, A	Normal
F, A, S	Sickle cell trait
F, S	SS, Sβ^0 thalassemia or S-HPFH
F, S, C	HbSC disease
F, S, A	Sickle β^+ thalassemia
F, A, S, Barts	Sickle cell trait with *a* thalassemia trait
F	β-thalassemia major
β thalassemia trait is not diagnosed in the newborn period with most current newborn screening techniques. A-HbA; C-HbC; F-Fetal Hb; S-HbS; HPFH- hereditary persistence of Fetal Hb.	
Source: McCavit TL. Sickle cell disease. Pediatrics in Review 2012;33(5):195-206[7]	

Table 2. Typical Laboratory Findings in Sickle Cell Disease

Genotype	Hb (g/dL)*	HbS (%)	HbA (%)	HbA_2 (%)	HbF (%)	HbC (%)
SS	6-9	>90	0	<3.5	<10	0
$S\beta^0$-thalassemia	7-9	>80	0	>3.5	<20	0
$S\beta^+$-thalassemia	9-12	>60	10-30	>3.5	<20	0
SC	9-14	50	0	<3.5	≤1.0	45
AS (sickle cell trait)	normal	≤40	>60	<3.5	≤1.0	0

*The hemoglobin values in this table apply in the absence of a blood transfusion in the last 4 months, are not absolute, and are applicable to adults and children only (not newborns). Hb - hemoglobin; HbS - sickle hemoglobin; HbA - normal adult hemoglobin; HbA2 - minor variant of adult hemoglobin; HbF - fetal hemoglobin; HbC - common variant that causes manifestations of SCD when paired with HbS.

Source: National Heart, Lung, and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014. 2014. Available at: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report%20020816.pdf.[8]

Health Maintenance for Patients with Sickle Cell Disease

Early identification and improved supportive care, including penicillin prophylaxis, appropriate vaccinations, fever education and routine transcranial Doppler screening have improved survival for pediatric patients with sickle hemoglobinopathies. Nearly 95% of infants born with sickle cell disease in developed countries in 2017 are expected to survive into adulthood, increased from 60-70% 40 years ago.[9]

Regular visits with primary care providers and hematologists are critical so that family members and patients can be educated about sickle cell disease complications and early identification of possible life-threatening complications, like splenic sequestration (see Chapter 6), acute chest syndrome (Chapter 5) or sepsis (Chapter 3). Guidelines for visit frequency and recommended laboratory evaluations and screening exams can be found in Tables 1 and 2 on the next page.

Table 1. Pediatric Care Guidlelines

Age	Visit Frequency	Laboratory Evaluations	Screening Tests/ Education	Medications/ Vaccines
0-24 months	Q3-4 months**	• CBC/retic at every visit • Renal and Liver function tests once in the second year of life	• Fever • Spleen Palpation • Pain Management • Stroke Risk Education*	• Penicillin prophylaxis • Hydroxyurea* (not before age 9 months) • Complete PCV13, Hib, Menveo series • Annual Influenza Vaccination
24-60 months	Q3-6 months**	• CBC/retic at every visit • Renal and Liver function tests annually	• Transcranial Doppler*$ • Fever • Spleen Palpation • Pain Management • Stroke Risk Education* • Developmental Screen	• Penicillin prophylaxis • Hydroxyurea* • Pain medications (Ibuprofen, Opioid) as needed • Annual Influenza Vaccination • PPSV23 at age 2 and 5 years
5-10 years	Q3-6 months**	• CBC/retic at every visit • Renal and Liver function tests annually • Urinalysis annually	• Transcranial Doppler*$ • Fever • Spleen Palpation • Pain Management • Stroke Risk Education* • School Achievement Screen • Pulmonary Function Tests^	• Hydroxyurea* • Pain medications (Ibuprofen, Opioid) as needed
10-20 years	Q3-6 months**	• CBC/retic at every visit • Renal and Liver function tests annually • Urinalysis annually	• Transcranial Doppler*$ • Fever • Pain Management • Stroke Risk Education* • School Achievement Screen • Pulmonary Function Tests^ • Annual Opthalomology Exam • Thorough History to Screen for Avascular Necrosis • Education/Preparation for Transition to Adult Care	• Hydroxyurea* • Pain medications (Ibuprofen, Opioid) as needed

**For patients with HbSS, HbSβ⁰thalassemia **Visits may become more frequent if patients start taking Hydroxyurea;$Frequency of TCD is based on results: Normal TCDs should be repeated annually until age 16 years, conditional TCDs should be repeated every 3-6 months, abnormal TCD should be repeated within 2 weeks and if repeat is abnormal, chronic transfusion therapy should be instituted.[10,11] ^In children with history of Acute Chest Syndrome or Asthma (Personal History OR Family History)*

Table 2. Adult Care Guidelines

Interval	Once	Every Visit	Every 6 Months	Yearly	Q 2 years	Q 4 years	Q 5 years
Lab	• Hepatitis screen • Extended RBC Antigen typing	• CBC • Retic • BMP		• CMP • Ferritin • UA and Microalbumin	• Vitamin D • HIV* • Hep C* • Testosterone		
Radiology					CXR		
Assessment		• Blood Pressure • Pulse Oximetry • Weight • History of febrile episodes • Pain assessment • Chest pain • Priaprism • Leg Ulcers	• Contraception • Transfusion history	• Chelation therapy - if appropriate • Hydroxyurea • Update Acute Care Plan			
Other			• Dental Visit	• Ophtho exam (1-2 years) • Psychosocial Assessment • Primary Care Visit • Nutrition Education • Disease Education		• Consider TTE, especially in patients 22-28 years	
Vaccines	• Hepatitis A and B • Hib • HPV if <26 years			• Flu Vaccine			• Pneumococcal • Tetanus every 10 years • Meningitis

**High risk patients - order at provider's discretion*

Infection Prophylaxis and Fever Management

Infection is a common cause of death in children with sickle cell disease. The risk of pneumococcal sepsis is 400 times greater in young children with sickle cell disease. Infection with *Hemophilus influenzae* sepsis is up to 4 times as common. This is due to splenic dysfunction involving both the clearance of bacteria from the circulation and impaired opsonization of bacteria. Auto-infarction of the spleen from recurrent intravascular sickling impairs its ability to filter encapsulated bacteria. In general, the organisms causing infection in this population are commonly found in the community.[12]

Infections cause more morbidity, disseminate more rapidly, and are more difficult to eradicate in persons with sickle cell disease. Infections can precipitate aplastic crisis and exacerbate hemolytic events as well as precipitate painful vaso-occlusive episodes.

Recommended prevention/immunization: Children with sickle cell disease show normal antibody response to live and killed vaccines. Please check the Centers for Disease Control website for the most up-to-date vaccination schedule and guidelines. All patients with sickle hemoglobinopathies should be considered functionally asplenic and be vaccinated as such. Please see Table 3 from the NHLBI Evidence Based Management Guidelines for more information on vaccination recommendations for patients with sickle cell disease.

Hib, Pneumovax, and Meningococcal boosters may also be given >2 weeks prior to surgical splenectomy.

Antibiotic prophylaxis with penicillin has been shown to be effective in preventing life-threatening pneumococcal infections in children with sickle cell disease from birth to age 5 years. Penicillin is standard practice for all children birth to age 5 with sickle cell disease. The standard prophylactic dose for oral PenVK is 125 mg BID until age 3 years, then 250 mg BID. For penicillin allergic patients, use erythromycin 250 mg BID. (NHLBI Guidelines [8], Red Book)

Table 3. Immunization Recommendations as Adapted from the Advisory Committee on Immunization Practices (ACIP)

Recommendations
All individuals should be immunized as recommended by the ACIP. The most up-to-date schedule should be followed, as changes can be made up to four times per year. Consult the immunization schedule at: https://www.cdc.gov/vaccines/schedules/. The following immunizations are of special importance to people with sickle cell disease as recommended by the ACIP. These recommendations may also change periodically, and the above ACIP recommendations should be consulted for confirmation. • **Pneumococcal (PCV13) vaccine -- Children** - Children aged 6 to 18 years with functional or anatomic asplenia should receive one dose of PCV13 (if not previously received) • **Pneumococcal vaccine-naïve -- Adults** - Adults aged ≥19 years with functional or anatomic asplenia who have not previously received PCV13 or PPSV23 should receive · One dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later · Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk - A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19-64 years with functional or anatomic asplenia - Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose • **Previous vaccination with PPSV23 -- Adults** - Adults aged ≥19 years with functional or anatomic asplenia who previously have received ≥1 dose of PPSV23 should · Be given a PCV13 dose (if not previously received) ≥1 year after the last PPSV23 dose was received - For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23 • **Hib** - One dose of Hib vaccine for people aged >5 years who have sickle cell disease if they have not previously received Hib vaccine • **Meningococcal vaccine** - Vaccinate infants at high risk (including those with sickle cell disease) at 2, 4, and 6 months of age, and again at 12 through 15 months with this vaccine, which is generically known as HibMenCY - Persons aged 9 months through 55 years at increased risk for meningococcal disease (e.g., adults with anatomic or functional asplenia or persistent complement deficiencies) should receive Men-ACWY - Children aged 2 months to 6 years should receive an additional dose of MenACWY 3 years after primary immunization; boosters should be repeated every 5 years thereafter - Children ≥7 years of age should receive an additional dose of Men-ACWY 5 years after primary immunization; boosters should be repeated every 5 years thereafter
Sources: National Heart, Lung, and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014. 2014. Available at: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report%20020816.pdf.[8] Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for persons aged 0 through 18 years – United States, 2013. Morbidity and Mortality Weekly Report 2013;62(01):2-8.[13]

Table 4. Penicillin Prophylaxis Recommendations and Strength of Evidence

Recommendations
1. Administer oral penicillin prophylaxis (125 mg for age <3 years and 250 mg for age ≥3 years) twice daily until age 5 years in all children with HbSS. (Strong Recommendation, Moderate-Quality Evidence) 2. Discontinue prophylactic penicillin in children with HbSS at age 5 unless they have had a splenectomy or invasive pneumococcal infection. When discontinuing penicillin prophylaxis at age 5, it is important to assure that the child has completed the pneumococcal vaccination series (both PCV13 and PPSV23), and if not, complete the series immediately. (Weak Recommendation, Moderate-Quality Evidence) 3. Consider withholding penicillin prophylaxis from children with HbSC disease and HbSβ$^+$-thalassemia unless they have had a splenectomy. (Weak Recommendation, Low-Quality Evidence) 4. Assure that people of all ages with sickle cell disease have been vaccinated against *Streptococcus pneumoniae*.* (Strong Recommendation, Moderate-Quality Evidence) 5. Remind people with sickle cell disease, their families, and caregivers to seek immediate medical attention whenever fever (temperature greater than 101.3˚F or 38.5˚C) occurs, due to the risk for severe bacterial infections. (Consensus – Panel Expertise)
* See Table 3 for more Immunization Recommendations as Adapted from the Advisory Committee on Immunization Practices (ACIP).
Source: National Heart, Lung, and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014. 2014. Available at: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report%20020816.pdf.[8]

Fever Management for a Child with Sickle Cell Disease

The fever accompanying septicemia in these patients is usually ≥101°F (38.3°C). Often the temperature rises quickly, and clinical deterioration can occur rapidly.

Administration of I.V. antibiotics should not be delayed while awaiting lab results. Blood cultures should be obtained in all patients, and urine cultures should be obtained in patients less than 2 years of age or in those with symptoms of a UTI. An antibiotic effective against S. *pneumoniae*, H. *influenza*, and other encapsulated, rapidly multiplying organisms such as ceftriaxone (50-75 mg/kg/dose, max dose 2 g) should be used.[14]

Lumbar puncture should be done for symptoms of meningitis. Patients with suspected meningitis or other serious bacterial infection should be admitted to the hospital. Culture positive sepsis requires at least 7 days of I.V. antibiotic therapy (from first negative culture), and for meningitis, at least 10 days. Strongly consider an Infectious Disease consult for all patients with culture positive sepsis.

For patients with evidence of cardiovascular compromise and fever, add vancomycin empirically until the blood cultures are negative for at least 48 hours.

Aplastic Crisis

An aplastic crisis should not be confused with hemolytic anemia, which is a constant feature of sickle cell disease. The aplastic crisis is temporary cessation of red cell production. Because of the markedly shortened red cell survival time in patients with sickle cell disease (10 days instead of the usual 120 day lifespan of a healthy erythrocyte), a precipitous drop in hemoglobin occurs in the absence of adequate reticulocytosis.[15]

Among patients with sickle cell disease, severe aplastic crisis is frequently associated with parvovirus B19 infections (childhood Fifth Disease). Other causes may be EBV or Strep infection. Patients typically present with increased fatigue, pallor, activity intolerance or shortness of breath. Pallor may replace the typical jaundice of sickle cell disease. In the case of parvovirus, the period of viremia lasts about one week. The CBC reveals a lower than relative normal hemoglobin without a compensatory reticulocytosis. In fact, the reticulocyte count is often close to zero. The aplasia usually persists for 5-10 days. Pancytopenia does not usually occur. The treatment is management of symptoms of anemia with simple transfusion using extended antigen-typed, leukodepleted RBCs. Recovery is heralded by increased peripheral NRBCs followed by reticulocytosis. The incidence of recurrent parvovirus B19 is very low. IgM titers begin to rise by about day 7 and peak by day 21. As normal erythroid function returns, IgG rises and remains elevated, indicating past infection. Children in the general community do not require isolation, though pregnant caregivers should avoid contact while the patient is contagious. Patients admitted to the hospital are often managed with contact and droplet isolation and should not have pregnant caregivers. Hematologically normal people who are infected by parvovirus usually do not develop red cell aplasia or other serious complications.

Treating Infections in Adults with Sickle Cell Disease

Pneumococcal infections are less common after the school-age years. Infections in adults tend to occur in areas of the body damaged by recurrent sickling such as the lungs, kidneys, or bones. Even mild infections have the potential to worsen rapidly in routine settings. Low grade fever (<101°F) often accompanies vaso-occlusive pain episodes, but infection must always be ruled out.

Pyelonephritis can be difficult to treat, can recur regularly, and can often be associated with septicemia. Sickling in the renal papillae leads to necrosis and increased risk of infection. This is especially a risk during pregnancy. Treatment consists of antibiotics and hydration. For severe cases, inpatient I.V. cephalosporin and/or aminoglycoside therapy is indicated.

Osteomyelitis can often be difficult to distinguish from diaphyseal bone infarcts. Blood and stool cultures should be obtained at the same time as a bone aspiration for culture looking for Salmonella, staphylococci, or other enteric organisms. Tuberculosis should also be ruled out.

Antibiotic resistant Salmonella can be a problem, so even if in vitro susceptibility tests suggest efficacy for tetracyclines, cephalosporins, or aminoglycosides, most practitioners recommend use of trimethoprim-sulfamethoxizole, ampicillin, or chloramphenicol. Salmonella produces chronic intracellular infections and requires prolonged administration of antibiotics (4-6 weeks). Typical treatment would be with I.V. ampicillin 150 mg/kg/d in 4 divided doses for 21-42 days, followed by oral ciprofloxacin. If chloramphenicol is used, careful monitoring for bone marrow suppression and reticulocytopenia should be done.

