Chapter 124: Sickle Cell Disease

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 34, Sickle Cell Disease.

KEY CONCEPTS

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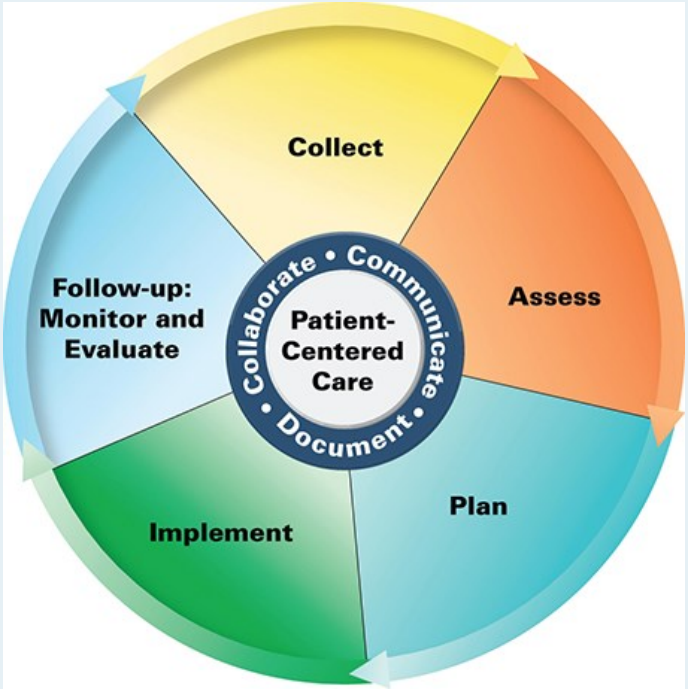
1. Sickle cell disease is an inherited disorder caused by a defect in the gene for β-globin, a component of hemoglobin. It is considered to be a qualitative hemoglobinopathy. Patients can have one defective gene (sickle cell trait) or two defective genes (sickle cell disease).
2. Although sickle cell disease usually occurs in persons of African ancestry, other ethnic groups can be affected. Multiple mutation variants are responsible for differences in clinical manifestations.
3. Sickle cell disease involves multiple organ systems. Usual clinical signs and symptoms include anemia, pain, splenomegaly, and pulmonary symptoms. Sickle cell disease is diagnosed through routine newborn screening programs available in all 50 states. Early diagnosis allows early preventive and comprehensive care.
4. Patients with sickle cell disease are at risk for infection. Prophylaxis against pneumococcal infection reduces death during childhood.
5. Hydroxyurea decreases the risk of painful episodes, but patients treated with hydroxyurea require careful monitoring.
6. Neurologic complications caused by vasoocclusion and hemolysis can lead to stroke. Screening with transcranial Doppler ultrasound to identify children at risk accompanied by chronic transfusion therapy programs can decrease the risk of overt and silent stroke in children with sickle cell disease.
7. Patients with fever greater than 38.5°C (101.3°F) should be evaluated, and appropriate antibiotics administered immediately, including coverage for encapsulated organisms, especially pneumococcal organisms.
8. Pain episodes can often be managed at home. Hospitalized patients require parenteral analgesics. Analgesic options include opioids, nonsteroidal anti-inflammatory agents, and acetaminophen. The patient characteristics and the severity of the pain should determine the choice of agent and regimen.
9. Patients with sickle cell disease should be followed regularly for healthcare maintenance issues and monitored for changes in organ function.

PATIENT CARE PROCESS

Patient Care Process for Vasoocclusive Episodes



Collect

- Patient characteristics (eg, age, sex, sickle cell disease genotypes)
- Patient medical history (include organ function and psychosocial issues)
- Immunization history
- Social history (eg, tobacco use)
- Pain diary
- Medication use
- Blood transfusion history
- Objective data
  - Vital signs: blood pressure, heart rate, respiratory rate, height, weight, O_2 saturation
  - Labs: complete blood count (CBC), reticulocytes, basic chemistry, lactate dehydrogenase, ferritin, urine analysis, hemoglobin fractionation
  - Additional labs or imaging per presenting symptoms (see Table 124-2)

Assess

- Hemodynamic stability
- Pain scale
- Adherence to home medication
- Sign or symptom associated with sickle cell acute complications (see Table 124-2)

Plan*

- Fluid
- Pain management (see Table 124-6)
- Initiate antibiotics if febrile
- Oxygen

Implement

- Provide education on current pain regimen
- Develop individualized plan for pain management
- Evaluate for initiation of hydroxyurea, L-glutamine, voxelotor, crizanlizumab
- Schedule follow-up

Follow-up: Monitor and Evaluation

- Ongoing evaluation of pain level
- Monitor for adverse drug reactions of pain medication and initiate supportive care if needed

****Collaborate with patients, caregivers, and other healthcare professionals.***

BEYOND THE BOOK ACTIVITY

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https://tinyurl.com/tel4648

Watch the short video entitled “Sickle Cell Anemia” in the DNA Learning Center. This short 1-minute video provides 3D animation of the gene mutation resulting in sickle cell disease.

https://tinyurl.com/vb4g9ye

Then listen to the podcast in EM Basic by Dr Jared Walker on evaluation and management of sickle cell disease in the emergency room.

INTRODUCTION

1 Sickle cell syndromes, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are a group of hereditary conditions characterized by the presence of sickle cell hemoglobin (HbS) in red blood cells (RBCs). SCT is the heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene, producing HbS (HbAS). Individuals with SCT are usually asymptomatic. SCD can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia (SCA), which now also includes HbSβ^0-thal due to similarities in clinical severity. The heterozygous inheritance of HbS with another qualitative or quantitative β-globin mutation results in sickle cell hemoglobin C (HbSC), sickle cell β-thalassemia (HbSβ^+-thal and HbSβ^0-thal), and some other rare phenotypes.[1-4]

Over the years, progress has been made in our understanding of the relationship between clinical severity and genotype, as well as the pathological cascades leading to complications and morbidities associated with SCD. Ongoing research focuses on disease modification, organ damage prevention,

and curative treatment. Advances in the care of patients with SCD have increased life expectancy to adulthood. Therefore, the transition from pediatric to adult medical care has become a focus to further improve survival and quality of life.[1-7]

SCD is a chronic illness with financial and emotional challenges for patients and their caregivers and high economic impact on society. Frequent hospitalizations can interrupt schooling and result in employment difficulties.[8,9] Acute complications of the disease can be unpredictable, rapidly progressive, and life-threatening. Later in life, chronic organ damage and cognitive or emotional impairment can develop.[3,7,10,11] Because of the complexity of the illness, comprehensive care must be available to all patients and that all providers have a good understanding of disease progression and management.[1,10,11]

EPIDEMIOLOGY

SCD affects millions of people worldwide. The condition is most common in people with African heritage.[2,3] The most common SCD genotype is HbSS (60%-65%), followed by HbSC (25%-30%), HbSβ^+-thal, and HbSβ^0-thal (5%-10%). Other variants account for less than 1% of patients.[1,2,5] The prevalence of SCD is highest in sub-Saharan Africa. The sickle mutation can also be found in the Arabian Peninsula, the Indian subcontinent, and the Mediterranean region.[1,3-5] An estimated 300,000 children are born each year with SCD-HbSS and another 50,000 to 100,000 births per year for other forms of SCD.[8] In the United States, about 100,000 Americans have SCD with a prevalence of 1 in 2,500 newborns of all ethnicities, 1 in 365 Black births, and 1 in 36,000 Hispanic births.[1,5]

The prevalence of SCD in a region is determined by the frequency of SCT. An estimated 300 million people are carriers worldwide.[12] The distribution of SCT reflects the survival advantage in regions where malaria is endemic as the gene mutation offers partial protection against serious malarial infection. Since RBCs carrying the abnormal sickle hemoglobin (Hb) prevent the normal growth and development of *Plasmodium falciparum* within RBCs, individuals with SCT are more likely to survive an acute malarial illness.[13] The overall incidence of SCT reported in the United States is 15.5 per 1,000 newborns, with a rate of 7.3% in Black, 0.6% in Hispanics, and 0.3% in White.[14,15]

ETIOLOGY

Normal hemoglobin (HbA) is composed of two α-chains and two β-chains ($\alpha_2\,\beta_2$). The biochemical defect that leads to the development of HbS involves the substitution of valine for glutamic acid as the sixth amino acid in the β-polypeptide chain. Another abnormal hemoglobin, hemoglobin C (HbC), is produced by the substitution of lysine for glutamic acid as the sixth amino acid in the β-chain. Structurally, the α-chains of HbS, HbA, and HbC are identical. Therefore, it is the chemical differences in the β-chain that account for sickling and its related sequelae.[1-4]

Homozygous HbSS, the most common form of SCD, occurs when an individual inherits both maternal and paternal β-globin alleles that code for HbS. Figures 124-1 to 124-4 show the probability of inheritance with each pregnancy for the offspring of parents with HbA, SCT, and HbSS. β-Thalassemia is a quantitative hemoglobinopathy resulting from a genetic defect in β-globin production that may vary from no β-globin production (β^0) to some β-globin production (β^+). β-Thalassemia can be co-inherited with HbS. Individuals with HbSS and HbSβ^0-thal have a more severe course than those with HbSC and HbSβ^+-thal and are now both referred to as SCA.[2,4,10]

FIGURE 124-1

Sickle cell gene inheritance scheme for both parents with SCT. Possibilities with each pregnancy: 25% normal (AA); 50% SCT (AS); 25% SCA (SS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

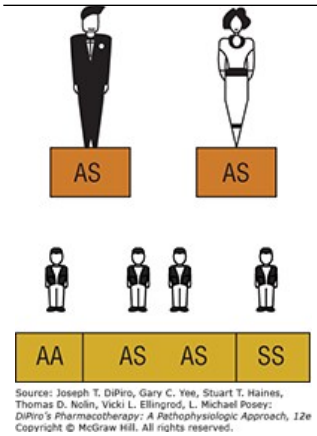


FIGURE 124-2

Sickle cell gene inheritance scheme for one parent with SCT and one parent with no sickle cell gene. Possibilities with each pregnancy: 50% normal (AA); 50% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