Staphylococcal osteomyelitis requires high-dose beta lactamase resistant penicillin (I.V. nafcillin) for several weeks. Surgical debridement may also be indicated.[14]

Vaso-Occlusive Pain Management

Many patients with chronic diseases suffer pain as a component of the disease process. This is especially true for patients with sickle cell disease.

The 2014 NHLBI Evidence Based Management Guidelines state: “Nearly all affected individuals living with sickle cell disease will experience a vaso-occlusive crisis in their lifetime.”

90% of hospitalizations for this population are due to sickle pain. Like other populations of patients with chronic illness, there are both physical and psychosocial factors involved in the management approach to pain control.

The Nature of Sickle Cell Pain

Sickle cell painful episodes are thought to be caused by ischemic tissue injury from obstruction of blood flow by sickled red blood cells. Lack of blood flow results in regional hypoxia and acidosis, which perpetuate the sickling process. Considerable evidence also supports the hypothesis that interactions between sickled cells and vascular endothelium contribute to the clinical manifestations of sickle cell disease.[16] Adhesion of sickled cells to endothelial cells may augment circulatory flow and promote deoxygenation of red blood cells, resulting in sickling. Up-regulation of adhesive and hemostatic properties of endothelial cells by certain viruses may explain how viral infections often precipitate vaso-occlusive episodes.[17]

Painful episodes usually last 4-10 days, but can persist for weeks. Hypoxia, infection, dehydration, acidosis, menstruation, sleep apnea, and exposure to cold temperatures can precipitate vaso-occlusive pain episodes. Commonly, no precipitating factors can be identified. Understandably, anxiety, depression, and physical exhaustion are also identified as contributing factors.

A painful crisis can occur in the absence of known precipitating events or any objective clinical findings. The frequency and severity of pain episodes is extremely variable among patients with sickle cell disease. Indeed, one of the great puzzles regarding understanding sickle cell disease is how a *single* DNA deviation which causes a change in a *single* amino acid in a *single* protein in a single type of cell (RBC) can cause *such variability* in the clinical course.

Sickle cell related pain usually involves the low back, legs, arms, chest, or abdomen. The pain may migrate or be very localized. It may be sharp or dull; stabbing or throbbing. Patients with sickle cell disease can have chronic pain syndromes and additionally experience acute painful episodes.[16,18] Dactylitis (painful swelling of the hands or feet) is often the first manifestation of sickle cell disease seen in affected infants and can occur as early as 6 months of age. In older children and adults, musculoskeletal pain is the most common complaint. It may be difficult to distinguish a vaso-occlusive pain episode from osteomyelitis, septic arthritis, toxic synovitis, rheumatic fever, or gout. For patients with abdominal complaints, pancreatitis, cholecystitis, urinary tract infection, pelvic inflammatory disease, pneumonia, or malignancy must be ruled out.

Acute Pain Syndromes:

- Vaso-occlusive episodes
- Acute chest syndrome
- Right upper quadrant syndrome
- Dactylitis (hand-foot syndrome)
- Splenic sequestration
- Priapism
- Cholecystitis with calculus (gallstones)
- Renal colic

Syndromes of Chronic Pain:

- Avascular necrosis
- Vertebral body collapse
- Arthritis
- Leg uclers

The NIH practice guidelines for management and therapy of sickle cell disease recommend **immediate medical evaluation for complaints of pain associated with any of the following**:

- Fever ≥101°F, lethargy, pallor, recurrent vomiting, and dehydration
- Acute pulmonary symptoms
- Acute neurologic symptoms
- Pain associated with extremity weakness or loss of function
- Acute joint swelling
- Pain which is unrelieved with oral analgesics and routine supportive measures
- Priapism (persistent or recurring)
- Acute flank or back pain

Lab Monitoring as Part of the Pain Evaluation

It is NOT possible to diagnose a painful vaso-occlusive episode with a specific clinical finding or laboratory test. ***No biomarker or imaging study can validate pain or assess its severity.*** However, certain lab tests can help discern precipitating or complicating factors.

CBC with Reticulocyte Count

During a pain episode, the patient's hemoglobin can range from normal relative to their baseline to decreased by 1-2 g/dL because of acute hemolysis. White blood cell (WBC) counts are commonly elevated in patients with SCD, even at baseline. Acute pain crisis can cause WBC counts to increase to as high as 30,000/microliter. When WBC count exceeds 30,000, infection should be ruled out. Platelet count can also increase during an acute pain crisis. Reticulocyte counts are important to evaluate the bone marrow's response to the acute anemia.

If the hemoglobin and reticulocyte counts are lower than baseline, an underlying viral process or aplastic crisis may be the cause. Worsening anemia accompanied by brisk reticulocytosis could signal liver or splenic sequestration. In cases of dehydration, the hemoglobin may seem falsely elevated. If the WBC is elevated with a differential shift to the left, infection should be suspected. If the platelet count is low, splenic sequestration should be considered.

Renal and Liver Function Testing

- Serum electrolytes may not give the practitioner a real indication of renal function. Many people with sickle cell disease have renal salt wasting. Most also have some degree of hyposthenuria, or inability to concentrate urine efficiently. Hydration status is not accurately measured by serum electrolytes or urine specific gravity.[18]
- Hyperuricemia is another common finding. This occurs due to increased urate production associated with accelerated red cell production/turnover and diminished renal clearance of uric acid.
- Hematuria is a common finding among patients with sickle cell disease. Pain with hematuria warrants further evaluation for renal or ureteral stones, infection, clots, or malignancy.
- Abdominal pain (right upper quadrant syndrome) accompanied by elevated liver transaminases may indicate a need for further hepatitis evaluation.
- Most patients with sickle cell disease have elevated indirect bilirubin as a result of chronic hemolysis. Because of increased bile production, gallstones are quite common in sickle cell disease (occurring in 75% of adults by age 30).
- Elevations of direct bilirubin suggest biliary obstruction and warrant further evaluation.

Radiologic Testing

- Chest X-ray and oxygen saturation reading for complaints of pain when acute chest syndrome is being considered. If the peripheral circulation is normal, the oxygen saturation measured by pulse oximetry should be >93%. Most patients with sickle cell disease have a low Pa02 during their steady state, but an 02 saturation below 90% indicates acute hypoxemia in most cases.
- Plain abdominal films or ultrasound should be considered for patients presenting with abdominal pain to rule out gallstones, severe constipation (due to use of opioid analgesia), liver, spleen, or pancreatic enlargement which could be contributing to the patient's complaints of pain. An acutely enlarged and painful liver (right upper quadrant syndrome) may suggest red cell sequestration during a vaso-occlusive crisis. This is also usually accompanied by increased jaundice and decreased hemoglobin and hematocrit.
- If osteomyelitis or septic arthritis is suspected, cultures from a direct bone biopsy or joint aspiration should be done. In addition, radiographs and/or radioisotope scans can sometimes be helpful to differentiate infarction from infection. Blood cultures should be obtained for fever ≥101°F.

Analgesia

Measurement of Pain and Relief

For older children and adults, a verbal pain scale is quite helpful during periods of acute pain. This simply involves asking the patient to rate the pain from 0 (no pain) to 10 (worst pain imaginable). Written assessments of pain and relief, such as a Visual Analog Scale, may be helpful tools to use during inpatient hospitalizations. This involves marking the level of pain and percentage of pain relief achieved on a scale and identifying the location of the pain on a drawn body figure. Interestingly, reports from these scales confirm that many patients continue to have moderate pain at the time of discharge. It is important to note that many patients with sickle cell disease experience a great deal of anxiety over anticipatory pain or improper pain management, which tends to make treatment more difficult.

For younger children, pain can be measured in small interval categorical scales using visual markers. One such scale uses tokens to represent amounts of pain or "hurt". Another uses colored crayons to shade on a body outline where the pain is located and how much it hurts. The "Faces" and "Oucher" scales use 6 pictures or drawings of children depicted in various stages from happy (no pain) to sobbing and upset (severe pain). It is important to realize that expression of pain is very individual. Many children remain active at play while in pain as a coping mechanism.

See Faces scale on the next page.

Wong-Baker FACES® Pain Rating Scale

Management of Pain

OUTPATIENT

When patients feel that a painful episode is impending, early treatment with analgesics, warmth, rest, and oral hydration can ameliorate the process.

Home-based management includes the following guidelines:

Step 1: Mild Pain

Use non-opioid medications + adjuvant measures:

Oral hydration:

Weight (lbs)	Cups (8oz)
≤ 25	2 - 3
≤ 30	4 - 6
≤ 45	5 - 8
≤ 55	6 - 9
≤ 75	7 - 10

Weight (lbs)	Cups (8oz)
≤ 100	8 - 11
≤ 130	9 - 13
≤ 150	10 - 15
≤ 175	11 - 17
> 175	12 - 18

Acetaminophen:

- 10-15 mg/kg every 4 hours for children
- 325-1000 mg every 4 hours for adults (max dose 65mg/kg/24 hours)

Ibuprofen:

- 10 mg/kg every 6-8 hours for children
- 400-800 mg every 6-8 hours for adults (max dose 2400mg/24 hours)
- OR other NSAID as indicated

Adjuvant measures include the use of heating pads, massage, relaxation therapy, diversion, self-hypnosis, yoga, acupuncture.

Step 2: Moderate Pain

Weak opioid + non-opioid + adjuvant measures: use fixed doses around the clock, alternating with opioid and anti-inflammatory medication.

Oxycodone:

- 0.1-0.15mg/kg every 4-6 hours for children
- 5-10mg every 4-6 hours for adults

Hydrocodone:

- 0.1-0.2 mg/kg every 4-6 hours for children
- 5-10mg every 4-6 hours for adults

*If using acetaminophen and oxycodone/hydrocodone preparations, do not exceed recommended amounts of acetaminophen on an every 4-hour schedule

*Continue NSAID dosing around the clock. Ketorolac is a good choice for patients with moderate or severe pain. It is available in PO, IM, and I.V. forms. Do not use ketorolac in conjunction with other NSAIDs. Adequate hydration is mandatory. Do not use ketorolac for more than 5 days. The dosing is 0.5 mg/kg/dose (max dose 30mg) every 6 hours, not to exceed 60mg/day in children or persons weighing less than 50kg (110lb).

Step 3: Severe Pain

Strong opioid + non-opioid + adjuvant measures: use fixed doses around the clock

Oral morphine:

- 0.3-0.6mg/kg every 3 hours (dose may depend on prior use)
- Usual dose: 15-20mg every 3 hours for adults (half-life 2-3.5 hours)

Oral hydromorphone:

- 0.02-0.04 mg/kg every 4 hours
- Usual dose: 4-8mg every 4 hours for adults (half-life 2-3 hours)

Meperidine is not recommended for analgesia use inpatients with sickle cell disease due to high incidence of seizures and accumulation of the drug in the presence of renal dysfunction.

To add longer acting pain relief agents to short acting analgesia:

Morphine sulfate controlled release is available in 15, 30, 60 and 100mg tablets. Thirty milligrams of MS Contin every 12 hours equals a dose of oral immediate release morphine at 10mg every 4 hours.

Fentanyl transdermal patches come in a 25mcg/24-hour delivery system (also available in 12, 50, 75, and 100mcg/24 hour strengths). The patch provides 72 hours' worth of continuous release fentanyl. A fentanyl 25mcg patch is equal to between 45-135mg of immediate release morphine over a 24-hour period.

Other adjuvant oral medications may include:

- Antihistamines (hydroxyzine or diphenhydramine) to manage opioid-induced pruritus
- Antiemetics (promethazine, prochlorperazine, ondansetron, granisetron) to manage narcotic-induced nausea
- Laxatives and stool softeners [colace, peri-colace, senekot, sorbitol, polyethylene glycol (Miralax), magnesium citrate] to manage constipation
- Benzodiazepines (lorazepam, alprazolam,) to manage short term anxiety and sleep disorders
- Tricyclic antidepressants to manage depression, sleep disorders and as pain adjuvant therapy
- Anticonvulsants as adjuvant pain medications
- H2 blockers include ranitidine or cimetidine

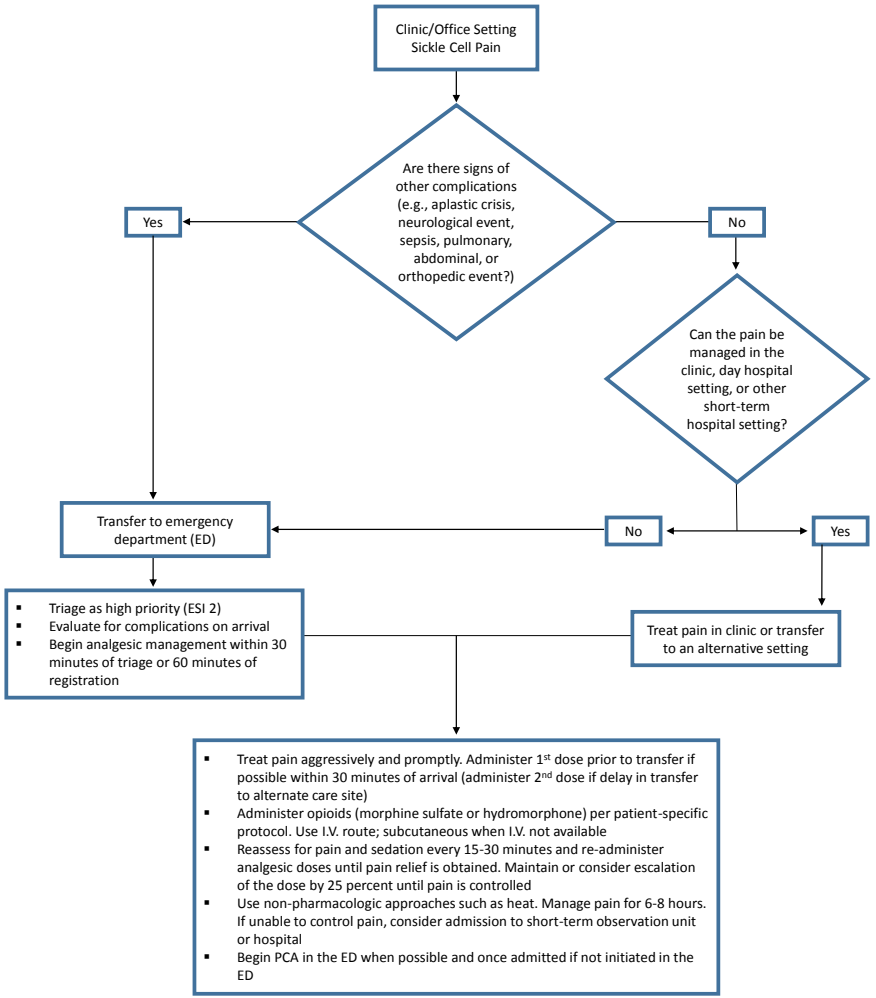
EMERGENCY ROOM AND INPATIENT HOSPITAL SETTING

It is important to realize that most patients with sickle cell disease only present to the hospital for pain relief after other measures have failed at home. ***Patients often report fear of not being believed about their pain, being labeled a "drug seeker" or receiving inadequate pain control when presenting to urgent care.***

These additional concerns can exacerbate the pain already being experienced. Acute pain in patients with sickle cell disease is often treated in a standard fashion by medical staff: a dose of opioid that would seem to be appropriate is given. The dose may be excessive for opioid-naïve patients leading to oversedation, or insufficient in the opioid-tolerant patient leading to inadequate relief. It is often wrongly assumed that if the patient did not receive the expected relief from a "standard" dose of opioid that they must have addictive or "drug seeking" behavior. Individualizing the loading dose of narcotic based on the patient's history and use of measurable pain scales to document relief are very helpful to change this experience.