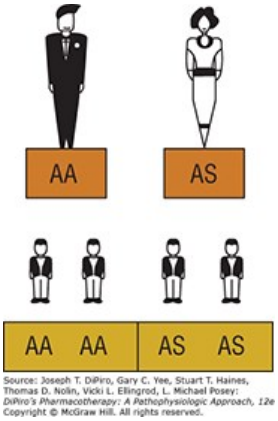


FIGURE 124-3

Sickle cell gene inheritance scheme for one parent with SCT and one parent with SSA (SS). Possibilities with each pregnancy: 50% SCA (SS); 50% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)

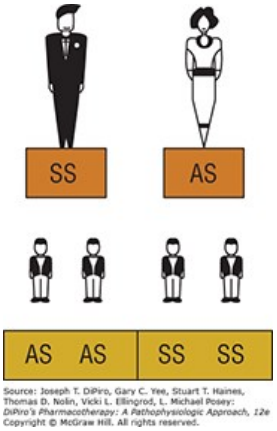
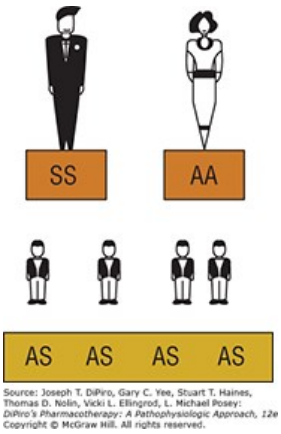


FIGURE 124-4

Sickle cell inheritance scheme for one parent without sickle cell gene and one parent with SCA. Possibilities with each pregnancy: 100% SCT (AS). (A, normal hemoglobin; S, sickle cell hemoglobin.)



SCD is most commonly found among people with ancestors from sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries. Genetic analysis shows that the haplotype containing the sickle mutation found in Arabic patients differs from the haplotype in those of African descent. These haplotype variants associated with different geographic regions may be responsible for variations in the clinical manifestations and response to therapy.[1-3,7] The three most common haplotypes in the United States are the Bantu haplotype, characterized by severe disease; the Senegal haplotype, characterized by mild disease; and the Benin haplotype, characterized by a course intermediate to that of the other two haplotypes. Although there are a number of other haplotypes seen around the world, the major types outside of the United States are found in Saudi Arabia and Cameroon, both with milder courses of illness.[1-3,7,10,16] Other genetic modifiers such as coincident α-thalassemia and the levels of fetal hemoglobin concentration also affect the clinical severity of SCD.[1]

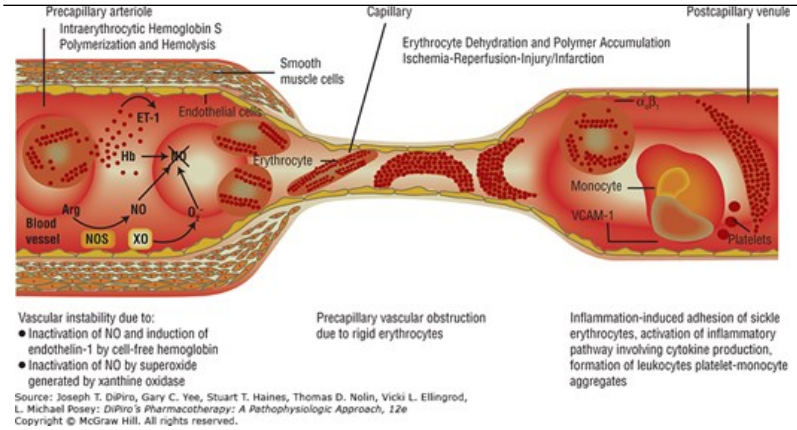
PATHOPHYSIOLOGY

Normal adult RBCs contain predominantly HbA (96%-98%). Other forms of Hb are HbA_2 (2%-3%) and fetal Hb (<1%). Normal RBCs have a biconcave shape and are able to deform to squeeze through capillaries. Fetal hemoglobin (HbF) is a tetramer of two α-globin chains and two γ-globin chains ($\alpha_2\gamma_2$) that is present predominantly in fetal RBCs.[2,3,7,13] Prior to birth, HbF is the predominant Hb type. At around 32-week gestation, a switch from the production of γ chains to β-chains occurs and consequently an increase in HbA production occurs. Increased HbF production occurs under severe erythroid stress, such as anemia, after hematopoietic stem cell transplantation (HSCT) or chemotherapy, or in the hereditary condition, hereditary persistence of fetal hemoglobin (HPFH), where a mutation in the β-globin gene cluster results in continued HbF production after birth. HPFH is a benign, asymptomatic condition.[2,3,17] HbF does not participate in the formation of the HbS polymer, so its presence in the HbSS RBC in sufficient quantity can prevent the sickling phenomenon described below.

In the pathogenesis of SCD, the following are responsible for the various clinical manifestations: impaired circulation, destruction of RBCs with release of RBC content to the plasma, stasis of blood flow, and ongoing inflammatory responses. These changes result directly from two major disturbances involving RBCs: abnormal Hb polymerization and membrane damage (Fig. 124-5).

FIGURE 124-5

Pathophysiology of sickle cell disease. (Arg, arginine; ET-1, endothelin-1; NO, nitric oxide; NOS, nitrous oxide synthase; VCAM-1, vascular cell adhesion molecule 1; XO, xanthine oxidase.) (*Reproduced, with permission, from Kato GJ, Gladwin MT. Sickle cell disease. In: Hall JB, Schmidt GA, Wood LDH. Principles of Critical Care. 3rd ed. New York: McGraw Hill, 2005:1658.*)



The solubilities of HbS and HbA are the same under conditions of normal oxygenation, but the solubility of deoxygenated HbS is reduced because of the valine substitution. Deoxy-HbS leads to intermolecular binding and formation of thin bundles of fibers, which initially are unstable. However, the increased binding of deoxy-HbS eventually results in cross-linked fibers and stable polymers. This process is influenced by mean corpuscular Hb concentration, temperature, intracellular pH, and the circulating amount of HbS. Polymerization allows deoxygenated Hb molecules to exist as a semisolid gel that protrudes into the cell membrane, leading to distortion of RBCs (sickle shaped) and loss of deformability. The presence of sickled RBCs increases blood viscosity and encourages sludging in the capillaries and postcapillary venules. Such obstructive events lead to local tissue hypoxia, which tends to accentuate the pathologic process.[4,18,19]

When reoxygenated, polymers within the RBCs disassemble and the RBCs eventually return to normal shape. This process contributes to vasoocclusion because the HbS-containing RBCs are able to enter the microvasculature when oxygenated, but sickle as Hb releases oxygen to the tissues. The cycle of sickling and unsickling results in damage to the cell membrane, loss of membrane flexibility, and rearrangement of surface phospholipids. Membrane damage also alters ion transport, resulting in potassium and water loss, which can lead to a dehydrated state enhancing the formation of sickled forms. After continual repetitions of the process, the RBCs develop into rigid irreversibly sickled cells (ISCs). Unlike the reversible sickled cells, which have normal morphology when oxygenated, ISCs are elongated cells that remain sickled when oxygenated. The more rigid membranes of these ISCs retard flow, particularly through the microcirculation. In addition, sickled RBCs tend to adhere to vascular endothelial cells, which further increases polymerization and obstruction.[1,6,18,19]

Intermolecular binding and polymer formation are reduced by HbF and to a lesser degree by HbA_2. RBCs that contain HbF sickle less readily than cells without. ISCs, not surprisingly, have a low HbF level. Increased levels of HbF, as in the case of the Saudi Arabian haplotype, result in a more benign form of SCD. The amount of HbF and HbA_2 in relation to HbS influences the clinical manifestations and accounts for some of the variability in severity among SCD genotypes.[2,3,5]

Intravascular destruction of sickle cells occurs at an accelerated rate. The stress of repetitive sickle–unsickle cycles leads to damage to the cell membrane that promotes recognition and removal of the damaged RBCs by macrophages. Rigid ISCs are easily trapped, resulting in short circulatory survival and chronic hemolysis. The typical sickle cell survives for about 10 to 20 days, while the life span of a normal RBC is 120 days.[7,10] Anemia triggers the release of immature RBCs (reticulocytes) from the bone marrow prematurely. Surface adhesion proteins of reticulocytes adhere to the endothelium in postcapillary venules, further decreasing the movement of mature HbS-containing RBCs through the microvessels.[1-3]

SCD is a complex disease of inflammation as evidenced by leukocytosis, particularly an increase in monocytes and neutrophil counts. Coagulation abnormalities in SCD are the result of continuous activation of the hemostatic system or disorganization of the membrane layer. Sickled cells interact with leukocytes, endothelial cells, and platelets to form an occlusive clot. Hemolysis releases free Hb resulting in generation of reactive oxygen species, nitric oxide (NO) depletion, and vascular inflammation. Chronic NO depletion contributes to vasoconstriction, activation of platelets and adhesion molecules such as vascular cell adhesion molecule 1 and production of the potent vasoconstrictor peptide endothelin-1.[2,3,6,13,20]

Obstruction of blood flow in the spleen by sickle cells can result in functional asplenia, defined as the loss of splenic function with an intact spleen, and eventually splenic atrophy. These patients can have deficient opsonization. Impaired splenic function increases susceptibility to infection by encapsulated organisms, particularly pneumococcal bacteria.[1,5,13]

CLINICAL PRESENTATION

Since 2006, universal newborn screening for SCD is performed in all 50 states. The sensitivity and specificity of screening methods such as isoelectric focusing, high-performance liquid chromatography, and Hb electrophoresis approach 100%. For infants with a positive screening result, a second test should be performed before 2 months of age to confirm the diagnosis. More than 98% newborns in the United States are screened for SCD. Some infants with SCD may not be identified because of extreme prematurity, prior blood transfusion, inability to contact family, and/or immigration from countries where universal screening is not performed.[4,8,21] SCD involves multiple organ systems, and its clinical manifestations vary greatly among genotypes (Table 124-1).[2,21,22]

TABLE 124-1

Clinical Features of Sickle Cell Trait and Common Types of Sickle Cell Disease

Type	Clinical Features
Sickle cell trait (SCT)	Rare painless hematuria; heavy exercise under extreme conditions can provoke gross hematuria and complications (normal Hb)
Sickle cell anemia (SCA- HbSS)	Pain episodes, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstones, priapism, leg ulcers; anemia (Hb 6-9 g/dL [60-90 g/L; 3.72-5.59 mmol/L])
Sickle cell hemoglobin C (HbSC)	Painless hematuria and rare aseptic necrosis of bone; pain episodes are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 9-14g/dL [90-140 g/L; 5.59-8.69 mmol/L])
Sickle cell β^{+}-thalassemia (HbSβ^{+}-thal)	Rare pain; milder severity than HbSS because of the production of some HbA; Hb 9-12 g/dL (90-120 g/L; 5.59-7.45 mmol/L) with microcytosis
Sickle cell β^{0}-thalassemia (HbSβ^{0}-thal)	No HbA production; severity similar to SCA; Hb 7-9 g/dL (70-90 g/L; 4.34-5.59 mmol/L) with microcytosis

Data from References 1-4 and 22-24.

Persons with SCT are usually asymptomatic. However, under certain extreme situations where Hb oxygenation is altered, RBC sickling can occur in SCT. Sickling of RBCs in the renal medulla, an area with low-oxygen tension, can result in the inability to concentrate urine. Individuals with such impairment can be at risk of dehydration. Microscopic hematuria has been observed, and gross hematuria can occur after heavy exercise. Other reported complications associated with SCT are delayed hemorrhage after eye trauma, venous thromboembolism (VTE), particularly pulmonary embolism, and chronic kidney disease.[12,23] Individuals with SCT should be cautious when participating in exercise under extreme conditions, such as athletic or military training. The US Sudden Death in Athletes Registry reported that 0.9% of 2,462 deaths occurred in athletes with SCT. The events in those 23 athletes with SCT were sudden cardiovascular collapse followed by several minutes of gradually worsening symptoms including dyspnea, fatigue, and weakness during or after vigorous physical activity.[24] Preventive strategies such as gradual conditioning, adequate rest, and hydration are recommended to minimize the risk of sudden death in personnel undergoing athletic or military training.[12,24]

The cardinal features of SCD are hemolytic anemia and vasoocclusion. In individuals with HbSS, anemia usually develops from 4 to 6 months after birth. The delay is due to the presence of HbF in fetal RBCs. HbF production is gradually replaced by HbS, leading to the clinical manifestations of the disease, such as pain and swelling of the hands and feet, commonly referred to as *hand-and-foot syndrome* or *dactylitis* in infants.[4,5,10]

The common clinical signs and symptoms associated with HbSS include chronic anemia and pallor, fever, arthralgia, scleral icterus, abdominal pain, weakness, anorexia, fatigue, hematuria, and enlargement of the liver, spleen, and heart. Laboratory findings include low hemoglobin level around 6 to 9 g/dL (60-90 g/L; 3.72-5.59 mmol/L), elevated reticulocytes of 10% to 25%, elevated lactate dehydrogenase, and elevated platelet and white blood cell (WBC) counts. Mean corpuscular volume (MCV) is normal. The peripheral blood smear demonstrates sickled RBC forms.[4,22]

Individuals with HbSC disease usually present with less severe symptoms than HbSS. The condition is characterized primarily by mild anemia (Hb levels of 9-14 g/dL [90-140 g/L; 5.59-8.69 mmol/L] and reticulocytes of 5%-10%), persistence of splenomegaly into adult life, and excessive target cells in the peripheral blood smear. In individuals with heterozygous HbSβ-thalassemia syndrome, severity of disease depends on the thalassemia mutation involved.[4,22]

Many factors can influence disease severity and mortality in children and adults with SCD. Markers for disease severity in children include dactylitis before 1 year of age, average Hb less than 7 g/dL (70 g/L; 4.34 mmol/L) in the second year of life, and leukocytosis in the absence of infection. Reticulocytosis has been associated with increased death and morbidity in both children and adults.[25,26] Early acute chest syndrome (ACS) during the first 3 years of life is a predictor for recurrent episodes throughout childhood. Children with concomitant SCD and asthma have an increased risk of ACS and pain episodes and increased mortality. Factors associated with decreased survival in adults with SCD include frequency of sickle cell pain, elevated WBC, cerebrovascular events, renal failure, proteinuria, and pulmonary hypertension.[25-28] With improved survival for SCD, chronic manifestations of the disease contribute to the increased morbidity later in life. Additionally, genetic modifiers also affect the severity of SCD. For example, BCL11A is associated with the HbF concentration, and coincident α thalassemia reduces hemolysis.[1]

CLINICAL PRESENTATION: Sickle Cell Disease

General

- Most patients in the United States with SCD are diagnosed during newborn screening
- Patients usually have a history of anemia and vasoocclusive pain crisis

Symptoms

- Acute or chronic pain, painful swelling of hands and feet, weakness, anorexia, and fatigue

Signs

- Chronic anemia and pallor, scleral icterus, hematuria, and enlargement of spleen

Laboratory Tests

- Hemoglobin electrophoresis shows over 90% hemoglobin S without the presence of hemoglobin A for the HbSS or HbSβ^0 genotype, about 50% hemoglobin S and C respectively for the HbSC genotype. Low hemoglobin level, elevated reticulocytes, elevated lactate dehydrogenase, and elevated platelet and WBC count. The peripheral blood smear demonstrates sickled RBC forms.

COMPLICATIONS

Acute Complications

Fever and Infection

Functional asplenia and failure to make antibodies against encapsulated organisms contribute to the high risk of overwhelming sepsis in individuals with SCD. Penicillin prophylaxis and vaccination have significantly reduced the overall risk of *Streptococcus pneumonia* bacteremia, but nonvaccine serotypes of *Streptococcus pneumonia* have been reported.[4,6,13,29] Children with SCD remain at a greater risk of invasive pneumococcal infections

when compared to those with other underlying diseases or healthy children.[29,30] Other encapsulated organisms are *Haemophilus influenzae, Neisseria meningitidis,* and *Salmonella*, with the latter known to cause osteomyelitis and pneumonia in SCD. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* should be considered in older children with infiltrates on chest radiograph. Viral infections such as respiratory syncytial virus, influenza, and parvovirus B19, can result in severe morbidity.[4,31] In children with SCD admitted for bacteremia, coagulase-negative *Staphylococcus* was associated with central venous access; this infection should be considered for those with a permanent indwelling venous catheter. In adults, overt pneumococcal bacteremia is less common. Pathogens such as *Staphylococcus aureus* and gram-negative organisms are associated with immunosuppression, indwelling catheter, and bone and joint infections.[5,32]

All patients with SCD with fever greater than 38.5°C (101.3°F) must be evaluated for infection or sepsis and considered for empiric antibiotic therapy; those with temperature 39.5°C (103.1°F) and appearing ill should be hospitalized. Lumbar puncture may be needed, especially in young and toxic-appearing children.[3,4,22,32]

Children with SCD may experience an aplastic crisis, which is characterized by a decrease in the reticulocyte count, the rapid development of severe anemia, and hypoplastic bone marrow (Table 124-2). An aplastic crisis is most often associated with a viral infection, particularly parvovirus B19.[3,4]

TABLE 124-2

Acute Sickle Cell Complications

Acute chest syndrome[a]
Clinical features: Peak incidence between ages 2 and 4 years. Clinically resembles pneumonia. Viral causes are more common in children than adults. Hypoxia is associated with outcome.
Signs and symptoms: New radiographic pulmonary infiltrate with one or more of the following: cough, dyspnea, tachypnea, chest pain, fever, wheezing, and new-onset hypoxia (greater than 2% decrease from baseline).
Evaluation: Chest x-ray, CBC, Type and Screen, frequent O_2 monitoring, sputum culture, serology for respiratory organisms.
Acute splenic sequestration[b]
Clinical features: Acute exacerbation of anemia due to sequestration of large blood volume by the spleen. More commonly seen in patients with functioning spleens (eg, infants with HbSS and older children and rarely adults with HbSC disease); onset often is associated with viral or bacterial infections; recurrences are common and can be fatal.
Signs and symptoms: Sudden onset of fatigue, dyspnea, and distended abdomen; rapid decrease in Hb and Hct with elevated reticulocyte count, abdominal pain, splenomegaly, vomiting, hypotension, and shock.
Evaluation: Close monitoring of vital signs, spleen size, and oxygen saturation, CBC, reticulocyte count, type and screen and blood cultures.
Aplastic crisis[c]
Clinical features: Acute decrease in Hb with decreased reticulocyte count (usually <1%); transient suppression of RBC production in response to bacterial or viral infection, most common being parvovirus B19.
Signs and symptoms: Headache, fatigue, dyspnea, pallor, and tachycardia; can also present with fever, upper respiratory or gastrointestinal infection symptoms.
Evaluation: CBC, reticulocyte count, type and screen, cultures (blood, urine, and throat), evaluation of viral infection (eg, parvovirus titers).