The goal of emergency room care is to assess the clinical problem, initiate a trial of analgesic therapy, assess the outcome, and decide with the patient whether or not hospitalization is necessary.

See Table 5, and steps on next page.



Graph recreated and based on the NHLBI guidelines for Acute Pain Algorithms

Guideline for ER evaluation for pain:

Step 1: Assessment

- Patients should be triaged as high prioity (ESI 2)
- Believe the patient
- History and physical exam, including prior experience with pain management agents
- Document location and intensity of pain on a simple measurement scale
- Note that symptoms of opioid withdrawal can mimic a pain crisis (hyperalgesia)
- Vital signs with oxygen saturation measurement
- CBC with differential, reticulocyte, and platelet count
- Renal function test, if H&P raises concerns
- Blood cultures for fever $\geq$ 101°F (38.3°C)
- Serum or urine pregnancy test for pre-menopausal women
- Radiologic studies (plain film, ultrasound, CT) as indicated

Step 2: Action

- Correct dehydration and electrolyte imbalances with I.V. fluids
  - Patients with sickle cell disease become easily dehydrated due to reduced oral intake during pain episodes or nausea from analgesic medications. They also may have insensible losses from fever. Hyposthenuria (inability to concentrate the urine) is common, so measurement of the specific gravity of the urine does not adequately reflect hydration status. D5W 1/2NS at 1.5 times maintenance rate is appropriate. Care must be given to avoid iatrogenic congestive heart failure or electrolyte imbalances. Due to the chronic nature of salt wasting in most patients, serum sodium levels of 130-135mEq/L do not usually need correction.
- Oxygen therapy most likely does not help in management of vaso-occlusive pain episodes unless hypoxemia (compared to the patient's baseline) is present (oxygen saturation <92%)
- Sodium bicarbonate therapy does not improve the clinical course of a painful episode. It should only be used to correct acidosis
- Vasodilator therapy has no role in management of painful episodes with the exception of severe priapism (see chapter on priapism)
- Administer an oral or parenteral (preferably I.V.) analgesic agent mutually agreed upon with the patient, taking into consideration prior experiences and use of home medications
  - The oral route of administration for opioids is about one third as effective as the parenteral route. Synthetic opioids (pentazocine, butorphanol, nalbuphine) should be avoided because of antagonist induction of withdrawal symptoms or psychomimetic effects
  - Most adult patients with sickle cell disease require an initial dose of morphine 2-10 mg or hydromorphone 0.5-2mg to control pain; opioids should be dosed in a weight based fashion for pediatric patients

Step 3: Assessment Of Efficacy

- After administration of narcotic analgesia, monitor for side effects of respiratory depression, nausea, vomiting, pruritus, hypotension, secretion of antidiuretic hormone, urinary retention, or changes in the seizure threshold. A respiratory rate < 10/minute is a sign of opioid-induced respiratory depression
- *10-15 minutes after initial administration of I.V. opioid analgesic, reassess pain location and intensity with a simple measurement scale.* Believe the patient. If there has been no relief of pain, 50% of the initial dose should be given. If the patient is mildly sedated but still reporting pain, 25% of the initial dose should be given
- If the patient remains comfortable for 3 hours, administer an oral opioid and observe for another hour. If moderate or severe pain returns within 30 minutes of the oral opioid dose, administer a repeat dose of the initial I.V. opioid
- If same pain persists, the patient should be admitted to the hospital for pain control
- If the patient is discharged to home, a prescription for a 1-week supply of opioid analgesia and adjuvant medications is appropriate

Narcotic Tolerance, Pseudo-Addiction, and Withdrawal

The pain in sickle cell disease has similarities to pain produced by trauma, surgery, acute ischemia, and cancer. However, the occurrence of sudden and severe pain for patients with sickle cell disease is a lifelong experience. Health care professionals often do not exhibit the same degree of empathy for patients with sickle cell pain. This may contribute to under-treatment, patient dissatisfaction, mistrust, and maladaptive learned coping behaviors.[16]

Addiction is defined as a compulsive use, loss of control, and continued use of the substance despite harm. Opioid use has been more widely studied in cancer populations. Tolerance and physical dependence do not equal addiction in the cancer population. Euphoria varies inversely with analgesia. Analgesia can occur in the absence of mood elevation. There are differences in the metabolism of opioids among certain individuals and groups.

Inadequate pain management can initiate pseudo-addiction syndrome. This phenomenon is identified by behaviors directly or indirectly taught by health care workers to patients with sickle cell pain. The fear over not receiving adequate pain control perpetuates behaviors which are often viewed as “drug seeking” by medical staff. The result is often maladaptive coping strategies, anger and isolation for the patient. This in turn leads to frustration and avoidance behaviors on the part of the healthcare providers.[20]

After an aggressive pain management course with opioid analgesia, the doses should be tapered over 1-2 weeks to avoid symptoms of withdrawal or abstinence syndrome. Tolerance causes changes in the brain that mimic those seen with persistent injury. Symptoms of opioid withdrawal or abstinence syndrome can easily mimic or even precipitate vaso-occlusive pain.

Frequent Utilizers of Care Facilities:

Individuals who are felt to overutilize the hospital services create the most difficult management problems. This group is the minority of patients with sickle cell disease, but they account for the majority of ER visits and hospitalizations.[21] In most cases, high utilizers of services are equated with “drug-seeking” behaviors.

This stereotyping results in under-treatment of pain with opioids for other patients with sickle cell disease. Frequent utilizers of services (“frequent flyers”, etc.) are often quickly labeled as “problem patients.”

They may belong to any of the following subclasses:

The Under-Treated
Secondary Gain
Convenience
Drug Seekers

The Under-Treated:
These are patients who are not adequately treated for pain as outpatients. Investigating and correcting this issue can change the pattern of service utilization.

Secondary Gain:
These patients rely on medical services because of social, financial, or psychological problems. They may be admitted often, but use minimal amounts of pain medications while their other needs are being met.

Convenience:
These individuals find it easier to use the ER staff than to make and keep regular outpatient visits. They may not have established a trusting rapport with a practitioner who can give them guidance regarding home management of pain.

Drug Seekers:
This is the most difficult group of patients to deal with or help. Investigating these individuals may reveal prescription alteration, selling, or substance abuse. Formulating a treatment plan should include intensive counseling, psychiatric evaluation, rehabilitation, and appropriate pain control for real events.

It is appropriate to make a treatment contract with these types of patients. The goals of such a contract should include relief of pain. It should also include the setting of strict limits within the context of a consistent plan for management of pain. The patient and family must understand that the complaint of pain will be addressed. However, in addition to receiving opioids for the treatment of pain, the importance of a consistent, coordinated plan that includes behavior modification and patient/family involvement is equally important.

Inpatient Pain Management

When attempts at outpatient pain control have failed, hospitalization for pain management is necessary.

A management plan should be documented in the medical record at the time of admission. Documentation of pain measurement scales should be done at regular intervals. The patient should be educated to expect that they may not have complete relief of pain at discharge, and that the development of positive coping skills are beneficial to help with pain management. I.V. continuous opioid analgesia, bolus dose ("patient controlled analgesia" or PCA), or both are appropriate. Continuation or addition of adjuvant medications such as NSAIDS, antiemetics, antianxiety agents, or antipruretics is also appropriate. Many institutions offer a "short stay" or "day hospital" setting in which patients can receive up to 23 hours of I.V. analgesia and are discharged to home when comfort on oral medications is achieved. This can avoid congestion in the emergency room. It also encourages patients to seek medical intervention in the early phase of a painful episode in an attempt to avoid an ER visit or hospitalization.

Patient Controlled Analgesia (PCA)

Begin PCA by using 20-25% of the quantity of the opioid bolus that was used in loading the patient to be delivered with a 6-10 minute lockout interval. Reassess and document the patient's perception of pain every 4 hours using a simple measurement scale. Determine the hourly use of opioid during the day and give 66% of the hourly dose as a continuous infusion at night to promote sleep and rest.

Continuous Infusion Narcotic Analgesia

A continuous infusion of opioid analgesia (for an adult) typically uses morphine sulfate in D5W or NS at a concentration of 0.5mg morphine sulfate per milliliter of D5W or NS fluid.

For example: Morphine sulfate 125mg in D5W 250ml. Using 250ml I.V. diluent bags avoids accidental confusion with I.V. "piggybacks" and accidental overdose. It also permits delivery of morphine sulfate up to 100mg in a 24-hour period without changing I.V. bags.

Most adult patients with severe pain require morphine sulfate at a dose of between 2-4 mg per hour continuously with additional bolus or rescue (PCA) doses of 2-4mg as often as every 15 minutes as needed. If the patient is using bolus doses in excess of 1.5 times the basal morphine rate every 15 minutes over a 1 hour period without achieving pain relief, and in the absence of adverse side effects, it is reasonable to increase the basal rate or increase the PCA bolus dose, or both. After pain control has been achieved, the basal morphine rate can be decreased in 25% increments while oral opioids are added on a scheduled basis. Obviously, these are very patient/practitioner specific interventions, which require very frequent monitoring and titration.

Pediatric Sickle Cell Pain Pathway

Patient Presents to ED in Acute Pain

Assessment

» Triage as high priority (ESI 2). Evaluate for fever or respiratory symptoms.

» Administer analgesia within 30 minutes of triage or 60 minutes of ED registration. Assess pain using developmentally appropriate scale (N-PASS, FLACC, FACES, Numeric)

» Place patient on continuous CR monitor, pulse oximetry

» Order initial labs: CBC/differential, reticulocyte count, CMP. Additional labs may be indicated according to history and clinical presentation.

Initial Pain Management

» Select IV opioid based on patient-reported pain level, clinical presentation, and history of opioid use and response. Consider an initial dose of **0.1 mg/kg of IV morphine** or **0.015 mg/kg of IV hydromorphone**.

» For children > 6 mos of age, administer **Toradol (ketorolac) 0.5 mg/kg Q6H** (max. dose 30 mg IV Q6H). Verify that renal function is WNL. *Do not need to wait for CMP results before giving first dose of Toradol.

» Administer an initial NS bolus of 10 mL/kg followed by hydration with D5 ½ NS at **1.5x maintenance**. (Max. rate is ≤ 150 mL/hr)

» Nonpharmacologic intervention: heat application to affected area, distraction, deep breathing with the help of incentive spirometry/pinwheels.

Reassessment

» Reassess for response to pain medication and changes in clinical status every 15-30 minutes.

» Manage opioid side effects as indicated (ondansetron, Benadryl, etc).

» Call hematologist with update.

Pain Improved

» If pain is controlled, discharge patient with oral opioid for home.

- Drink plenty of fluids.
- Apply heat packs/heating pad to painful area.
- Alternate oral opioid pain medication with ibuprofen as outlined on your home pain plan.
- Call your hematologist for worsening pain.
- Add bowel regimen to prevent constipation.

Pain Relief Inadequate

» If pain relief is inadequate 30 minutes after initial dose, may give rescue opioid dose (typically 1/2 of initial dose).

» If pain control is unable to be achieved with 3-4 hours of ED management, consider hospital admission with PCA.

**Evaluate for signs of complications, e.g. aplastic crisis, sepsis, acute chest syndrome, osteomyelitis, neurological, pulmonary, or abdominal event.*

Disclaimer: This pain pathway is not intended for patients with complex pain management needs.

INDIANA HEMOPHILIA & THROMBOSIS CENTER, INC.

*** IF YOU WOULD LIKE COPIES OF THIS DOCUMENT, PLEASE CONTACT THE IHTC DIRECTLY**

Acute Chest Syndrome

This term is used to cover conditions characterized by pulmonary infiltrate in patients with sickle cell disease accompanied by one or more of the following: chest pain, cough, fever, hypoxia, wheezing or tachypnea.[22]

Acute chest syndrome may be the result of sickling in the microvasculature causing pulmonary infarction/emboli or the result of viral or bacterial pneumonia. It may develop as an isolated event, or during the course of a painful vaso-occlusive episode. The clinical course is usually self-limited when small areas of the pulmonary parenchyma are involved, but without proper supportive care the syndrome can rapidly progress and result in death. Acute chest syndrome is the leading cause of death in sickle cell patients and the second most common cause for hospitalization. Incidence increases in patients with a history of asthma or prior acute chest syndrome.[22]

Clinical Picture

Pleuritic chest pain is the most common presenting complaint in adults. Fever, cough, tachypnea, hypoxemia or abdominal pain are common presentations for infants and children. It is always best to assume an infectious etiology in these cases and obtain appropriate cultures and serologic studies. There may or may not be radiographic evidence of pulmonary infiltrates at the initial time of presentation. Lung pathology must be differentiated from rib infarction, gastric ulcer, or cholecystitis. Abdominal pain may be a result of involvement of the diaphragmatic pleura. There may be physical findings of pleural effusion or pulmonary consolidation.

Evaluation

Chest radiographs may be nondiagnostic for the first 24-48 hours, especially if the patient was dehydrated at presentation. Infiltrates in one or more lobes, with or without effusion, are common findings. It is not uncommon for blood, sputum, or pleural fluid cultures to reveal a bacterial pathogen (usually *S. pneumoniae* or *H. influenzae*). Viral and mycoplasma antibody titers are usually helpful only in retrospect since the results are inconclusive until late in the course of the illness.

Serial CBCs and reticulocyte counts are helpful for the first three days of hospitalization and then only when the patient's clinical status changes. An elevated neutrophil count, especially if shifted to the left, suggests bacterial infection. A decreasing hemoglobin/hematocrit are common as the syndrome evolves and may contribute to tissue hypoxia. Patients with acute chest syndrome can deteriorate rapidly and should be transferred to a tertiary care center at the earliest sign of decompensation.

Evaluation (continued)

Patients who have had repeated episodes of acute chest syndrome often develop restrictive lung disease. They may become at increased risk for recurrence of acute chest syndrome as well as pulmonary hypertension and cor pulmonale. These patients require regular pulmonary function monitoring. Some benefit from chronic transfusion therapy. Treatment with hydroxyurea should also be offered for long term prevention of recurrent acute chest syndrome.

Fat embolization syndrome can mimic acute chest syndrome. This involves widespread embolization of liquefied bone marrow fat into the pulmonary vessels and then into the systemic circulation. Adult patients with sickle cell disease (especially HbSC disease) are vulnerable to this syndrome during severe vaso-occlusive episodes. In advanced cases, disseminated intravascular coagulation with severe microangiopathic hemolytic anemia is possible. Presence of fat globules in the urine, petechiae, presence of refractile bodies on fundoscopic exam or necrosis seen in bone marrow samples support the diagnosis. A high index of suspicion is essential for early diagnosis and treatment with exchange transfusion and supportive care.

Intervention

Patients with acute chest syndrome must be admitted to the hospital and monitored for a potentially rapid deterioration in respiratory status. Aggressive use of incentive spirometry can help to minimize disease progression. Depending on the degree of pathology and hypoxia, positive pressure ventilation in an intensive care setting may be appropriate. I.V. fluid hydration should be given so that oral intake + I.V. equals the hourly maintenance rate. Avoid overhydrating the patient as it can lead to pulmonary edema and worsening respiratory status. It is appropriate to treat accompanying vaso-occlusive pain with opioids as needed. Relief of pain avoids splinting or shallow breathing, which can prolong or complicate the course. This requires close monitoring to find a dose of analgesia that provides comfort without hypoventilation or over-sedation.

Since it may not be possible to initially differentiate between pulmonary infarction and bacterial or viral preumonia, antibiotic therapy should be initiated with a broad spectrum penicillin or cephalosporin, pending culture results. Only about 5% of patients will have positive blood cultures. The typical organisms are *S. pneumoniae* or *H. influenzae*. A macrolide antibiotic should be added for coverage of atypical organisms.

Treatment with exchange transfusion should be used for patients who have multi-lobar involvement, hypoxemia, or progressive respiratory distress/respiratory failure. Simple transfusion may be used if the baseline hemoglobin is low and the patient is hypoxemic. The goal of simple transfusion is a hemoglobin of 10 g/dL. It is important to avoid transfusing above this hemoglobin to avoid complications of hyperviscosity.

The following equation can be used to calculate transfusion volumes for pediatric patients[23]:

$$\frac{\text{Weight (kg)} * [\text{desired Hb} - \text{current Hb (g/dL)}] \ * 3}{\text{Hct of RBCs}}$$

Abdominal Complications

Splenic Complications

Splenic Sequestration

Normally flexible and smooth red blood cells pass swiftly through the spleen. The spleen receives about 3 to 5% of the total blood volume per minute. The immunologically competent portion of the spleen (white pulp) receives a relatively small portion of blood flow as compared to the splenic filter portion (red pulp). In most older children and adults with HbSS disease, the repetitive intrasplenic sickling and local infarction eventually results in scarring, fibrosis, and a non-functional spleen (called functional asplenia or auto-splenectomy). In infants and young children (up to age 5-6 years), some splenic congestion and splenomegaly is not unusual.[24]

Acute splenomegaly, pallor, or lethargy can be the first clinical signs of a potentially life threatening splenic sequestration crisis.

Splenic sequestration refers to an acute condition of intrasplenic pooling of large amounts of blood. Children with sickle cell disease between ages 5 months and 2 years represent most cases of splenic sequestration. During severe sequestration crisis, the blood-filled spleen may enlarge to the point of filling the entire abdomen. The child's hemoglobin may drop acutely (to as low as 1-3g/dL) resulting in hypovolemic shock and death within hours of initial onset. Prompt treatment with volume expanders and blood transfusion to reverse the hypovolemic shock can help remobilize the blood sequestered in the spleen and lead to regression of the splenomegaly over a fairly short period of time.[25]

Minor sequestration events are common in young children with sickle cell disease. Some cases are associated with viral illnesses. Mild episodes are characterized by moderate splenomegaly and often a 1-3g/dL decrease from the patient's baseline hemoglobin with compensatory reticulocytosis and accompanying thrombocytopenia.

Due to overall less sickle related infarction, the spleens of older children and young adults with HbSC or sickle β^+thalassemia may remain enlarged (hypersplenism) or retain the ability to enlarge. Therefore, they are also at risk for sequestration.[26,27]

In patients with acute splenic sequestration, aggressive I.V. hydration (1.5-2X maintanence fluids) and transfusion with RBCs are the mainstays of therapy. Small aliquots of RBCs should be transfused (5cc/kg over 2-3 hours) because of the risk of hyperviscosity that can occur from auto-transfusion. Auto-transfusion can occur when the sickled red cells causing the obstruction of the splenic venules are removed by the hydration or transfused red cells and the trapped red cells are released back into circulation.

Splenic sequestration tends to recur and, because of the acute nature of potentially catastrophic symptoms, outcomes can sometimes be fatal. For this reason, splenectomy is often recommended for children with recurrent splenic sequestration. Splenectomy is often delayed until age 2 years to allow patients to receive the first dose of PPSV23 prior to splenectomy. If recurrent splenic sequestration occurs before the age of 2 years, chronic transfusion therapy is often instituted until patients can be properly vaccinated against encapsulated organisms.

Hypersplenism

Patients are considered to have hypersplenism if they have chronic splenomegaly that is typically accompanied by at least one of the following laboratory abnormalities: anemia, thrombocytopenia, or leukopenia. Anemia should be accompanied by an appropriate reticulocytosis. Since patients with sickle cell disease often have leukocytosis at baseline, a normal white blood cell count may be considered leukopenia, but this determination should be made on a case by case basis. The prevalence of hypersplenism in patients with sickle cell disease is unknown.[24] Splenectomy may be necessary in patients with hypersplenism who are receiving hydroxyurea, if the cytopenias prevent the escalation of hydroxyurea dosing. A nuclear liver spleen scan may be helpful to determine the amount of splenic function and help guide decisions about the need for splenectomy.

Hepatobiliary Complications

Cholelithiasis/Choledocholithiasis

Sickle red cells have a life expectancy of 7-14 days, less than 10% of the average life span of a healthy erythrocyte. The chronic hemolysis of sickle cell disease leads to increased bilirubin production which in turn increases the risk for cholelithiasis and gallbladder sludge. Almost 50% of pediatric patients with sickle cell disease will have gallstones, and the prevalence increases to 75% in adults. Most patients have asymptomatic cholelithiasis, but the gallstones can occasionally cause choledocholithiasis and pancreatitis. Acute cholecystitis occurs in approximately 10% of patients with sickle cell disease. Patients with sickle cell disease who present with acute abdominal pain should have laboratory evaluation that includes liver function tests (including a direct bilirubin and GGT) and pancreatic enzymes to evaluate for cholelithiasis and choledocholithiasis. Providers should have a high index of suspicion for gallbladder disease and a low threshold for abdominal ultrasound.

Laparoscopic cholecystectomy is an appropriate intervention for patients with symptomatic cholelithiasis. The decision to evaluate for choledocholithiasis prior to cholecystectomy should be based on laboratory evaluation (direct hyperbilirubinemia and elevated GGT are concerning for choledocholithiasis) and consultation with surgery and gastroenterology. Endoscopic or magnetic retrograde cholangiopancreatography (ERCP or MRCP) may be indicated to rule out or rule in choledocholithiasis.

Hepatic Sequestration

Similar to splenic sequestration, acute hepatic sequestration is enlargement of the liver accompanied by an acute drop in hemoglobin of 2g/dL with brisk reticulocytosis. Liver function tests may be only mildly elevated. Since patients with sickle cell disease often have baseline mild hepatomegaly, other causes of hemolysis and transaminitis should be ruled out.[28]

Acute Intrahepatic Cholestasis

Patients with acute intrahepatic cholestasis typically present with acute onset right upper quadrant pain, worsening jaundice, rapidly worsening and tender hepatomegaly, and extreme hyperbilirubinemia (> 50mg/dL). Thombocytopenia and coagulopathy can also accompany this condition. Rapid clinical deterioration and death may occur if this condition is not recognized and treated promptly. Clinicians should have a low threshold for transfer to a tertiary care center with expertise in caring for patients with sickle cell disease.[29]

Exchange transfusion should be considered for all patients with acute intrahepatic cholestasis. Simple or exchange transfusion should be utilized for acute hepatic sequestration. Hematologists experienced in the care of patients with sickle cell patients should be consulted for assistance in managing patients with hepatopathy.

Stroke Evaluation and Emergent Intervention

Stroke is defined as an acute neurological syndrome caused by occlusion of an artery or a hemorrhage with resultant ischemia and neurological signs and symptoms lasting more than 24 hours. Prior to routine transcranial Doppler (TCD) screening, approximately 10% of children with sickle cell anemia (HbSS or HbSβ^0thalassemia) under age 20 years suffered a stroke. Overt stroke is rarely seen before the age of 1 year. The incidence is highest between ages 2 and 9 years. In general, hemorrhagic strokes occur in older persons (peak incidence 20-30 years of age) while cerebral infarctions occur in younger groups.[5] Cerebral infarctions are due to vascular occlusion.

In children with sickle cell anemia (HbSS or HbSβ^0 thalassemia), the internal carotid and middle cerebral artery distributions are the most common areas of infarction. It is now understood that the etiology of vascular occlusion in sickle cell disease is likely a combination of accumulated sickled red blood cells in the microvasculature and vascular intimal hyperplasia. Vascular intimal hyperplasia and thrombosis may be related to the abnormal adhesive and procoagulant properties of erythrocytes containing HbS. Marrow or fat emboli secondary to bone marrow infarction has also been implicated in strokes among patients with sickle cell disease. Altered vascular reactivity (inability to develop compensatory vasodilatation) and vasospasm can also be contributing factors.

Children who have experienced a stroke are managed with chronic transfusion therapy to maintain a HbS of < 30%. This significantly reduces the risk of repeated stroke, though does not eliminate it completely. Chronic transfusion therapy ultimately requires iron chelation therapy.[30]

Primary stroke prevention with regular, monthly blood transfusion is the standard of care for children who have abnormally high cerebral arterial flow velocities measured by TCD.

Manifestations of stroke include:

- Completed stroke with neurological deficits lasting > 24 hours
- Transient ischemic attack (ischemia without infarction) – neurologic symptoms lasting < 24 hours
- Hemorrhagic infarct
- Seizures
- Moya-moya syndrome
- Vascular occlusions and stenosis
- Cerebral atrophy

There is now data about the incidence of stroke and risk factors from the stroke study of the Cooperative Study of Sickle Cell Disease (CSSCD) which included over 4000 patients with sickle hemoglobinopathies. Although most patients who have strokes have HbSS disease, it can occur in other genotypes.

Risk factors for stroke among patients with sickle cell disease include:

- Prior TIA or previous stroke
- Acute chest syndrome within the past two weeks
- Multiple episodes of acute chest syndrome
- High systolic blood pressure
- Flow velocity of ≥ 200 cm/sec on TCD (an abnormal reading)

Signs and symptoms of a stroke include:

- Seizures
- Somnolence or disorientation
- Worst headache of the patient's life – should raise concern for subarachnoid hemorrhage
- Weakness or numbness usually on one side of the body, "painless limp"
- Slurred speech or aphasia
- Visual or auditory changes
- Silent cerebral infarcts ("silent strokes") typically occur in the deep white matter of the cerebral cortex and often lead to psychometric problems and learning delays. Neurologic exam should be normal in patients with silent infarcts

Diagnostic evaluation for stroke:

Transcranial Doppler ultrasound (TCD) is primarily used as a screening tool to identify children with sickle cell anemia who may be at increased risk for stroke. TCD is normally recommended for ages 2-16 years. TCD measures the flow velocity through the cerebral arterial circulation, particularly in the internal carotid and middle cerebral arteries. An increased flow velocity (measured in cm/seconds) correlates with the presence of a narrowed vessel or segment. Flow velocities of ≥ 200 cm/sec. are strongly associated with increased risk of stroke. These findings were the result of a large multi-center study [Stroke Prevention Trial in Sickle Cell Anemia (STOP)] which was published in the New England Journal of Medicine in 1998. TCD is currently the only predictive tool available to identify patients at increased risk for stroke. If two consecutive TCD studies are abnormal, the family should be offered prophylactic chronic monthly blood transfusions and chelation therapy.[30]

CT SCAN (initially without contrast) remains very important. It is readily available in most hospitals, is accurate, and can be performed rapidly when a patient presents with an acute stroke. The CT may be normal at the onset in cerebral infarction, but is helpful to rule out hemorrhage, abscess, or tumor as the causes of symptoms. A repeat CT 2 to 7 days after an infarction may show the edematous infarcted area.

MRI/MRA studies, which should include diffusion weighted imaging (DWI) sequences, should be performed instead of CT if available emergently. If MRI/MRA/DWI are not available emergently, the CT scan should be performed. Brain MRI/MRA are also valuable when looking for evidence of prior vascular occlusion or infarct ("silent strokes") and cerebral atrophy. MRI scans are performed in the axial and coronal planes. Infarcts are seen on the T2 weighted images as areas of abnormal signal. It may not be possible to distinguish between ischemia and infarction, but the size and number of lesions can be documented with precision. The lesions are classified according to the size of the areas of increased signal intensity. MRA can be helpful in detecting vasculopathy which may help in clarifying the diagnosis in a symptomatic patient with normal CT and MRI findings. Contrast is not needed when performing MRI/MRA for a patient with sickle cell disease who is suspected of having a stroke. If contrast is needed to assess for other causes of neurologic symptoms (intracranial abscess or tumor), caution must be exercised in the use of hyperosmolar contrast material for angiography in patients with sickle cell disease. Adequate hydration and close monitoring are important in minimizing risks.

Table 7. NIH Suggested Evaluation of Neurological Events in Sickle Cell Disease

Recommendations
1. In people with sickle cell disease who present with severe headache, altered level of consciousness, seizures, speech problems, and/or paralysis, evaluate for stroke by seeking neurologic consultation and performing an urugent head computerized topography (CT) scan followed by magnetic resonance angiography (MRA) if available. (Consensus - Panel Expertise)
2. In consultation with a sickle cell disease expert, perform exchange transfusion in people with sickle cell disease who develop acute stroke confirmed by neuroimaging. (Consensus - Panel Expertise)
3. Initiate prompt evaluation, including neurologic consultation and neuroimaging studies, in people with sickle cell disease who have mild, subtle, or recent history or signs or symptoms consistent with transient ischemic attack. (Consensus - Panel Expertise)
4. In children and adults who have had a stroke, initiate a program of monthly simple or exchange transfusions. (Moderate Strength, Low-Quality Evidence)
5. In children and adults who have had a stroke, is it is not possible to implement a transfusion progaram, initiate hydroxyurea therapy. (Moderate Strength, Low-Quality Evidence)

Source: National Heart, Lung, and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014. 2014. Available at: https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report%20020816.pdf.[8]

Treatment of acute infarctive stroke:

Rapid evaluation and monitoring of progression of symptoms (i.e. increased intracranial pressure) are crucial. Hyperventilation therapy should be avoided. Cerebral edema should be managed pharmacologically. Mechanical ventilation may be necessary. Seizures are common and require anticonvulsant therapy. Transfusion of normal red blood cells to a goal hemoglobin of 10 g/dL emergently will help prevent the progression of the acute stroke. Simple transfusion should be followed by an exchange transfusion with a goal HbS level of < 30%. Patients should be maintained on chronic monthly transfusions with a goal HbS level of < 30% indefinitely.[31] Patients with sickle cell anemia who have suffered an overt stroke are candidates for matched related donor (MRD) and matched unrelated donor (MUD) hematopoietic stem cell transplant (HSCT). Human leukocyte antigen (HLA) typing should also be performed on the patient, parents and full siblings to identify potential donors for HSCT.