Overt stroke[d]
Clinical features: Sudden onset but often proceeded by a transient ischemic attack. Commonly seen in patients with HbSS and HbSβ^0-thal genotypes.
Signs and symptoms: Headache, paralysis or weakness, aphasia, visual disturbances, facial droop and convulsions.
Evaluation: Imaging, CBC, reticulocyte count, HbS quantification, type and screen, prothrombin time, activated partial thromboplastin time, and basic chemistry.
Vasoocclusive pain episodes[e]
Clinical features: Acute painful infarction without changes in Hb; almost all patients with SCA will have episodes of acute pain. Recurrent acute pain results in bone, joint, and organ damage and chronic pain. Vasoocclusive episodes most commonly involve the bones, liver, spleen, brain, lungs, and penis. Acute pain in long bones can be accompanied by signs of inflammation, making it difficult to differentiate from osteomyelitis. Abdominal involvement can resemble a surgical abdomen. Precipitating factors include infection, extreme weather conditions, swimming, excessive physical activity, dehydration, and stress.
Signs and symptoms: Deep throbbing pain; local tenderness, erythema, and swelling can be seen. Fever and leukocytosis are common. Dactylitis usually occurs in young infants. Jaundice and increased transaminases can be present if the liver is involved.
Evaluation: Frequent physical examination, CBC, reticulocyte count, and urinalysis. Based on symptomatology, the following may be needed: needle aspiration to rule out osteomyelitis, abdominal studies (radiograph, computed tomography scan, etc.), liver function tests, bilirubin, blood culture, and chest radiograph.

[a] *Data from References 1,4,33, and 34.*

[b] *Data from References 1,4,13,22, and 35.*

[c] *Data from References 2-4, 22, and 32.*

[d] *Data from References 1,2,4,22, and 36.*

[e] *Data from References 1,3,4,22, and 37.*

Hct, hematocrit.

Neurologic

Neurologic abnormalities and cognitive deficits are well documented in patients with SCD. Vasoocclusive processes can lead to cerebrovascular occlusion that manifests as signs and symptoms of overt stroke (Table 124-2). The risk of stroke is highest for HbSS and lowest for HbSβ$^+$-thal. The incidence of cerebral infarction in HbSS is 11% by age 20 years and 24% by age 45 years with a recurrence rate as high as 70% in 3 years. The highest risk occurs during the first decades, in particular ages 2 to 5 years. The risk is lowest before age 2 secondary to the protective effect of HbF. Ischemic strokes occur in 54% of cerebrovascular accidents with the highest risk before age 10 years and after 30 years of age, whereas hemorrhagic strokes are more common when patients are in their twenties and are associated with poor outcome.[1,4,19,36,38]

In addition to neurologic examination, evaluation of acute events includes computed tomography scan and magnetic resonance imaging (MRI) of the brain. Asymptomatic or silent infarcts are detected by screening MRI. Transcranial Doppler ultrasound (TCD) is important in primary stroke prevention to identify children between 2 and 16 years with abnormal cerebral artery velocities, which are associated with a 40% risk of overt stroke in the subsequent 3 years. Other imaging studies are magnetic resonance angiogram to evaluate for cerebral vasculopathy in patients with persistently abnormal TCD, overt stroke or silent stroke; and magnetic resonance venography to evaluate for cerebral vein thrombosis. In addition,

electroencephalography can be helpful in patients with a history of seizure.[4,5,22,36]

About 10% to 30% of individuals who have HbSS with no prior history of stroke have changes on MRI of the brain consistent with infarction or ischemia. Silent cerebral infarcts can be associated with an increased risk of stroke, decreased neurocognitive function, behavioral changes, and poor academic performance.[39] Neurological complications predispose aging adult patients to dementia. Finally, lower intelligence, visual-motor impairments, and neuropsychological dysfunction have been reported in patients not affected by acute or silent strokes and are associated with severity of anemia.[4,5,22,39]

Acute Chest Syndrome

ACS, defined as a new pulmonary infiltrate associated with fever and/or respiratory symptoms, is the second most common cause of hospitalization and a leading cause of death among individuals with SCD (Table 124-2).[1,33,34] The primary causes of ACS are pulmonary vascular occlusion and infection. Vascular occlusion can be caused by fat emboli released from bone marrow, VTE, or direct adhesion of RBCs to the pulmonary vasculature resulting in a vicious cycle of inflammation, hypoxia, and injury to the lung. The most common infectious pathogens causing ACS are *M. pneumonia,* respiratory syncytial virus*, C. pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.[1,4,33,34]

Risk factors for ACS and recurrence include young age, lower HbF, higher leukocytes, history of asthma or bronchial hyper-responsiveness, smoke exposure, and recent history of stroke (overt or silent) or vasoocclusion. Genotype and haplotype also influence risk. Patients with HbSS and HbSβ^0-thal have a higher risk than those with HbSC and HbSβ^+-thal and the risk is higher with African haplotypes than that of Saudi Arabia.[1,4,33,34]

ACS is more common in children but more severe in adults. Hypoxia is a predictor of severity and outcome. In severe cases, computed tomography scan, perfusion scintigraphy, transthoracic echocardiography, and bronchoscopy may be helpful to identify the etiology. Pulmonary changes often involve the lower lobes of the lungs and may cause pleural effusions. Bilateral infiltrates or multiple lobe involvement is associated with poor prognosis.[4,33,34] Pulmonary manifestations must be recognized early and managed aggressively as ACS can rapidly progress to pulmonary failure and death.[33,34]

Priapism

Stasis and sickling of RBCs within the sinusoids of the corpora cavernosa is the primary mechanism of priapism, a sustained painful erection of the penis. The pathophysiology of priapism at the molecular level includes abnormal NO signaling as the result of chronic NO depletion. Stuttering priapism is repeated intermittent attacks up to several hours before remission; ischemic priapism is a persistent painful erection greater than 4 hours and should be considered an emergency. Thirty percent to 45% of boys/men with SCD will present with at least one episode of priapism during their lifetime. The first episodes often occur during childhood. Impotence has been reported after repeated episodes and is directly related to the duration prior to treatment.[1,22,40]

Sickle Cell Pain

Acute episodes of pain are the most common reason for seeking treatment in SCD (Table 124-2). The usual cause of sickle cell pain is microvascular occlusion in the bone marrow. Although fever, infections, dehydration, hypoxia, acidosis, and sudden temperature alterations can precipitate pain, episodes are often unpredictable with no known triggers.[1,4,22] Dactylitis (hand-and-foot syndrome) is a subtype of sickle cell pain occurring in infancy and early childhood that usually does not result in permanent damage.[1,22] Each painful episode is associated with residual damage from inflammation that worsens with recurrence leading to more serious complications such as ACS.[37]

Sickle cell pain may be localized or migratory and is continuous and throbbing. The most common locations are the back, chest, and extremities but pain can occur in any location such as the abdomen or the head and lead to confusion with other acute complications such as stroke.[1,22] Risk factors associated with painful episodes include older age, iron overload, higher Hb, and lower HbF.[2,4,37]

Splenic Sequestration

Splenic sequestration is the sudden massive enlargement of the spleen resulting from the sequestration of sickled RBCs in the splenic parenchyma

(Table 124-2). Hct and Hb concentrations fall dramatically with associated reticulocytosis and no evidence of marrow failure or accelerated hemolysis. The trapping of the sickled RBCs by the spleen leads to a decrease in circulating blood volume, which can result in hypotension and shock. The condition is most often seen in infants and children because their spleens are intact; it can cause sudden death in young children due to hypovolemia. Splenic enlargement may also be acutely painful due to rapid capsular expansion. Over time, repeated splenic infarctions lead to autosplenectomy and the spleen can no longer become engorged. Sequestration usually occurs between 1 and 4 years of age for children with HbSS and HbSβ^0-thal and not at older ages because autoinfarction usually is completed by then. For HbSC and HbSβ^+-thal, autoinfarction is delayed and sequestration can occur even during adulthood.[1,4,13,22,35]

Venous Thromboembolism

Patients with SCD are susceptible to VTE due to a hypercoagulable state, endothelial dysfunction, and impaired blood flow. In addition to inflammation and hemostatic abnormalities associated with the disease, other risk factors for thrombosis include central venous access, decreased mobility, and frequent hospitalizations. An increased risk of VTE, deep vein thrombosis, and pulmonary embolism has been reported to be independent of hospitalization frequency.[7,11,13,41] Prevalence rates of 7.4% by age 30 and 11.3% by age 40 were reported.[7] In addition, a recurrence rate of about 25% has been reported.[11] D-dimer testing cannot be used to detect deep vein thrombosis because elevated D-dimers are found in more than 90% of patients with SCD as a result of hemolysis.[13] Awareness of VTE is essential when evaluating patients presenting with ACS or vasoocclusive episodes. Management of VTE is based on the anticoagulation guidelines for the general public and the role of prophylaxis in patients with SCD is unclear.[7]

Chronic Complications

Pulmonary

Over 90% of children survive into adulthood, increasing the contribution of pulmonary manifestations to the morbidity and mortality of SCD. Physical exam and history should be performed to identify signs and symptoms of respiratory conditions such as asthma, restrictive lung disease, and chronic obstructive pulmonary disease. Pulmonary function testing is recommended in symptomatic patients but not as a routine screening tool. Lower predicted FEV1% was associated with earlier death in SCD.[2]

Pulmonary hypertension, defined as a resting mean pulmonary arterial pressure of 25 mm Hg or greater by right heart catheterization, is associated with increased morbidity and mortality in SCD. Symptoms of pulmonary hypertension include shortness of breath during normal activities, fatigue, syncope, and peripheral edema. A less invasive test, tricuspid regurgitant jet velocity by Doppler echocardiography, is frequently performed initially to estimate systolic pulmonary arterial pressure, but this test is not diagnostic of pulmonary hypertension. Serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP) measurement is an alternative test that can be used to estimate the risk of pulmonary hypertension in patients with normal renal function when Doppler echocardiography is not an option. The American Thoracic Society recommends assessment of mortality risk with noninvasive (indirect) or invasive direct measurement to guide management of pulmonary hypertension (Table 124-3).[22,42,43]

TABLE 124-3

Risk Stratification and Management Recommendation for Pulmonary Hypertension

	Recommendations	Strength	Evidence Quality
Increased risk for mortality[a]	Hydroxyurea	Strong	Moderate
Increased risk for mortality, unresponsive or not candidates for hydroxyurea	Chronic transfusion therapy	Weak	Low
RHC-confirmed PH, venous thromboembolism, no risk factors for hemorrhage	Indefinite anticoagulant therapy	Weak	Low
Elevated TRV alone	No PAH therapy[b]	Strong	Moderate
Elevated NT-pro-BNP alone	No PAH therapy[b]	Strong	Moderate
RHC-confirmed marked elevation of pulmonary vascular resistance, normal pulmonary artery wedge pressure, presence of related symptoms	• A trial of prostacyclin agonist or endothelin receptor antagonist • Phosphodiesterase-5 inhibitor should not be used as first-line therapy	Weak Moderate	Very low Moderate

[a]Increased risk for mortality: (1) Tricuspid regurgitant jet velocity (TRV) greater than or equal to 2.5 m/s, (2) an N-terminal pro-brain natriuretic peptide (NT-pro-BNP) level greater than or equal to 16 pg/mL (ng/L; 1.9 pmol/L), or (3) right heart catheterization (RHC)-confirmed pulmonary hypertension (PH).