Treatment of hemorrhagic stroke:

Patients with intracerebral or subarachnoid hemorrhage may present with focal neurologic deficits, severe headache, increased ICP, or coma. If hemorrhage is present on initial CT or MRI, arteriography is necessary to determine if a surgically correctable lesion is present. Immediate exchange transfusion is recommended to decrease the risk of vasospasm in the area of hemorrhage which can lead to secondary cerebral edema. Hemorrhagic stroke is associated with increased mortality in the acute phase.

Treatment of coma due to generalized arterial hypoxia:

This is a rare situation, but can occur in patients with sickle disorders after experiencing arterial hypoxia. The hypoxia is usually induced by acute or chronic pulmonary disease, which impairs the capacity to exchange oxygen. It can also be induced by right-to-left shunting of blood through a patent foramen ovale due to acute pulmonary hypertension. The red cell sickling that occurs in the arterial circulation tend to lodge randomly in the terminal arterioles of the cerebral vasculature. This results in sufficient hypoxia to cause neuronal dysfunction, but usually not necrosis if the process is reversed in timely order.

The presenting symptoms may mimic embolism. There is usually a rapid, progressive, generalized neurologic deterioration without focal findings. Decorticate or even decerebrate posturing can be seen. Head CT is often normal. There may be other accompanying signs of acute tissue injury from the hypoxia like renal dysfunction, acute centrilobular liver necrosis, or bone marrow necrosis. The treatment is immediate exchange transfusion, and treatment with hyperbaric oxygen for 2-3 hours at 2 atm/d. Aggressive treatment of the hypoxia with positive-end-expiratory pressure ventilation is helpful. Supportive care to other involved organs should not be overlooked. If managed promptly, the patients have the potential for complete recovery.

Correlation of neuropsychometric testing and MRI findings:

Over 35% of children with HbSS or HbSβ^0 thalassemia disease have evidence of “silent” infarcts and cerebral atrophy.[32]

Since the mid-1980s, studies have shown that some children with sickle cell anemia may experience subtle neuropsychological abnormalities thought to be related to silent infarction. The recently published Silent Infarct Transfusion Trial (SIT Trial) confirmed significant neurocognitive deficits in children who had silent cerebral infarcts compared to unaffected sickle cell controls. Most clinically apparent infarcts are in the deep white matter of the frontal lobes. 60% of silent infarcts are bilateral. Standard type IQ testing may not detect the type of problems encountered by children with sickle cell disease.[33]

Therefore, thorough neuropsychometric testing should include assessment of the following:

- Processing speed: This is often impaired in regards to interpretative processing rather than repetitive work
- Memory: Visual memory is more affected than verbal memory, and patterns of recall may be variable and inconsistent
- Attention and concentration: High rates of omission errors and variable patterns in responses are seen. Periods of “spacing out” and inability to sustain attention for prolonged periods of time are common. Some impulsivity may be seen, but clinical hyperactivity is rare.
- Visual-motor integration: handwriting skills may be impaired. Essay writing and test taking may be difficult. Many find typing easier than writing.
- Mathematics: Basic calculation skills can be impaired partly due to problems with memory. Application skills are less affected.
- Reading: Comprehension may be good but is affected by weak decoding skills

Patients found to have neurocognitive delays should have individualized education plans (IEP) in place throughout elementary, middle and high school as well as post-secondary school and beyond. Memory aids for medication timing and medical appointments should be utilized whenever possible given the prevalence of silent infarcts in people with sickle cell disease and the known effects on cognitive function.

Hydroxyurea in the Treatment of Sickle Cell Disease

Fetal hemoglobin (HbF) contains two alpha chains and two gamma globin chains. Following birth, there is a normal switch from gamma to beta chains for production of hemoglobin A instead of HbF. However, in patients with sickle cell disease HbF production switches to HbS production. Most patients with sickle cell disease, regardless of age, have some circulating red cells that contain HbF and are called "F cells." Children and adults whose red cells still contain a high concentration of HbF have a mild clinical course. This led to a search for a drug that would stimulate a switch from beta to gamma globin synthesis. Production of HbF is an inherent property of adult red cells and can be induced when there is sudden erythroid regeneration or "stress" erythropoiesis. Drugs that can trigger rapid erythroid regeneration include cytotoxic agents that are used to treat cancer and are cell cycle specific. Examples include 5-azacytidine, cytosine arabinoside, busulfan, methotrexate, vinblastine and hydroxyurea. Erythropoietin also triggers erythroid regeneration and has been shown to increase total hemoglobin and HbF in a small series of patients.

Hydroxyurea is a simple substance that inhibits ribonucleotide reductase and decreases production of all three cell lines in the bone marrow. Hydroxyurea was selected for study in clinical trials because it is much less toxic than the other chemotherapy drugs mentioned and can be taken once daily by mouth.

In May 1990, a multicenter, placebo-controlled, double-blind trial funded by the National Heart, Lung, and Blood Institute (NHLBI) was initiated. The aim of the trial was to evaluate the effect of hydroxyurea in patients with symptomatic sickle cell disease over a period of 5 years and to determine whether daily oral therapy could decrease the frequency of painful vaso-occlusive episodes by 50%. The results of this trial were published in the New England Journal of Medicine in early 1995. The trial was stopped before all the patients had completed 24 months of therapy and 10 months before the projected end of the study because of the beneficial effects observed in the group receiving hydroxyurea. Treatment with hydroxyurea resulted in a 44% reduction in the rate of vaso-occlusive episodes. Fewer patients assigned to the treatment arm experienced chest syndrome, and fewer underwent transfusion.[34]

As a result of this study, long-term oral daily treatment with hydroxyurea may be offered to adults with sickle cell disease who experience fairly frequent vaso-occlusive episodes or who have had chest syndrome. More recent evidence supports offering hydroxyurea to any patient with HbSS or HbSβ^0 thalassemia who is over 9 months of age, regardless of clinical symptoms. Use of the drug has been extended to patients who have hemoglobinopathies other than hemoglobin SS, such as SC or Sβ^+ thalassemia. It has also been provided to children. There is little question that it has efficacy in attenuating the severity of the disease in the case of SS patients.

Although hydroxyurea has not been shown to be a carcinogen, it is a mutagen and teratogen. There have been no cases of birth defects reported in children born to women with sickle cell disease receiving hydroxyurea but both men and women should be advised repeatedly about the need for contraception if they are going to take this medication. There is no evidence that hydroxyurea increases the risk of leukemia development in adult or pediatric patients with sickle cell disease. The proven benefits of hydroxyurea treatment include fewer painful crises, higher hemoglobin levels, decreased organ damage and extended life span.

Treatment with hydroxyurea is initiated at a starting dose of 15 mg/kg/day to the nearest 500 mg capsule. All capsules can be taken once a day. A complete blood count should be obtained two weeks after any dose adjustment including treatment initiation. The dose may be increased by 5 mg/kg/day if tolerated (ANC>2 K/uL, platelets>80 K/uL, Hb>6.0 g/dL, and retic >95 K/uL). The highest dose level in the clinical trial was 35 mg/kg/day. Most of the adult patients who have been treated on a long term basis are on a dose between 500 mg and 1500 mg/day. Most children tolerate doses in the 25-35 mg/kg/day range.

The most frequent side effects of hydroxyurea are myelosuppression, gastro-intestinal symptoms and dermatological reactions such as maculopapular rash and facial erythema.

There may not be any evidence of clinical benefit for at least one month and possibly not for three months. The patient must be advised and warned about the possible dangers of treatment, including the possibility of teratogenic effects. Women of child bearing age and men who are taking hydroxyurea should be counseled about the use of contraception. It should also be emphasized that the drug has to be taken on a daily basis and that its beneficial effects will be lost if it is discontinued. Finally, it should be explained that the mechanism of action of hydroxyurea is not fully understood and that the optimum dose and schedule is still uncertain.[35]

Please see the Table on the next page for initiating hydroxyurea as well as dose escalation and monitoring recommendations.

Table 8. Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy

The following laboratory tests are recommended before starting hydroxyurea:

- Complete blood count (CBC) with white blood cell (WBC) differential, reticulocyte count, platelet count, and RBC MCV
- Quantitative measurement of HbF if available (e.g., hemoglobin electrophoresis, high-performance liquid chromatography (HPLC))
- Comprehensive metabolic profile, including renal and liver function tests
- Pregnancy test for women

Initiating and Monitoring Therapy

- Baseline elevation of HbF should not affect the decision to initiate hydroxyurea therapy
- Both males and females of reproductive age should be counseled regarding the need for contraception while taking hydroxyurea
- Starting dosage for adults: 15 mg/kg/day (round up to the nearest 500 mg); 5-10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day
- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage
- Aim for a target absolute neutrophil count >2,000/uL; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/uL
- Maintain platelet count > 80,000/uL
- If neutropenia or thrombocytopenia occurs:
  - Hold hydroxyurea
  - Monitor CBC with WBC differential every two weeks until counts normalize
  - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias
- If dose escalation is warranted based on clinicial and laboratory findings, proceed as follows:
  - Increase by 5 mg/kg/day increments every 8 weeks
  - Give until mild myelosuppression (absolute neutrophil count 2,000/uL to 4,000/uL) is achieved, up to a maximum of 35 mg/kg/day
- Once a stable dose is established, laboratory safety monitoring should include:
  - CBC with WBC differential, reticucyte count, and platelet count every 2-3 months
- People should be reminded that the effectiveness of hydroxyurea depends on their adherence to daily dosing. They should be counseled not to double up if a dose is missed
- A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence of failure to respond to therapy
  - Monitor RBC MVC and HbF levels for evidence of consistent or progressive laboratory response
- A lack of increase in MCV and/or HbF is not an indication to discontinue therapy
- For the patient who has a clinical response, long-term hydroxyurea is indicated
- Hydroxyurea therapy should be continued during hospitalizations or illness

Hydroxyurea Prescribing Guidelines

Hydroxyurea (HU) is the only oral medication available to mitigate sickle cell disease (SCD) symptomatology. Hydroxyurea has a bone marrow modulating effect which elevates fetal hemoglobin (HbF) production and has been shown to reduce the incidence of vaso-occlusive (pain) events (VOEs), acute chest syndrome (ACS), and unplanned blood transfusions. The increased erythrocyte life span decreases the rate of hemolysis, and by default, decreases reticulocyte counts. Hydroxyurea also reduces the level of leukocytes, which are implicated in VOEs, and has been shown to reduce elevated transcranial Doppler (TCD) velocities, which are associated with an elevated stroke risk.

Hydroxyurea is FDA approved for use in adults with SCD and is utilized off-label in pediatrics. Over 15 years of data have supported the safety and efficacy of this medication in treating SCD in children, and randomized controlled trials in children have shown similar beneficial effects as in adults. Based on encouraging Baby-HUG results [HU and Growth in Babies], the NIH recommends initiating hydroxyurea at 9 months of age in all children with HbSS or HbSβ^0thalassemia.[1] Hydroxyurea initiation should be preceded with a family discussion of risks and benefits of this therapy as well as the need for monitoring and clinic visit frequency.

Consider hydroxyurea in a child >5 years of age with HbSC or HbSβ^+thalassemia who:

- Has had ≥ 2 hospital admissions in the past year for VOEs
- Has had >1 SCD-related event per month in the past year
- Has missed >2 days of school per month for SCD-related complications
- Has had ≥ 2 episodes of Acute Chest Syndrome (ACS) in their lifetime or
- Has family interest in initiating hydroxyurea

Consider hydroxyurea in adult patients with HbSS, HbSβ^0thalassemia, HbSC, and HbSβ^{0+}thalassemia who:

- Have had ≥ 3 SCD-related moderate to severe pain crises in the past year
- Report SCD-related pain that interferes with activities of daily living
- Have a history of severe or recurrent ACS
- Have severe, symptomatic, persistent anemia that interferes with activities of daily living
- Has interest in initiating hydroxyurea

Baseline Evaluation

- History and physical exam, including a review of indications for hydroxyurea therapy
- Lab evaluation: Complete Blood Count (CBC) with differential and reticulocyte count, Complete Metabolic Panel (BMP + liver function tests), HbF quantitation, Urine pregnancy test, if indicated
- Counsel males and females of reproductive age regarding the need for contraception while taking hydroxyurea.

Treatment Recommendations

Infants and Children >9 months

- Initiate hydroxyurea at 20 mg/kg in a single daily dose (round to the nearest 10mg). Medication should be taken at the same time every day.
- Escalate dose by 5 mg/kg/day (round to the nearest 10mg) every 8 weeks in the absence of dose-limiting cytopenias until Maximum Tolerated Dose (MTD) is achieved. MTD is defined as 35 mg/kg/day or the dose beyond which 2 episodes of drug toxicity have occurred.
- Monitor CBC with differential and reticulocyte count every 4 weeks while in dose escalation. Maintain absolute neutrophil count (ANC) ≥1500/µL (goal ≥2000/µL). Maintain platelet count ≥80,000/µL.

- If neutropenia or thrombocytopenia occurs, hold hydroxyurea and repeat CBC with differential in 2 weeks. If toxicity is associated with illness and subsequently resolves, hydroxyurea should be restarted at previous dose and dose escalation may continue. If there is no associated illness, restart hydroxyurea at 5 mg/kg/day lower than dose associated with cytopenias.

Adults

- Initiate hydroxyurea at 15 mg/kg in a single daily dose (round up to the nearest 500 mg). In patients with chronic kidney disease, initial dose should be 5-10 mg/kg/day. Medication should be taken at the same time every day.
- Escalate dose by 5 mg/kg/day every 8 weeks in the absence of dose-limiting cytopenias until MTD is achieved. MTD is defined as 35 mg/kg/day or the dose beyond which 2 episodes of drug toxicity have occurred.
- Monitor CBC with differential and reticulocyte count every 4 weeks while in dose escalation. Maintain ANC ≥2000/µL. Maintain platelet count and absolute reticulocyte count ≥80,000/µL *(absolute reticulocyte count= Total RBC count * Reticulocyte %)*.
- If neutropenia (ANC <1300/µL) or thrombocytopenia occurs, hold hydroxyurea and repeat CBC with differential in 2 weeks. If toxicity is associated with illness and subsequently resolves, hydroxyurea should be restarted at previous dose and dose escalation may continue. If there is no associated illness, restart hydroxyurea at 5 mg/kg/day lower than dose associated with cytopenias. If unable to escalate hydroxyurea dose beyond 20 mg/kg/day due to cytopenias, contact hematology for additional assistance.

Contraindications:

- Pregnancy, breastfeeding
- Use with caution in other hepatically metabolized medications (such as certain anti-epileptics)

Laboratory Monitoring

- Once MTD has been achieved, laboratory monitoring should include CBC with differential and reticulocyte count every 2-3 months. CMP (BMP + liver function tests) should be obtained every 6 months.
- Increases in mean corpuscular volume (MCV) and HbF indicate an appropriate laboratory response to hydroxyurea
- Pregnancy testing should be obtained routinely in sexually active female adolescents and adults as clinically indicated.