[b]PAH therapy: (1) prostacyclin agonist (epoprostenol, treprostinil, iloprost), (2) soluble guanylate cyclase stimulator (riociguat), (3) endothelin receptor antagonist (bosentan, macitentan, ambrisentan), and (4) phosphodiesterase-5 inhibitor (sildenafil, vardenafil, tadalafil).

Data from References 42 and 43.

Airway inflammation and hyper-responsiveness are common in SCD. Therefore, careful screening for respiratory symptoms in adults and children with SCD is essential. Asthma and wheezing (with or without a diagnosis of asthma) in individuals with SCD have been associated with ACS and vasoocclusive pain episodes and increased mortality. Symptoms of asthma exacerbation can overlap with ACS making it difficult to differentiate the two.[1,4,13,27] For the management of asthma, the National Asthma Education and Prevention Program asthma management guideline should be utilized and inhaled corticosteroids are first line for persistent symptoms.[27]

Skeletal and Skin Diseases

Musculoskeletal complications from vasoocclusion are common in SCD and have a significant impact on quality of life. Osteonecrosis, particularly of the femoral or humeral heads, causes chronic pain, permanent damage, and disability.[11,44] Low bone mineral density can occur early with a prevalence of over 70% reported in adults with SCD. Osteopenia and osteoporosis associated with low bone formation have been reported in individuals with SCD.[4,45] Vitamin D deficiency is common in SCD, especially in children, and is associated with increased bone fragility and vasoocclusive pain episodes.[3-5] Children with SCD also have an increased incidence of osteomyelitis; the organism most often responsible is *Salmonella*.[4,45] Septic arthritis occurs in up to 5% of children but is rare in adults.[44] In addition to necrosis of joints, chronic leg ulcers, most commonly seen in the medial and lateral malleolus (ankles), can become a difficult and painful problem for adults. Ulcers are often seen after trauma or infection and are usually

slow to heal.[5,22]

Ocular Manifestations

Ocular problems seen in patients with SCD include orbital and retinal manifestation. The incidence of proliferative sickle retinopathy and vitreous hemorrhage is up to 50%. Vasoocclusion in the eye can occur as early as 20 months of age. Clinically detectable retinal diseases usually occur during adolescence and early adulthood. Orbital involvement is uncommon but has a high potential for severe vision loss. Despite less systemic manifestations, individuals with HbSC develop serious retinal complications more often and earlier than those with HbSS. Lack of visual symptoms does not indicate the absence of ocular manifestations. Annual retinal examination starting at age 10 years is recommended for patients with SCD to prevent blindness from retinopathy and other complications.[22,46]

Hepatobiliary Diseases

Cholelithiasis is a common complication of SCD resulting from chronic hemolysis and increased bilirubin production, leading to biliary sludge and/or stone formation. The risk of gallstones increases with age: 12% for age 2 to 4 years, 43% by age 15 to 18 years, and 70% to 75% in adults. Cholecystitis, exemplified by pain in the right upper quadrant, can be confused with an acute sickle pain episode in the abdomen. Mild baseline hepatomegaly and elevation of liver function tests can occur in individuals with SCD. Cirrhosis occurred in 18% of young adults with SCD. Causes for the development of chronic hepatic disease include repeated occlusion in the liver, iron overload, and hepatitis.[22,47]

Cardiac Diseases

Cardiovascular complications associated with anemia, including cardiac enlargement and various murmurs, can occur in patients with SCD. Patients experience varying degrees of exertional dyspnea, tachycardia, and palpitation because of the decreased oxygen-carrying capacity of the blood. Left ventricular diastolic dysfunction has been reported in 18% of adults with SCD and is associated with increased mortality, especially in patients with pulmonary hypertension. Left ventricular stiffness and left ventricular hypertrophy have been reported, and can progress to diastolic dysfunction later in life. Acute myocardial infarction in adults with SCD may be under-recognized due to the high incidence of sickle cell acute chest pain.[1,10,48]

Renal Diseases

Renal dysfunction in SCD begins during infancy, as evidenced by glomerular hyperfiltration. Other manifestations include the inability to concentrate urine, hematuria, tubular acidosis, papillary necrosis, glomerulonephritis, microalbuminuria, and proteinuria. Enuresis, as a result of increased urine production, occurs in 42% of children ages 6 to 8 and 9% in young adults ages 18 to 20. Microalbuminuria, present in 42% of adults with the HbSS disease, is typically the first sign of chronic kidney disease, which has been associated with increased mortality.[6,7,22,49,50] In adults with SCD, cystatin C may better correlate with eGFR compared to serum creatinine.[7]

TREATMENT

Desired Outcomes

The goal of treatment is to reduce hospitalizations, complications, and mortality as well as improve quality of life. Management involves the use of general measures to meet the unique demands with the goal of preventing or treating complications of the disease. When an acute complication occurs, the type and severity of the episode determine the appropriate therapeutic plan.

With the availability of public health programs and comprehensive care, most children in developed countries survive through childhood and the burden of reducing mortality has shifted to focus on adults with SCD.[1,7,10] The life expectancy for individuals with SCD is lower than the general population by at least 20 years and a particularly vulnerable period appears to be during the transition to adult medical care.[4,7] Outcome evaluation for management of SCD should include assessment of health-related quality of life in both adults and children.

All patients with SCD should receive regularly scheduled comprehensive medical evaluations. Because of the complexity of the disease, an interprofessional team is needed to provide high-quality medical care, education, counseling, and psychosocial support. Appropriate comprehensive

care can have a positive impact on both longevity and quality of life. This care includes the use of evidence-based treatment combining general symptomatic supportive care, preventative medical therapies, and specific disease modifying therapies aimed at altering hematologic capacity and function.

Routine Health Maintenance

SCD is a complex chronic disease involving multiple organs. In addition to the preventive care recommended for the general population, individuals with SCD also need health maintenance and screenings that focus on minimizing complications (Table 124-4).

TABLE 124-4

Health Maintenance

Invasive Pneumococcal Infection Prevention

1. Oral penicillin until age 5 for children with HbSS/Sβ°-thal
   a. Discontinue penicillin prophylaxis at age 5 unless have had splenectomy or invasive pneumococcal infection
2. Consider no penicillin prophylaxis for children with HbSC disease and HbSβ^{+}-thal unless they have had a splenectomy

Immunization

1. All individuals should receive immunization according to the Advisory Committee on Immunization Practices
2. Pneumococcal Vaccine
   a. All infants should receive complete series of PCV13
   b. All children should receive PPSV23 at age 2 years and second dose at age 5 years
   c. Children age 2-5 years with incomplete PCV13 vaccination
      i. Unvaccinated or less than three doses PCV13: Two doses of PCV13 with second dose 8 weeks apart
      ii. Received three doses of PCV13 but none after 12-month of age: One dose of PCV13
      iii. Give two doses of PPSV23 after the PCV13 series completed. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   d. Children age 6-18 years not received PCV13 should receive one dose of PCV13.
   e. Children age 6-18 years not received PPSV23 should receive two doses of PPSV23. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   f. Adults age 19-64 years not previously received PCV13 or PPSV23:
      i. One dose PCV13
      ii. Two doses PPSV23. First dose at least 8 weeks after PCV13 and second dose at least 5 years later
   g. Adults age 19-64 years previously received PPSV23
      i. One dose PCV13 at least 1 year after last PPSV23
      ii. One dose of PPSV23 at least 5 years after first dose and no sooner than 8 weeks after PCV13
3. Haemophilus Influenza (Hib) Vaccine
   a. Children age greater than 5 years who have not previously received Hib vaccine should receive one dose
4. Meningococcal Vaccine (indicated for persons have functional or anatomic asplenia)[a]
   a. Four-dose primary series to be administered with MenACWY-CRM (2, 4, 6, and 12 months)
   b. Booster dose to be administered with MenACWY-CRM or MenACWY-D
      i. Primary series completed prior to age 7: Booster dose 3 years after primary series and repeat every 5 years thereafter
      ii. Primary series completed age 7 or older: Booster dose 5 years after primary series and repeat every 5 years thereafter
   c. Unvaccinated children 7-23 months: Two doses of MenACWY-CRM with second dose at least 12 weeks after the first dose AND after first birthday
   d. Unvaccinated children age 2 years or older and adults: Two doses of MenACWY-CRM or MenACWY-D 8-12 weeks apart
      i. MenACWY-D to be given at least 4 weeks after completion of all PCV13 doses
   e. Adults previously vaccinated should receive MenACWY-CRM or MenACWY-D every 5 years
   f. Serogroup B Meningococcal (MenB): Age 10 or older

i. MenB-FHbp (Trumenba®): Three-dose series (at 0, 1-2, and 6 months); or two-dose series (at 0 and 6 months)
ii. MenB-4C (Bexsero®): Two-dose series at least 1 month apart
5. Influenza vaccine annually for age 6 months and older

Renal
1. Screen for proteinuria by age 10 and annually if negative
2. Initiate ACE inhibitor for adults with microalbuminuria or proteinuria without apparent cause

Pulmonary Hypertension (PH)
1. Noninvasive tests (Doppler echocardiography or alternatively, serum NT-pro-BNP measurement) can be used to assess mortality risk
2. Echocardiogram to screen for PH and associated cardiac problems by age 8 for those with frequent cardiorespiratory symptoms
3. The optimal frequency for Doppler echocardiography is unknown but every 1-3 years seems to be reasonable
4. Children with evidence of PH by echocardiogram should be further evaluated: Pulmonary function test, polysomnography, oxygenation assessment, and thromboembolic disease
5. Cardiac catheterization should be performed before initiation of PAH-specific therapy

Ophthalmological Evaluation
1. Dilated eye examination begins at age 10 and rescreen at 1-2 year intervals

Stroke Prevention
1. Children with SCA: Transcranial Doppler (TCD) annually beginning at age 2 until at least age 16
2. Chronic transfusion therapy for stroke prevention in children with elevated (>200 cm/s) TCD results

[a]Brand name for meningococcal vaccine: MenACWY-CRM (Menveo®) and MenACWY-D (Menactra®)

Data from References 22,32,35,42, and 51-54.