Treatment Endpoints

Patients should be counseled that hydroxyurea therapy may require up to 6 months at the MTD before clinical response is seen. Treatment efficacy is defined as a decreased frequency of SCD related-complications (e.g. VOE, ACS), increased HbF, or improved anemia with absent or acceptable treatment-related side effects.

- Effectiveness of hydroxyurea depends on adherence to daily dosing.
- If a dose is missed, the usual dosing should be continued on the next day (do not double the dose to make up for missed doses.)
- Continue hydroxyurea therapy during hospitalizations and acute illness, unless a dose limiting toxicity is present as described above.

Hydroxyurea treatment may be discontinued for the following reasons:

- o No improvement in clinical status despite dose escalation to MTD and reassurance of adherence.
- o Documented pregnancy or refusal to use contraception in males or females of child bearing age.

Abbreviations

ACS	acute chest syndrome	**MTD**	maximum tolerated dose
ANC	absolute neutrophil count	**NIH**	National Institutes of Health
BMP	Basic Metabolic Panel	**RBC**	red blood cell
CBC	Complete Blood Count	**SCD**	sickle cell disease
CMP	Complete Metabolic Panel	**TCD**	transcranial Doppler
HbF	fetal hemoglobin	**VOE**	vaso-occlusive event
MCV	mean corpuscular volume		

References

1. National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. Bethesda, MD: National Heart, Lung, and Blood Institute, US Department of Health and Human Services; 2014.

* IF YOU WOULD LIKE COPIES OF THIS DOCUMENT, PLEASE CONTACT THE IHTC DIRECTLY

Transfusion Therapy

Blood transfusions are used for management of acute conditions and prevention of complications associated with sickle cell disease. Methods of transfusion depend upon the underlying goal of therapy. The genotypes most likely to need transfusion therapy at some time are homozygous sickle cell anemia (HbSS) and HbSβ^0thalassemia.

Simple transfusion involves transfusing RBC without removing any of the patient's blood volume. Partial exchange transfusion refers to manually phlebotomizing a percentage of the patient's whole blood prior to or concomitantly with RBC transfusion. Exchange transfusion involves removal and replacement of the patient's blood volume by pheresis. This is achieved by exchanging equal volumes of between 50-80 mL/kg donor whole blood for the patient's blood. This method rapidly and substantially reduces the concentration of sickle cells without increasing the overall hematocrit or blood viscosity.

Blood viscosity is determined by the red cells themselves as well as the hematocrit. Sickle cells are intrinsically more rigid and viscous. Substantially raising the hematocrit without first reducing the proportion of sickle cells can lead to dangerous levels of blood viscosity. For this reason, simple transfusions must be used with caution for patients with hematocrit >25%.

NIH indications for transfusion in sickle cell disease (see Tables on the following pages for level of evidence and strength of recommendation for the 2014 Expert Guidelines):

A need to increase oxygen carrying capacity via simple transfusion

- Acute anemia secondary to aplastic crisis, splenic sequestration, acute blood loss or other causes
- Symptoms of high output cardiac failure, postural hypotension, angina, or cerebral dysfunction
- Symptoms of fatigue and dyspnea with a low hemoglobin (usually < 5g/dL)
- Prior to surgery requiring general anesthesia

A need to improve microvasculature perfusion and to decrease the proportion of HbS via partial exchange or exchange transfusion therapy

- Acute, impending, or suspected cerebrovascular events (stroke, partial stroke, TIA)
- Arterial hypoxia (fat embolization) and progressive lung disease (acute chest syndrome)
- Unresponsive priapism
- Eye surgery (even when done under local anesthesia and in the nonanemic patient)

In the presence of certain chronic conditions, it may be desirable to keep the proportion of HbS below 30% via simple transfusions on a routine schedule

- History of stroke
- Leg ulcers
- Pregnancy: Usually in the 3rd trimester, earlier in women with evidence of chronic organ dysfunction or poor fetal growth
- Chronic organ failure
- Short duration chronic transfusion therapy (6 months or less) may be useful when extreme and frequent vaso-occlusive episodes interrupt activities of daily living

Transfusion therapy is usually not helpful or indicated for:

- Asymptomatic anemia
- Uncomplicated pain episodes
- Minor infections
- Minor surgery with brief anesthesia or conscious sedation (<30 minutes of anesthesia time)
- Aseptic necrosis of the hip or shoulder

Blood products for patients with sickle cell disease:

- Must be sickle negative (even sickle cell trait) and should be leukodepleted
- Patients who have been previously transfused should be checked for the presence of alloantibodies
- Full antigenic typing of the red cells to be transfused should include at least: C, E, Kell
- If not an emergent transfusion, please call blood bank at the hospital where patient is regularly transfused or last transfused to obtain antibody history

Table 9. Acute Complications - Graded Recommendations to Tranfuse

Indication	How to Transfuse	Quality of Evidence	Strength of Recommendations
Symptomatic acute chest syndrome (ACS) combined with a decreased Hb of 1g/dL below baseline	Simple transfusion	Low	Weak
Symptomatic severe ACS (as defined by an oxygen saturation less than 90% despite supplemental oxygen)	Exchange transfusion	Low	Strong
Acute splenic sequestration plus severe anemia	Simple transfusion	Low	Strong
Stroke	Simple or exchange transfusion	Low	Moderate

Table 10. Acute Complications - Consensus Recommendations to Transfuse

Indication	How to Transfuse
Hepatic sequestration	Exchange or simple transfusion
Intrahepatic cholestasis	Exchange or simple transfusion
Multisystem organ failure (MSOF)	Exchange or simple transfusion
Aplastic crisis	Simple transfusion
Symptomatic anemia	Simple transfusion

Table 11. Acute Complications - Graded Recommendations When Transfusion is NOT Indicated

Indication	Quality of Evidence	Strength of Recommendation
Uncomplicated painful crisis	Low	Moderate
Priaprism	Low	Moderate

Table 12. Acute Complications - Consensus Recommendations When Transfusion is NOT Indicated

Indication
• Asymptomatic anemia • Acute kidney injury, unless mulitsystem organ failure (MSOF)

Table 13. Chronic Complications - Graded Recommendations When to Initiate a Chronic Transfusion Program

Indication	How to Transfuse	Quality of Evidence	Strength of Recommendation
Child with transcranial Doppler (TCD) reading* ≥200 cm/sec	Exchange or simple transfusion	High	Strong
Adults and children with previous clinically overt stroke	Exchange or simple transfusion	Low	Moderate

Table 14. Chronic Complications - Graded Recommendations When Initiation of a Chronic Transfusion is NOT Indicated

Indication	Quality of Evidence	Strength of Recommendation
Recurrent splenic sequestration	Low	Weak

** TCD reading is the time averaged mean maximal cerebral blood flow velocity*

Tables are from NHLBI Guidelines

Transfusion Administration

Simple transfusion usually consists of giving 10-15cc/kg of PRBC over 3-4 hours. A manual partial exchange transfusion usually involves pre-transfusion phlebotomy of 5cc/kg whole blood followed by replacement of phlebotomized blood volume with normal saline and transfusion with 10-20mL/kg RBC. Another method is to remove whole blood from an I.V. in one arm while transfusing RBCs into the other arm. In some cases, diuretics can be used to avoid fluid overload with transfusion.

Rapid partial exchange technique:
These formulas can be used to achieve HbS concentrations below 30% without increasing the hematocrit above 35% (assuming that RBC units have a hematocrit of 80%, and whole blood units have a hematocrit of 40%). The total volume of blood to be infused is proportional to the patient's weight and hematocrit.

For patients with hematocrit < 15%:
Option 1: Exchange equal volumes (50cc/kg) of donor whole blood for the patient's blood
Option 2: Exchange equal volumes (30cc/kg) of packed red blood cells for the patient's blood

For patients with hematocrit between 16-30%:
Option 1: Exchange equal volumes (80cc/kg) of donor whole blood for patient's blood
Option 2: First exchange equal volumes of RBC (10cc/kg) for patient's blood; then exchange equal volumes (70cc/kg) of donor whole blood for patient's blood

In adults with hematocrits between 20-26% who are hemodynamically stable, an adequate exchange can be obtained by removing 1 unit of blood, infusing 500cc of saline, removing a second unit of blood, and then infusing 5 units of RBC.

For patients with hematocrit >30% (usually patients with HbSC or $S\beta^+$ thalassemia):
- First remove 10cc/kg of patient's blood and replace with an equal volume of normal saline
- Then exchange with equal volumes (90cc/kg) of donor whole blood for patient's blood. Avoid using packed red blood cells to avoid excessively raising the hematocrit

<u>Automated exchange transfusion:</u>
Automated full red cell exchange uses continuous flow instrumentation to rapidly and effectively replace patient blood with donor packed red blood cells. Goal is for 25-30% fraction of cells remaining (which is roughly equivalent to a HbS level of 30%).

<u>Chronic transfusion therapy:</u>
Once a HbS of <30% has been achieved as a therapeutic intervention, giving simple transfusions on a 2-4 week schedule can maintain the HbS at or below 30% to prevent further complications.

Complications of transfusion therapy

Iron overload is generally defined as serum ferritin levels > 1000 ng/mL. Chelation therapy with deferasirox (Exjade or Jadenu) is indicated when 2 consecutive ferritin levels exceed 1000 ng/mL. This is expensive, long term therapy for patients on chronic transfusions. Exjade must be dissolved into 8 ounces of orange juice and taken once a day. Jadenu is a new formulation of deferasirox that can be swallowed whole, making it much more tolerable for patients. Deferoxamine (Desferal) requires long (10-12 hours) subcutaneous infusion usually 5-7 days or nights per week. Untreated iron overload can result in cardiac disease/failure, hepatic disorders/failure, brain damage, and endocrine abnormalities.[37]

Alloimmunization to red cell antigens occurs in 25-30% of transfused patients with sickle cell disease. This is higher than in the general public, and results in difficulty in obtaining compatible blood and a high incidence of delayed (5-20 days post) hemolytic transfusion reactions. The risk of alloimmunization can be significantly reduced by:
- Maintaining accurate transfusion and phenotyping records
- Limiting the number of transfusions given; giving transfusions for only clear-cut indications
- Screening for newly acquired antibodies
- Typing the patient for antigens of the Rh and Kell blood groups and avoiding the transfusion of cells having these antigens (especially E, C, and Kell) if the patient lacks the antigen
- Increasing the numbers of African American donors for more likely phenotypical matches
- Provide frequently transfused patients with a card identifying their red cell phenotype and any identified antibodies

Some highly alloimmunized patients can develop autoimmune hemolytic anemia after a transfusion. Often, the Direct Antibody Test remains positive long after the transfused cells are gone. This is attributed to the development of antibodies directed at self-antigens (auto-antibodies). In this case, future transfusions will be with the *least incompatible* donor blood available.

Alloimmunization to antigens on donor white cells can be minimized by using a leukodepletion filter for transfusion. Some patients also benefit from pre-treatment with anti-pyretics and anti-histamines to minimize reactions to donor cell proteins.[37]

Transmission rates of hepatitis and HIV virus in transfused sickle cell patients are the same as in other multiply transfused patients.

Chronic Problems Associated with Sickle Cell Disease

EYE DISEASE

Erythrocyte sickling that occurs in the microvascular beds of the eye has the potential to cause vision loss. Ophthalmic complications that can affect vision depend on the tissue involved and anatomical location. Ophthalmoscopic evaluation for these patients must include thorough examination of the posterior and peripheral retina through a dilated pupil.[38]

Proliferative sickle retinopathy can lead to vitreous hemorrhage and retinal detachment. Laser photocoagulation is often helpful for many patients with this complication. Retinal detachment and loss of vision can be avoided in some patients who develop retinal holes or traction by early detection and treatment. Once detachment or significant vitreous hemorrhage is present, surgical intervention is necessary in an attempt to restore vision.

The eye may be affected in patients with sickle cell disease in two main forms:
1. Sickle cell retinopathy
2. Hyphema

1. Retinopathy

Sickle cell retinopathy is more commonly seen in patients with HbSC disease (~33% affected), than in patients with either HbSβthalassemia (~14%) or HbSS disease (~3%).[6]

The retina is exquisitely sensitive to oxygen deprivation. Even temporary vaso-occlusion, longer than 90-120 minutes, can result in permanent infarction. If this event occurs in the peripheral retina, it rarely causes loss of vision. However, it may initiate a chain of events leading to neovascular malformations growing internally from the surface of the peripheral retina into the vitreous chamber. The bleeding from fragile vessels into the vitreous gel can lead to permanent damage, manifesting clinically along a spectrum from the sensation of black “floaters” to progressive retinal detachment.

Vitreous Hemorrhage and Retinal Detachment

Proliferative sickle retinopathy causes vitreous hemorrhage. Degeneration and fibrosis of the vitreous cavity can lead to traction detachment of the retina, or retinal hole formation sometimes followed by retinal detachment.

Vitreous hemorrhage and retinal detachment are the most common causes of blindness in sickle cell disease patients. If a vitreous hemorrhage does not clear in 3-6 months, or if traditional detachment occurs, vitrectomy in combination with operative intervention for detachment is the treatment of choice. If surgery is indicated, partial exchange transfusion is recommended before the procedure.

Trauma to the eye and the following conditions should be treated as an ophthalmologic emergency in these patients.

2. Hyphema
The anterior chamber of the eye, between the cornea and the iris, is ordinarily filled with a colorless non-cellular liquid, the aqueous humor, which is low in oxygen concentration and pH. Hyphema is the presence of blood in the anterior chamber of the eye. Individuals with hemoglobinopathies, including sickle cell trait, have the risk of sickling within this chamber, obstructing the normal drainage of this space. This will lead to increased intra-ocular pressure, a process that, if not reversed promptly can obstruct blood flow to the retina and optic nerve causing permanent damage.

Central Retinal Artery Occlusion
Occurring mainly in pediatric and young adult patients, central retinal artery occlusion, from thrombus formation in the retinal artery, is a rare cause of acute blindness in patients with sickle cell disease. Typical presenting signs and symptoms are sudden, painless unilateral or bilateral vision loss. Emergent exchange transfusion is the treatment of choice.

Orbital Bone Infarction
Infarction of the orbital bone, though rare, usually occurs during a vaso-occlusive crisis. Hematomas and inflammation of the surrounding tissues often accompany orbital bone infarcts and can impinge on the optic nerve and other important structures. Surgical intervention to relieve pressure on the optic nerve may be necessary with rapidly evolving infarcts that are unresponsive to medical management.[38]

Recommended Routine Eye Care
Ophthalmologic examination is recommend yearly beginning at age 10 years. A retinal specialist should evaluate patients with evidence of retinopathy.

Immediate referral to an ophthalmologist is indicated when a sudden change of visual acuity is noted or in the event of trauma to the eye.

First decade of life
Routine yearly regular vision screen with regular well child visits.
If there is evidence of deterioration, an ophthalmology consult is indicated.

After 10 years of age
Annual retinal exam by an ophthalmologist for evaluation of sickle cell retinopathy.

LEG ULCERS
Proper gentle debridement, control of local edema, treatment of superinfection, identification and correction of nutritional deficiencies, and prevention of significant anemia may influence outcomes. However, transfusion therapy is unproven and not recommended by some practitioners.[39]

Local care: Saline wet-to-dry dressings two to three times a day can debride adherent eschar. If this is very painful, analgesic premedication should be administered 30 minutes prior to the dressing change. EMLA cream may also be applied directly onto the wound and covered with plastic wrap for 60 minutes prior to gentle manual wound debridement.

Crystalline sodium chloride-impregnated gauze (Mesalt of Sanulla, Inc.) can be useful if copious exudate interferes with drying. Debridement using hydrocolloid dressings (DuoDerm, Convatec) can be used to liquefy all dead tissue and is changed only every 4-7 days. The dressing is applied with ample margins so that the seal remains intact.

It must be changed immediately if the seal is lost or if there is leakage. If the wound is deep, it can be filled with granules and then covered with the hydrocolloid dressing. Due to the liquefication and removal of devitalized tissue, the wound can appear larger when the dressing is changed. It may also have a foul odor. Once a clean bed is obtained, compression dressings can be initiated with an Unna's boot (zinc oxide impregnated gel boots) even over a hydrocolloid dressing.

Once some healing has begun, a moist dressing may be more helpful. For example, applying antibiotic ointment to the wound, covered by a petroleum gauze dressing, followed by a plain gauze and elastic compression bandage wrap. Bed rest, leg elevation, and compression stockings or wraps (Coban, ACE wraps, TED hose) help control local edema.

Secondary infection with *Staphyloccus aureus* and *Pseudomonas aeruginosa* are common. Topical antibiotics in ointment or spray form (like mixtures of bacitracin, neomycin, and polymyxin B) can be helpful. Some have had success using polymyxin B powder (by itself or mixed with Dermagran solution) directly on the wound followed by a layer of Collagenase ointment. Systemic antibiotic therapy is not helpful unless the patient develops cellulitis. If cellulitis develops, or an underlying osteomyelitis is suspected, oral or parenteral antibiotics covering *S. aureus and Pseudomonas* should be initiated.

Regranex gel applied directly to the wound after gentle cleansing and debridement 1-3 times per day has been effective for some. This synthetic matrix of a tripeptide bound to a hyaluronate supports and stimulates migration of cells, granulation, and keratinocyte layer formation.

Elevation of fetal hemoglobin with administration of oral hydroxyurea with or without subcutaneous erythropoietin can facilitate healing of leg ulcers. Caution must be used to prevent myelosuppression with hydroxyurea that could adversely impact wound healing. The initial starting dose of hydroxyurea is 20 mg/kg/day. The dose may be escalated to a maximum of 35 mg/kg/day as tolerated by blood counts.

Zinc and vitamin D deficiencies are prevalent among patients with sickle cell disease. Wound healing increases metabolic demands for protein and calories. Supplements with zinc sulfate 220mg/day, vitamin D 1000 IU/day, vitamin C 500 mg/day, vitamin E 400 IU bid, and high protein nutritional supplements may be helpful.

Table 15. Wound Care Principles in Patients with Sickle Cell Disease and Ulcers

Systematic Treatment	Local Wound Care
Vasodilators for systemic hypertension	Debridement
ACEI/ARB* for proteinuria/microalbuminuria	Identify and treat infection
Chelation for iron overload	Absorb excess exudate
Pulmonary vasodilator and/or diuretics for pulmonary hypertension	Maintain moist wound surface
Correction of vitamin D or zinc deficiency	Open or excise closed wound edges
Supplements for protein-calorie malnutrition	Protect healing wound from infection or trauma
Anticoagulation for newly diagnosed DVT	Relieve periwound edema by compression
Psychological support	Comfortable footwear
Pain control	

* ACEI: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin II Receptor Blocker

Source: Minniti CP, Kato GJ. Critical Reviews: How we treat sickle cell patients with leg ulcers. Am J Hematol 2016;91:22-30.[9]

AVASCULAR NECROSIS (AVN)

Osteonecrosis can affect patients with all types of sickle cell disease and typically involves the shoulder or hips. The peak incidence in patients with HbSS is between 25 and 35 years, and slightly older than that for patients with HbSC or Sβ⁺thalassemia. A crescent sign often distinguishes early development of AVN radiographically and represents a fracture line within the necrotic femoral head beneath the cartilage. Other radiographic findings are sclerosis, deformity, or collapse. Plain radiographs are of limited utility when evaluating a patient with suspected AVN because they only detect late stages of the disease. MRI provides better detection of the early stage AVN than plain films. Since 40-80% of cases of AVN of the hip are bilateral, radiologic evaluation should include both hips. The diagnosis of AVN of the femoral head is usually made after the patient develops complaints of intermittent or constant pain in the buttock or groin that generally worsens with walking and improves with rest. Occasionally, AVN can have an acute onset of symptoms mimicking septic arthritis.

AVN can be staged based on the following criteria and treatment decisions are based on the disease stage and patient's level of function:

Table 16. Ficat Stages of Avascular Necrosis

Ficat Stage	Radiographic Signs
EARLY: Stage 0. Preclinical	None: marrow necrosis may be present histologically
EARLY: Stage I. Preradiographic	None: abnormal MRI with marrow and bone necrosis
EARLY: Stage II. Before flattening of head or sequestrum formation	Diffuse porosis, sclerosis, or cysts
TRANSITION	Femoral head flattening Crescent sign
LATE: Stage III. Collapse	Broken contour of head Sequestrum Joint space normal
LATE: Stage IV. Osteoarthritis	Flattened contour Decreased joint space Collapse of head

Most orthopedists consider core decompression to be the most beneficial for Ficat stage I and II of AVN of the hip.

Initial treatment consists of non-weight bearing, heat, massage, as well as analgesics and NSAIDs for up to 6 months. When AVN occurs before closure of the epiphyses, considerable healing and recovery is possible. Osteotomy with rotation of the femoral head to a new area of weight bearing can be tried for children. Core decompression of the femoral head has been helpful in reducing pain in older patients. However, a small study did not reveal significant differences in outcomes between core decompression and physical therapy alone. Surgical replacement of the joint is usually effective and is reserved for patients incapacitated by hip pain and unable to carry out activities of daily living. Joint replacement does not always relieve the pain and restore function successfully.[40,41]

RENAL DISEASE

A series of progressive and random pathologic events involving the kidney begin early in the first decade of life in patients with sickle cell disease and continue throughout life. Clinical and pathological data indicate that intravascular sickling occurs more readily in the kidney than in any other organ.

The distribution of blood flow in the kidney and the hypertonicity of the renal medulla create a milieu where red blood cells containing HbS readily undergo deoxygenation and sickling in an acidic and hyperosmolar environment. This combination of hypoxia, hypertonicity, and acidosis in the renal medulla leads to stasis in the vasa recta and subsequent ischemia of the renal medulla and papillary tip. Distortion of the regional blood flow may later result in focal interstitial nephritis, tubular dysfunction, atrophy, and papillary fibrosis.[18]

Important Facts to Remember about Renal Dysfunction in SCD patients

- Hyposthenuria (inability to concentrate urine appropriately) is the most common renal complication and results in urinary frequency and enuresis
- GFR may be overestimated by measurement of creatinine clearance because of increased creatinine secretion
- Tubular potassium excretion is also impaired in these patients with a tendency towards modest hyperkalemia. This is more pronounced in older patients, and if clinically apparent will be more resistant to kaliuretic agents such as furosemide. *The use of angiotensin converting enzyme (ACE) inhibitors may result in a marked hyperkalemia*
- Approximately 15% of children and 40% of adults with HbSS disease have high normal or elevated serum uric acid levels, due to increased urate production associated with increased erythropoiesis coupled with decreased renal clearance of urate. The possibility of uric acid nephropathy or clinical gout should be considered in adult patients with SCD

Gross Hematuria

Gross hematuria is one of the most prevalent manifestations of sickle cell kidney disease. Hematuria is much less common in patients with sickle cell trait, but is a well-documented entity. The bleeding is usually painless, although clot formation in the renal pelvis and ureter may produce renal colic. It is frequently unilateral, with the left kidney involved in 80% of cases. Hematuria may be intermittent, chronic but low grade, or persistent.

The pathogenic mechanism is thought to be sickling in the vasa recta, leading to stasis and ischemia, with subsequent extravasation of blood into the renal parenchyma and collecting system, or in some cases frank papillary necrosis.

Diagnostic evaluation should include:

- Renal ultrasonography
- Abdominal and Pelvic CT scan (with contrast is ideal if it can be performed safely, based on patient's renal function)
- Cystoscopy
- Urine culture
- Measurements of coagulation function

Treatment should include adequate hydration in order to maintain good urinary flow that will decrease the tendency for clot formation in the renal pelvis or ureter. Some patients may develop chronic hematuria. These individuals require bed rest and sustained effective urine output. Careful use of epsilon aminocaproic acid (EACA, Amicar) may be considered in some instances. Patients with chronic hematuria may require iron supplementation to compensate for the urinary iron loss.

Renal Papillary Necrosis

Renal papillary necrosis is a relatively common finding, occurring in almost 25% of patients with sickle cell disease. It may be asymptomatic or accompanied by hematuria or proteinuria. The etiology is identical to that described for hematuria; usually it is asymptomatic and is most commonly diagnosed at the time of an abdominal/pelvic CT scan due to irregularities or "pseudodiverticuli" of the renal pelvic seen on the contrasted films. The presence of papillary necrosis and interstitial nephritis may cause increased susceptibility to pyelonephritis.

Proteinuria and Nephrotic Syndrome

Approximately 25% of adults with HbSS disease developed chronic proteinuria. The etiology is related to hyperfiltration, glomerulopathy, and glomerular capillary hypertension. ACEI can decrease proteinuria acutely even without altering systemic blood pressure. The effectiveness of ACEI in diminishing proteinuria, and observation of glomerular hypertrophy in these patients implicate hemodynamic factors in the initiation and progression of the glomerulopathy. Patients with sickle cell disease on ACEI should have their potassium closely monitored. Nephrotic syndrome associated with membranoproliferative glomerulonephritis has been described in patients with HbSS disease.

The treatment of renal disease is generally unsatisfactory: steroids or cytotoxic drugs have shown no beneficial effect in this condition. If proteinuria persists for more than 4 weeks, it should be evaluated with 24 hour urine protein quantitation and creatinine clearance. In the presence of pre-nephrosis or frank nephrosis the patient should be referred to a nephrologist for evaluation.

Hypertension

Persistent elevation of diastolic blood pressure in patients with HbSS disease usually signals underlying renal disease. True hypertension occurs in less than 5% of patients; it is important to remember that patients with sickle cell disease often have a lower than normal blood pressure compared to healthy controls. Transient hypertension may appear during painful crisis or after red blood cell transfusion. The therapeutic management in patients with sickling disorders differs from non-affected individuals. Diuretics generally are to be used with caution, particularly in younger patients, as dehydration may predispose to vaso-occlusive crisis. The natriuretic response to loop diuretics is decreased, particularly in older patients. In patients with hypertension and proteinuria, ACEI may control hypertension and reduce the proteinuria.

Due to compensatory alterations of cardiovascular function in patients with sickle cell disease, the deleterious effects of hypertension on the heart and vascular system are likely to be amplified, and therefore effective control of the blood pressure is imperative.

Chronic Renal Failure
The course of renal disease is generally that of persistent and massive proteinuria, with slowly progressive glomerulosclerosis and ultimate development of renal failure. Chronic renal failure occurs in a small percentage of patients with sickling disorders. Patients in renal failure may be at first managed medically, however if renal failure progresses, the patient should be referred for hemodialysis or possible renal transplantation. Sickle cell disease is not a contraindication to either of these interventions.

In older patients, the anemia related to chronic renal failure may cause cardiopulmonary complications. These patients will benefit from a chronic transfusion program. The experience of the use of recombinant erythropoietin in patients with HbSS disease and renal failure is limited, but promising.

Routine Renal Function Screening and Care

Renal function testing
Annual urinalysis starting at age 10 as recommended by the NHLBI.
- The presence of hematuria, persistent proteinuria or casts in the urine sediment warrants further investigation.
- Persistent proteinuria should be evaluated by 24-hour urine collection for protein quantification and referral to nephrologist.
- Some authors suggest screening for renal damage by detecting microalbuminuria as an early indicator.

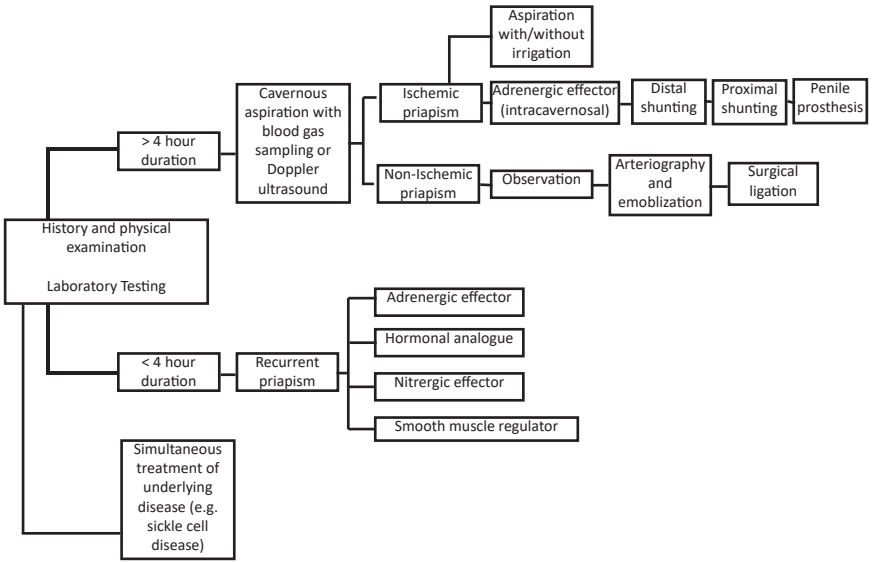
Blood pressure
Blood pressure should be measured annually after 2 years of age.
- If hypertension is associated with renal damage, it will require an effective management program considering the pathophysiology of this condition.
- It is important to remember that blood pressure in patients with sickle cell disease is often lower than the unaffected population. In a patient with sickle cell disease, a normal blood pressure may actually be hypertension. Unfortunately normative curves for blood pressure are not yet available for patients with sickle cell disease.