PCV13, 13-valent conjugate pneumococcal vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; ACE Inhibitor, angiotensin converting enzyme inhibitor; PAH, pulmonary artery hypertension; PH, pulmonary hypertension.

Growth and development in children with SCD should be monitored as delayed growth and sexual maturation are common.[4,10,39] Depression, anxiety, and other behavior issues are more common in children and adults with SCD than in the general population and have a significant impact on quality of life. Psychosocial supports are essential elements of care for individuals with SCD as well as their caretakers.[9,55] Pregnancy introduces an increased risk for the mother with SCD and for the fetus. Reproductive counseling and education should be incorporated into the care of individuals with SCD.[22,56]

Immunizations

Administration of routine immunizations is crucial preventive care in managing SCD. Children 6 months and older and adults with SCD should receive influenza vaccine annually. The COVID-19 vaccine should also be recommended to individuals with SCD. The most updated immunization and catch-up schedules are provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/schedules).

Impaired splenic function increases susceptibility to infection by encapsulated organisms, particularly *Streptococcus pneumoniae*. Prior to the routine use of penicillin prophylaxis and the development of pneumococcal vaccines, invasive pneumococcal disease was 20- to 100-fold more common in children with SCD than in healthy children. Reduced mortality has been associated with the introduction of pneumococcal vaccines.[1,4]

Two different pneumococcal vaccines are available. The 13-valent pneumococcal conjugate vaccine (PCV13) induces good antibody responses in

infants and children less than 2 years of age. Immunization with the PCV13 is recommended for all children, regardless of SCD status, younger than 24 months of age. Infants should receive the first dose after 6 weeks of age. Two additional doses should be given at 2-month intervals, followed by a fourth dose at age 12 to 15 months. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is recommended for all children with functional or acquired asplenia but must be given after 2 years of age because of poor antibody response. To cover different serotypes, PPSV23 should be given starting at 2 years of age, and be administered 2 months after the last dose of the PCV13. A booster dose of PPSV23 is recommended 5 years after the first dose. Both pneumococcal vaccines are recommended for adults with certain medical conditions, including SCD (Table 124-4).[51]

The risk of meningococcal disease is also higher in SCD and vaccination is recommended for individuals with functional or acquired asplenia. Two types of meningococcal vaccines are available: (1) quadrivalent (serogroups A, C, Y, and W-135) meningococcal conjugate vaccines (MenACWY-CRM and MenACWY-D) and (2) meningococcal group B vaccine (MenB-FHbp and Menb-4C). Infants with functional asplenia should receive four-dose series with MenACWY-CRM at 2, 4, 6, and 12 months. Children over 2 years and adults with functional or acquired asplenia should receive a primary immunization series with two doses of the quadrivalent vaccine given 8 weeks apart. MenACWY-D should be given at age 2 years or older and at least 4 weeks after completion of all PCV13. A booster is recommended every 5 years for individuals with SCD.[22,52,54] Group B meningococcal vaccination is given to children with functional asplenia 10 years of age or older as a two-dose (MenB-FHbp or Menb-4C) or three-dose (MenB-FHbp) immunization series and these two vaccines are not interchangeable (Table 124-4).[52,54]

Pharmacologic Therapy

Penicillin

4 Penicillin prophylaxis until at least 5 years of age is recommended in children with SCD HbSS or HbSβ^0-thal, even if they have received PCV13 or PPSV23 immunization, as prophylaxis against invasive pneumococcal infections. An effective regimen that reduces the risk of pneumococcal infections by 84% is penicillin V potassium at a dosage of 125 mg orally twice daily until the age of 3 years, followed by 250 mg twice daily until the age of 5 years. Individuals who are allergic to penicillin can be given erythromycin 20 mg/kg/day. Penicillin prophylaxis is not routinely given in older children, based on a study demonstrating no benefit over placebo beyond the age of 5 years. However, continuation of oral pneumococcal prophylaxis should be considered on a case-by-case basis and is recommended for anyone with a history of invasive pneumococcal infection or surgical splenectomy.[22,32]

Hydroxyurea

HbF reduces polymer formation of HbS due to its high oxygen affinity and its inability to polymerize with HbS. Higher HbF levels are associated with decreased RBC sickling and RBC adhesion and observational studies show a relationship between higher HbF concentration and lower severity of SCD. Individuals with SCD and low HbF levels experience more frequent pain and higher mortality. HbF levels of 20% or greater are associated with a lower risk of acute sickle cell complications. Based on these observations, HbF induction has become a treatment modality for patients with SCD.

Hydroxyurea, a chemotherapeutic agent, stimulates HbF production and increases the number of HbF-containing reticulocytes and intracellular HbF. The drug inhibits DNA synthesis by blocking the conversion of ribonucleoside to deoxyribonucleotides. The exact mechanism of HbF production is unknown, but its myelosuppressive effect stimulates stress erythropoiesis, triggers rapid erythroid regeneration, and shifts erythrocyte Hb production to HbF. In addition, hydroxyurea increases NO levels, reduces neutrophils and monocytes, has antioxidant properties, alters the RBC membrane, increases RBC deformability by increasing intracellular water content, and decreases RBC adhesion to the endothelium.

Hydroxyurea is FDA-approved for patients 2 years of age and older with recurrent moderate-to-severe painful crises to reduce the frequency of painful crises and the need for blood transfusions. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH Trial) was the first double-blind, placebo-controlled randomized controlled trial of hydroxyurea in adults with SCD. In that study, hydroxyurea significantly reduced the frequency of painful episodes, risk of ACS, need for blood transfusions, and number of hospitalizations in adults with SCD. A follow-up study showed a 40% reduction in mortality with hydroxyurea over a 9-year period and this trend continued when the original 299 patients from the MSH study were followed for 17.5 years.[10,26,57,58]

Studies in pediatric patients reported similar results to the MSH Trial with no adverse effects on growth and development. Some patients treated with hydroxyurea had possible recovery or preservation of splenic and brain function, including cognitive performance. The Transcranial Doppler with Transfusions Converting to Hydroxyurea study (TWiTCH) closed early after interim analysis showed that hydroxyurea was not inferior to chronic blood

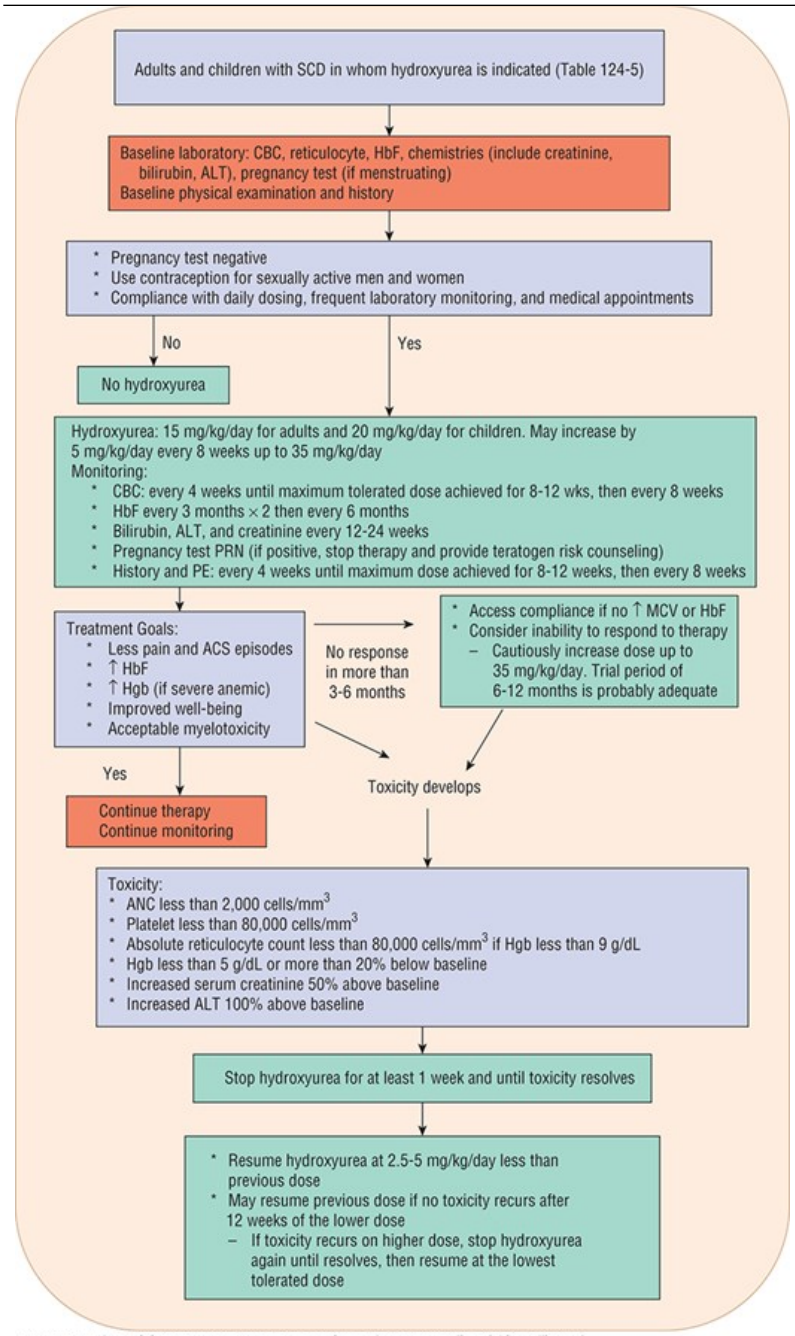
transfusions to prevent primary stroke. However, the Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial also closed early when the interim analysis showed that hydroxyurea was inferior to chronic transfusions to prevent recurrent stroke. Therefore, chronic transfusion with iron chelation to treat transfusion-related iron overload is the preferred therapy to prevent stroke.[10,26,57,58] Initiating hydroxyurea early, prior to the development of complications may be beneficial. The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) randomized young children ages 9 to 18 months to hydroxyurea or placebo. Although investigators found no significant difference in the primary endpoints (splenic and renal function), children treated with hydroxyurea had fewer episodes of pain and dactylitis with no significant toxicities.[6,57,59] Hydroxyurea reduced the risk of painful events, ACS, renal enlargement, hospitalizations, and transfusions. In addition, improved urine concentration ability as demonstrated by higher urine osmolality was reported.[57,58] In a retrospective study of hydroxyurea therapy in children aged 3 to 18 years with SCD, a significant reduction in mortality, fewer hospitalizations and emergency visits, and shorter hospital stays were reported.[60]

The most common adverse drug reaction of hydroxyurea is bone marrow suppression, resulting in neutropenia, thrombocytopenia, anemia, and decreased reticulocyte count. These hematologic adverse drug reactions usually recover within 2 weeks of therapy discontinuation. Other adverse drug reactions include dry skin and hyperpigmentation of skin or nails.[4,22,57,59] Long-term adverse effects of hydroxyurea therapy in patients with SCD are not fully known, although no serious adverse effects were reported in the long-term (17.5 years) follow-up study of the MSH trial. There is no delays in growth or puberty, increased risk of infections, or genotoxicity for children.[61] Myelodysplasia, acute leukemia, and chronic opportunistic infection associated with T-lymphocyte abnormalities have been reported in other patient populations treated with higher doses of hydroxyurea. Reproductive toxicity is also a concern. High-dose hydroxyurea is teratogenic in animals, but normal pregnancies have been reported in women with SCD who received hydroxyurea during pregnancy.[57]

Although hydroxyurea was only FDA-approved for patients age 2 years and older with SCD in 2017, the agent has been used in pediatric patients for years.[1,3,4,22] Clinical indications for hydroxyurea include frequent painful episodes, severe symptomatic anemia, a history of ACS, or other severe vasoocclusive complications (Table 124-5). The starting dose for adults is 15 mg/kg/day rounded to the nearest 500 mg as a single daily dose. A lower dose of 5 to 10 mg/kg/day is used for patients with chronic kidney disease. The recommended initial dose for children is 20 mg/kg. Dosage can be increased by 5 mg/kg up to a maximum of 35 mg/kg in 8-week intervals if the patient does not demonstrate adverse drug reactions and blood counts are stable (Fig. 124-6). Hydroxyurea dosage should be individualized based on response and toxicity. In general, 3 to 6 months of therapy are required before improvement is observed. Medication adherence can be an issue. Since the MCV generally increases as the level of HbF increases, monitoring MCV is an inexpensive and convenient method to monitor response and adherence.[1,3,4,22,57]

FIGURE 124-6

Hydroxyurea use in sickle cell disease. Blood test results expressed in SI units that are consistent with toxicity are $<2 \times 10^9$/L for ANC; $<80 \times 10^9$/L for platelets; $<80 \times 10^9$/L for absolute reticulocyte count if Hb <90 g/L (5.59 mmol/L); and Hb <50 g/L (3.10 mmol/L). (ALT, alanine aminotransferase; ANC, absolute neutrophil count; PE, physical examination; PRN, as needed.) (*Data from References 1, 3, 4, and 22.*)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 124-5

Recommendations on Hydroxyurea Therapy

	Recommendation	Strength	Evidence Quality
Adults with HbSS or HbSβ^0-thalassemia			
• Three or more sickle cell–associated moderate-to-severe pain crises per year	Treat with hydroxyurea	Strong	High
• Sickle cell–associated pain that interferes with daily activities and quality of life		Strong	Moderate
• History of severe and/or recurrent ACS		Strong	Moderate
• Severe symptomatic chronic anemia that interferes with daily activities or quality of life		Strong	Moderate
Infants 9 months of age and older, children, and adolescents with HbSS or HbSβ^0-thalassemia regardless of clinical severity	Offer hydroxyurea	Strong	High (age 9-42 months); Moderate (>42 months)
Sickle nephropathy with persisting proteinuria despite therapy	Consider hydroxyurea	Weak	Low
Chronic hypoxia	Treat with hydroxyurea	Strong	Low
HbSC or HbSβ$^+$-thalassemia with recurrent sickle cell–associated pain that interferes with daily activities or quality of life	Consider hydroxyurea	Moderate	Low
History of stroke and unable to implement chronic transfusion	Initiate hydroxyurea	Moderate	Low

Data from References 57 and 58.

5 Patients receiving hydroxyurea should be closely monitored for toxicity. Blood counts should be checked every 2 weeks during dose titration and every 4 to 8 weeks thereafter. Treatment should be interrupted if hematologic indices fall below the following values: absolute neutrophil count, 2,000 cells/mm^3 (2×10^9/L); platelet count, 80,000 cells/mm^3 (80×10^9/L); hemoglobin, 5 g/dL (50 g/L; 3.1 mmol/L); or reticulocytes, 80,000 cells/mm^3 (80×10^9/L) if the Hb concentration is less than 9 g/dL (90 g/L; 5.59 mmol/L). Other laboratory abnormalities warranting temporary discontinuation of therapy are a 50% increase in serum creatinine and a 100% increase in transaminases. After recovery has occurred, treatment should be resumed at a dose that is 5 mg/kg/day lower than the dose associated with toxicity. If no toxicity occurs after 12 weeks with the lower dose, the dose can be increased by 2.5 to 5 mg/kg/day. If the increased dose produces hematologic toxicity, the patient should be maintained at the last tolerated dose with no further escalation except for normal growth or weight gain.[22,57,58]

L-Glutamine

Sickled RBCs are susceptible to oxidative damage leading to hemolysis and vasoocclusion. Glutamine, an essential amino acid, is a precursor for nicotinamide adenine dinucleotide (NAD$^+$) synthesis. There is an increased uptake of glutamine by sickle RBCs, mainly to produce NAD$^+$. Children with

SCD have lower glutamine levels; an increase of NAD^+ can potentially restore the redox balance in oxidative stressed cells.

In a phase III double-blind, placebo-controlled trial, L-glutamine significantly reduced the median number of pain episodes and the number of hospitalizations over the study period of 48 weeks. L-glutamine was well tolerated overall but nausea, noncardiac chest pain, fatigue, and musculoskeletal pain were more commonly reported in the L-glutamine group.[62]

L-glutamine was FDA-approved in July 2017, becoming the first product approved for pediatric patients with SCD and the first new treatment for adults in almost 20 years. It is indicated for patients with SCD age 5 and older to reduce the acute complications of SCD. The product is available in 5-g packets and should be mixed with 8 ounces of liquid (~240 mL) or 4 to 6 ounces (~110-170 g) of food. The recommended dose is based on weight: 5 g twice a day for less than 30 kg; 10 g twice a day for 30 to 65 kg and 15 g twice a day for greater than 65 kg. The most common gastrointestinal adverse drug reactions are constipation, abdominal pain, and nausea.[63]

Crizanlizumab

Adherence of erythrocytes and leukocytes to the endothelium causes vascular obstruction in SCD and increased severity of the disease. The expression of adhesion molecules, including P-selectin, on the surface of endothelial cells and platelets, contributes to this process. Blockage of P-selectin reduces the adhesion of sickle erythrocytes and leukocytes, and improves microvascular blood flow. Thus, P-selectin plays an important role in vasoocclusion and microcirculatory abnormalities in SCD.[8,9]

Crizanlizumab is a monoclonal antibody against P-selectin. In a phase II double-blind, randomized, placebo-controlled trial (the SUSTAIN trial), high-dose crizanlizumab (5 mg/kg) significantly reduced the annual rate of vasoocclusive crises from 2.98 per year in the placebo group to 1.63 per year (45% reduction) and increased the median time to the first vasoocclusive crisis. The risk of serious adverse drug reactions was similar between crizanlizumab and placebo groups, with arthralgia, diarrhea, pruritus, vomiting, and chest pain more common in the crizanlizumab group.[10]

Crizanlizumab was granted FDA approval in November 2019; it is indicated for patients ≥16 years old with SCD. It is available as an intravenous (IV) solution (100 mg/10 mL). The dosing regimen is 5 mg/kg once every 2 weeks for the first two doses, followed by 5 mg/kg once every 4 weeks.