PRIAPISM

Priapism is a painful erection of the penis that occurs in males with sickle cell disease, although it can occasionally be painless. Priapism is an often difficult complication to manage in patients with sickle cell disease. Treatment is considered successful if detumescence occurs less than 4 hours after onset. Priapism is considered to be stuttering if multiple self-limited episodes occur in a less than 4 hour timeframe. Episodes of priapism that last for longer than 4 hours can result in impotence. Only one randomized control trial has been performed for patients with priapism, and the sample size was small, limiting the ability to draw far reaching conclusions.[42]

Typical interventions for priapism include:
- Hydration with I.V. fluids
- Pain control: Either po or I.V. opioids, depending on the patient's level of pain
- Injection of intracavernosal alpha adrenergic agonist (phenylephrine)- should be performed by Urology consultant
- Oral pseudoephedrine: Can be used as needed for acute priapism or on a daily basis for recurrent or stuttering priapism
- Exchange transfusion should be discussed with Hematology consultants as it may help to prevent a severe episode or recurrence of priapism while hydroxyurea is being initiated/ titrated.
- Hormonal blockade (GnRH agonist, Androgen antagonist, Estrogen receptor agonist)
- Phosphodiesterase type 5 inhibition (Sildenafil)

Management Algorithm for Priapism



Recreated from the British Journal of Haematology, 2013[42]

Reproductive Health and Pregnancy

Reproductive Health

Adolescents with sickle cell typically have delayed pubertal development which is 1-2 years later than age-matched healthy controls.[43]

Sickle cell disease is not a contraindication for use of oral contraceptives, nor is it an indication for sterilization. Low-estrogen oral contraceptives are safe and effective for most women with sickle cell disease, though they may slightly increase the rate of vaso-occlusive pain events and venous thromboembolism. Depo-provera is commonly prescribed for pregnancy prevention in women with sickle cell disease. In women who have increased vaso-occlusive pain around the time of their menses, Depo-provera may help to alleviate the pain. IUDs are not generally recommended due to the increased risk for bleeding and infection. Condoms are recommended as barrier protection against sexually transmitted infections.[44]

Infertility in men with sickle cell disease is multi-factorial with causes including hypogonadism, low sperm counts and poor motility, and erectile dysfunction secondary to priapism. Infertility rates are largely unstudied in women with sickle cell disease and it is currently unknown if women with sickle cell disease are at higher risk for infertility than healthy controls.[44]

Hydroxyurea should be discontinued 3 months prior to pregnancy in females who are planning to become pregnant or men who are planning to father children.

Pregnancy

Pregnancy carries some increased risk for a woman with sickle cell disease as well as for her fetus, but should not be a contraindication for childbearing. Prenatal care by a practitioner with expertise in high-risk pregnancy is desirable. Ideally, the monitoring should be every 2 weeks until the 36th week of pregnancy, then weekly thereafter.

Pregnant patients should receive 5mg folic acid daily. This may be given in addition to other prenatal vitamins, minerals, and iron supplements (unless the patient has increased iron stores from multiple prior transfusions).

All patients should have blood screening for presence of alloantibodies (regardless of transfusion history). Management of the alloimmunized mother should include Rh/antibody titers, administering Rh immunoglobulin if indicated, and performing amniocentesis to assess fetal development and bilirubin concentration.

Ultrasound should be performed initially during the first trimester followed by more in depth ultrasonography to look for congenital anomalies at week 20 of gestation. Ultrasound should be repeated at weeks 32 and 36 to monitor fetal growth and amniotic fluid level.

If intrauterine growth failure is detected, bed rest is recommended and early delivery considered if growth does not accelerate or if urinary estriol decreases. Stress tests should be used if there are question of uteroplacental inadequacy.[45]

Prophylactic red blood cell transfusions may be used to keep the HbS< 50% in an attempt to decrease sickling events during pregnancy; however, this should be decided on an individual basis and should be performed during the third trimester as the fetus grows and has an increased oxygen demand. Recent meta-analyses have revealed that prophylactic exchange transfusions with a goal HbS< 30% may be of special benefit to women with chronic organ injury, severe obstetric complications, are carrying multiple fetuses or a singleton who has complications. The benefits of transfusion should be balanced with the transfusion risks, most importantly alloimmunization which can cause hemolysis in the fetus/neonate.[37]

If painful vaso-occlusive episodes occur during pregnancy, they should be treated as usual. Opioids can be used in conventional doses. Use of NSAIDs as adjunctive analgesia is generally discouraged, especially in the third trimester because NSAIDs are known to cause closure of the ductus arteriosus.

Other complications, such as acute chest syndrome, stroke or septicemia, should be managed as they are for non-pregnant patients. Preexisting renal disease and congestive heart failure are likely to worsen during pregnancy. Toxemia, thrombophlebitis, pyelonephritis, and spontaneous abortions are more common in women with sickle cell disease. Treatments for these conditions remain the same as for any other pregnant patient.

If delivery is uncomplicated, local or regional anesthesia causes no problems. If general anesthesia is necessary for Cesarean section, pre-op simple transfusion and adequate I.V. hydration are recommended if time and conditions permit. It is desirable to have the HbS <50% for any general anesthetic and the hematocrit should be approximately 30%.

Standard postpartum care should be implemented with extra attention to maintenance of adequate hydration and prevention of pulmonary atelectasis. Fevers should be fully evaluated and treated aggressively. Four to six weeks of prophylactic anticoagulation postpartum for new mothers with sickle cell disease should be strongly considered given the increased risk of thrombosis during in the immediate postpartum period.

In the state of Indiana, all newborn infants are screened for hemoglobinopathies as well as other genetic disorders. The results are sent to the primary care provider and the Indiana State Department of Health.

Pregnancy Termination

If termination of pregnancy is considered at less than 13 weeks, local analgesia and curettage suction is recommended. Termination of the pregnancy before 7 weeks can be associated with increased risk of incomplete removal of fetal tissue leading to bleeding and infection. Beyond 13 weeks, hypertonic urea solutions are injected into the uterus and contractions are stimulated with prostaglandin F2. Hypertonic sodium chloride should not be injected, as it can induce sickling. Rh negative women should receive Rh immunoglobulin after spontaneous or therapeutic abortion.

Hematopoietic Stem Cell Transplant

The only cure for sickle cell disease currently available is hematopoietic stem cell transplant (HSCT). Matched sibling donor (MSD) transplants in patients with sickle cell disease have the highest overall survival (OS) rates (>90%), disease free survival (EFS) rates (82-100%) and lowest rates of graft rejection (8-18%) and graft versus host disease (GVHD) (6-35%). Unfortunately, less than 20% of patients with sickle cell disease have a matched sibling donor. Alternative donor HSCT utilizing stem cells from matched unrelated donors or haploidentical donors should only be performed in the context of a research study, and several large studies are ongoing to determine the best conditioning regimens and GVHD prophylaxis strategies.[46]

Patients with sickle cell disease undergoing HSCT are at higher risk for intra-transplant complications than other non-malignant HSCT candidates. Aggressive supportive care with RBC and platelet transfusions is necessary. Additionally, avoidance of hypertension and hypomagnesemia are especially important to avoid neurologic sequelae in the immediate post-HSCT period.[47]

The risks and benefits of HSCT should be carefully considered for each sickle cell patient. Cord blood banking through the Sibling Connection program[48] is available for all expectant parents of full siblings to children with HbSS or HbSβ^0thalassemia. Referral to transplant centers with experience in performing HSCT for sickle cell patients is imperative given the increased level of supportive care needed by this population. Please see the table for current indications for HSCT for patients with sickle cell disease.

Table 18. Indications for HSCT in SCD

Matched sibling donor (if available)	Matched URD transplant	Mismatched marrow donor, haploidentical donor, unrelated cord blood transplant
Consider early in life,* prior to or at onset of SCD symptoms, with the highest prioty given to patients with HbSS and HbSβ^0thalassemia	Stroke	Recurrent stroke despite adequate chronic transfusion therapy; progressive CNS changes
Stroke	Elevated TCD velocity	Severe SCD symptoms and inability to tolerate supportive care resulting in symptom persistence/progression
Elevated TCD velocity	Recurrent acute chest syndrome despite supportive care	
Recurrent acute chest syndrome despite supportive care	Recurrent severe VOE despite supportive care	
Recurrent severe VOE despite supportive care	Red cell alloimmunization despite intervention + established indication for chornic transfusion therapy	
Red cell alloimmunization despite intervention + established indication for chronic transfusion therapy	Pulmonary hypertension	
Pulmonary hypertension	Recurrent priapism	
Recurrent priapism	Sickle nephropathy	
Sickle nephropathy	Bone and joint involvement	
Bone and joint involvement		
Sickle retinopathy		

Source: King A, Shenoy S. Evidence-based focused review of the status of hematopoietic stem cell transplantation as treatment of sickle cell disease and thalassemia. Blood 2014;123:3089-94; quiz 210.

For all genotypes, the morbidity of the disease is the driving factor in pursuing a HSCT. Preventative HSCT should be considered for children with higher risk genotypes, HbSS and HbSβ^0. HSCT in adults with SCD is better tolerated with a low-intensity regimen, with the vaeat of requiring prolonged immune suppression to maintain mixed-donor chimerism, AVN, avascular necrosis; TCD, transcranial Doppler; VOE vaso-occlusive episodes.

* Especially in children with difficult access to adequte lifelong supportive medical care, we recommend reviewing statistics for OS, DFS, GR, and GVHD with families as they weigh these options.

References

1. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol 2010;85:77-8.

2. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Medicine 2013;10:e1001484.

3. Schechter AN. Hemoglobin research and the origins of molecular medicine. Blood 2008;112:3927-38.

4. Steinberg MH. Management of sickle cell disease. N Engl J Med 1999;340:1021-30.

5. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998;91:288-94.

6. Nagel RL, Fabry ME, Steinberg MH. The paradox of hemoglobin SC disease. Blood Rev 2003;17:167-78.

7. McCavit TL. Sickle cell disease. Pediatr Rev 2012;33:195-204; quiz 5-6.

8. National Heart Lung and Blood Institute (NHLBI). Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. 2014:http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines.

9. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. Blood 2010;115:3447-52.

10. Adams RJ, McKie VC, Carl EM, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. Ann of Neuro. 1997;42:699-704.

11. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.

12. Hirst C, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. Cochrane Database Sys Rev 2014:Cd003427.

13. Akinsanya-Beysolow I, Jenkins R, Meissner HC. Advisory Committee on Immunization Practices (ACIP) recommended immunization schedule for persons aged 0 through 18 years--United States, 2013. MMWR supplements 2013;62:2-8.

14. Sobota A, Sabharwal V, Fonebi G, Steinberg M. How we prevent and manage infection in sickle cell disease. Br J Haematol 2015;170:757-67.

15. Smith-Whitley K, Zhao H, Hodinka RL, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. Blood 2004;103:422-7.

16. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. Blood 2012;120:3647-56.

17. Lubin BH. Sickle cell disease and the endothelium. N Engl J Med 1997;337:1623-5.

18. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol 2015;11:161-71.

19. Feliu MH, Wellington C, Crawford RD, et al. Opioid management and dependency among adult patients with sickle cell disease. Hemoglobin 2011;35:485-94.

20. Weissman DE, Haddox JD. Opioid pseudoaddiction--an iatrogenic syndrome. Pain 1989;36:363-6.

21. Koch KL, Karafin MS, Simpson P, Field JJ. Intensive management of high-utilizing adults with sickle cell disease lowers admissions. Am J Hematol 2015;90:215-9.

22. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 2000;342:1855-65.

23. Davies P, Robertson S, Hegde S, Greenwood R, Massey E, Davis P. Calculating the required transfusion volume in children. Transfusion 2007;47:212-6.

24. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. Br J Haematol 2014;166:165-76.

25. Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. J Pediatr 1985;107:201-6.

26. Rivera-Ruiz M, Varon J, Sternbach GL. Acute splenic sequestration in an adult with hemoglobin S-C disease. Am J Emerg Med 2008;26:1064.e5-8.

27. Squiers JJ, Edwards AG, Parra A, Hofmann SL. Acute Splenic Sequestration Crisis in a 70-Year-Old Patient With Hemoglobin SC Disease. J Investig Med High Impact Case Rep 2016;4:2324709616638363.

28. Ebert EC, Nagar M, Hagspiel KD. Gastrointestinal and hepatic complications of sickle cell disease. Clin Gastroenterol Hepatol 2010;8:483-9; quiz e70.

29. Hosiriluck N, Rassameehiran S, Argueta E, Tijani L. Reversal of liver function without exchange transfusion in sickle cell intrahepatic cholestasis. Proc (Bayl Univ Med Cent) 2014;27:361-3.

30. Adams RJ, McKie VC, Brambilla D, et al. Stroke prevention trial in sickle cell anemia. Control Clin Trials 1998;19:110-29.

31. Adams RJ, Brambilla D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005;353:2769-78.

32. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood 2012;119:4587-96.

33. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371:699-710.

34. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995;332:1317-22

35. Ware RE. Optimizing hydroxyurea therapy for sickle cell anemia. Hematology Am Soc Hematol Educ Program 2015;2015:436-43.

36. Howell C, Douglas K, Cho G, et al. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products. British Committee for Standards in Haematology. Transfus Med (Oxford, England) 2015;25:57-78.

37. Chou ST, Fasano RM. Management of patients with sickle cell disease using transfusion therapy: guidelines and complications. Hematol Oncol Clin North Am 2016;30:591-608.

38. Lim JI. Ophthalmic manifestations of sickle cell disease: update of the latest findings. Curr Opin Ophthalmol 2012;23:533-6.

39. Minniti CP, Kato GJ. Critical Reviews: How we treat sickle cell patients with leg ulcers. Am J Hematol 2016;91:22-30.

40. Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol 2005;129:482-90.

41. Marti-Carvajal AJ, Sola I, Agreda-Perez LH. Treatment for avascular necrosis of bone in people with sickle cell disease. Cochrane Database Sys Rev 2014:Cd004344.

42. Olujohungbe A, Burnett AL. How I manage priapism due to sickle cell disease. Br J Haematol 2013;160:754-65.

43. Zemel BS, Kawchak DA, Ohene-Frempong K, Schall JI, Stallings VA. Effects of delayed pubertal development, nutritional status, and disease severity on longitudinal patterns of growth failure in children with sickle cell disease. Pediatr Res 2007;61:607-13.

44. Smith-Whitley K. Reproductive issues in sickle cell disease. Hematology Am Soc Hematol Educ Program 2014;2014:418-24.

45. Boga C, Ozdogu H. Pregnancy and sickle cell disease: A review of the current literature. Crit Rev Oncol Hematol 2016;98:364-74.

46. King A, Shenoy S. Evidence-based focused review of the status of hematopoietic stem cell transplantation as treatment of sickle cell disease and thalassemia. Blood 2014;123:3089-94; quiz 210.

47. Walters MC, Sullivan KM, Bernaudin F, et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. Blood 1995;85:879-84.

48. http://www.viacord.com/about/giving-back/sibling-connection-program/

Acknowledgments:

We are grateful to the IHTC physician staff for their critical review and input into development of this handbook with special thanks to Sarah Hall, Megan Snider, and Donna Winter of the IHTC for their detailed proofing, review, and layout; and to Chrissy Robertson/Hightower Graphics (Indianapolis, IN) for their editing and design of this handbook.

INDIANA
HEMOPHILIA &
THROMBOSIS
CENTER, INC.

8326 Naab Road, Indianapolis, IN 46260 | 877.256.8837 | www.ihtc.org