Voxelotor

The sickling and unsickling process of erythrocytes due to HbS polymerization damages the cell membrane and results in hemolysis. It contributes to SCD-related complications, including anemia, pulmonary hypertension, leg ulcers, priapism, and chronic kidney disease, and can be mitigated by inhibiting HbS polymerization.[11]

In a phase III double-blind, randomized, placebo-controlled trial (the HOPE trial), 274 patients with SCD were randomly assigned to the placebo, the 900 mg or the 1,500 mg voxelotor group. The percentage of patients with an Hb increase of more than 1 g/dL (10 g/L; 0.62 mmol/L) after 24-week treatment was significantly higher in the 1,500 mg voxelotor group than in the placebo group. The voxelotor group also experienced improvement in the hemolytic markers. The risk of adverse drug reactions was comparable in all three groups, with headache and diarrhea reported in ≥20% of the 1,500 mg voxelotor group.[12] Similar results were observed after 72-week treatment.[13]

In November 2019, FDA approved voxelotor for the treatment of SCD in patients ≥12 years of age. It is available in oral tablet of 500 mg, and the recommended dose is 1,500 mg taken once daily, with a dose adjustment to 1,000 mg once daily in severe hepatic impairment (Child Pugh class C). As a CYP3A4 substrate, concomitant use of voxelotor with strong CYP3A4 inducers or inhibitors should be avoided, or dose adjusted if not avoidable.

Chronic Transfusion Therapy

RBC transfusions play an important role in the management of SCD. In acute illness, transfusions can be life-saving. Chronic transfusion programs can prevent complications of SCD. The primary indication for chronic transfusion is primary and secondary stroke prevention and amelioration of organ damage.[4,64] Blood transfusions can be administered as a simple transfusion, a manual exchange or an automated exchange called erythrocytapheresis. Exchange transfusion frequently requires permanent venous access and is associated with higher cost but has the advantage of increasing normal (donor) HbA, limiting volume, minimizing hyperviscosity, and limiting transfusional iron overload.[22]

6 Chronic transfusions should be considered in children with SCD and adults with previous stroke or children with abnormal TCD measurements.[22] Prophylactic transfusions reduced the incidence of first stroke from 16% to 2% over a 2-year period in children 2 to 16 years of age who were at an increased risk for stroke based on abnormal annual TCD screening.[64] In children with an overt stroke, chronic transfusions reduced stroke recurrence from about 50% to about 10% over 3 years. Chronic transfusions may also be useful in patients with severe or recurrent ACS, debilitating pain, chronic organ failure, intractable leg ulcers, severe chronic anemia with cardiac failure, and complicated pregnancies, although support for the efficacy of chronic transfusion in these situations is limited.[65]

The goal of transfusions is to achieve and maintain an HbS concentration of less than 30% of total hemoglobin in the primary and secondary prevention of neurologic complications. Transfusions are usually given every 3 to 4 weeks, but the frequency of transfusion is adjusted to maintain the desired HbS levels. The risk of recurrent stroke decreases after 2 years of transfusion therapy and, in the absence of recurrent stroke, many clinicians will liberalize the HbS goal to less than 50%.[4,64] The optimal duration of primary prophylactic transfusion therapy in children with abnormal TCD is not clear. Based on the results of the TWiTCH trial, some patients can safely transition to hydroxyurea therapy after normalization of TCD and no evidence of cerebral vasculopathy with at least a 6-month overlap in transfusions and hydroxyurea therapy. Discontinuation of transfusions has been associated with a 50% stroke recurrence rate within 12 months in children with a previous stroke and abnormal blood flow velocity on TCD. For secondary stroke prevention, transfusions should be continued indefinitely.[4,57,64] Hydroxyurea could be started prior to discontinuation of transfusion for secondary stroke prevention with at least a 6-month overlap with transfusions. However, the phase III trial of switching hydroxyurea for transfusion in secondary stroke prevention, the SWiTCH trial, was closed early due to an increased risk of recurrent strokes in the hydroxyurea arm when compared to the transfusions arm.[38] The National Institutes of Health recommends hydroxyurea for prevention of recurrent stroke only if implementation of a transfusion program is not possible.[22]

Although the benefits of transfusion therapy are clear in some clinical situations, its role in other situations such as priapism or an acute pain episode remains controversial.[22] The risks of transfusion therapy must be weighed against possible benefits. The risks associated with transfusion therapy include alloimmunization (sensitization to the blood received), hyperviscosity, transfusion-transmitted viral infections, volume overload, iron overload, and nonhemolytic transfusion reactions. The use of leukocyte-reduced RBC transfusions in chronically transfused patients can reduce the risk of nonhemolytic transfusion reactions.[4,64,65] All patients should be immunized with hepatitis A and B vaccines. Other viruses that can be transmitted through blood products are parvovirus B19, hepatitis C, cytomegalovirus, and HIV.[32,64]

Alloimmunization or alloantibody formation results from antigen differences on the red cell surface between the primarily Caucasian donor pool and recipients with SCD and can cause delayed hemolytic transfusion reactions (DHTRs). Alloimmunization occurs in 19% to 37% of SCD patients who receive RBC transfusions and can make it difficult to find cross-matched blood. To prevent alloimmunization, patients receiving chronic transfusions should receive the best cross-matched blood including extended typing of other RBC antigens especially C, E, and Kell or full RBC phenotyping.[22,64,65]

The development of alloimmunization can be life threatening for individuals with SCD. DHTRs usually occur within 7 to 10 days after transfusion of blood to which the recipient is immunized, but it can occur as early as 2 days or as late as 20 days after transfusion. During a DHTR, patients develop worsening pain, especially abdominal pain, severe anemia due to hemolysis of the transfused unit and reticulocytopenia, further aggravating the anemia. Subsequent transfusions can further worsen the clinical situation because of the presence of multiple antibodies making cross-matching difficult. Life-threatening events can be treated with steroids and intravenous immunoglobulin. Recombinant erythropoietin has been used in patients with reticulocytopenia.[22,64,65] Recovery, as evidenced by reticulocytosis with a gradual increase in the Hb level, may occur only after further transfusions are withheld. Although some patients tolerate further transfusions after recovery, especially if the donor unit is negative for the offending alloantibody, others cannot avoid recurrent transfusions and may experience another hemolytic transfusion reaction. Rituximab has been used to prevent recurrent DHTR. It is generally preferable to prevent the development of DHTR by performing RBC phenotyping and, at a minimum, transfusing individuals with blood that is C, E, and Kell negative.[4,22,65]

Transfusional iron overload is an important complication of RBC transfusions and patients should be instructed to not take iron supplements.[64,65] Abnormal liver biopsy results showing mild-to-moderate inflammation, fibrosis, or cirrhosis have been reported. Iron overload assessments, including serum ferritin and liver function tests, should be performed semiannually. Iron overload can be confirmed by liver biopsy or less invasively by MRI.[22,65] Three chelating agents are available. Deferoxamine has been used as a chelating agent for decades but must be administered by subcutaneous or intravenous infusion. The oral chelation agents, deferasirox and deferiprone, are as effective as deferoxamine with acceptable safety profiles in long-

term studies up to 5 years.[66-68] Deferasirox is available in two forms. Exjade® is a dissolving tablet given once daily on an empty stomach starting at 20 mg/kg/day. Jadenu® is given as a film-coated tablet or sprinkle granule once daily on an empty stomach or with a light meal starting at a lower dose of 14 mg/kg/day. The common adverse drug reactions for deferasirox are transient skin rash and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. However, some patients may prefer film-coated tablets as it is more palatable and can be taken with food. Deferiprone has good oral bioavailability but a short half-life. The usual starting dose for deferiprone is 75 mg/kg/day, given in three divided doses. Similar to deferasirox, the common adverse drug reactions for deferiprone are rashes and gastrointestinal symptoms but the most concerning adverse drug reactions are neutropenia and agranulocytosis. For patients who require more aggressive management, deferoxamine in combination with either oral agent has been reported.[66-69]

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT is a curative therapy for patients with SCD. The overall and disease-free survival rate for children and young adults with human leukocyte antigen (HLA)-matched sibling donors has been reported at 95% to 98% and 87% to 92%, respectively.[70,71] The reported incidences of acute and chronic graft-versus-host disease (GVHD) ranged from 5% to 17% and 0% to 3%, respectively. Other complications included seizures, marrow rejection, and sepsis. Improved growth, stabilization or improvement of CNS abnormalities, and recovery of splenic dysfunction were observed in posttransplant patients with SCD, but gonadal failure and delayed sexual development in girls requiring hormonal replacement have been reported.[72]

The optimal candidates for matched sibling donor transplant are SCD patients with severe disease (HbSS and HbSβ^0) prior to the onset of SCD symptoms, but the procedure should also be considered in patients with a history of stroke, elevated TCD velocity, recurrent ACS, recurrent pain, red cell alloimmunization on chronic transfusion protocol, pulmonary hypertension, and sickle nephropathy.[73,74] Unfortunately, many children who are eligible for HSCT do not have an HLA-matched sibling donor and unrelated HLA-matched transplants are associated with higher transplant-related mortality. However, matched unrelated allogeneic HSCT is considered for SCD patients who are younger than 16 years of age and have severe complications from SCD. Because allogeneic HSCT performed in young children before organ damage and alloimmunization occur is associated with increased success, counseling and screening for HLA-matched sibling donors during the first year of life is recommended. The risks associated with allogeneic HSCT must be carefully considered, as the transplant-related mortality rate is about 5% to 10%, and graft rejection is about 10%. Other risks associated with allogeneic HSCT include secondary malignancies. Neurologic events, such as intracranial hemorrhage and seizures during transplant, were seen more frequently in patients with a history of stroke.[73,74] Tacrolimus and cyclosporine should be used with caution and the blood pressure aggressively controlled due to the increased risk of posterior reversible encephalopathy syndrome, estimated to be 22%, with calcineurin inhibitors in SCD patients undergoing allogeneic HSCT.[75]

Umbilical cord blood is another potential donor source of hematopoietic stem cells with some advantages over marrow donors, including a lower incidence of severe GVHD and a larger donor pool from which to select donors, but such advantages are offset by longer time to engraftment and a higher rate of graft rejection.[72-74] Several protocols are under investigation with haploidentical donors, such as parents, for patients with recurrent stroke on chronic transfusions or severe SCD symptoms with no HLA-matched sibling donors. Recent studies with haploidentical donors have reported stable engraftment and low rates of acute and chronic GVHD, leading to similar outcomes compared to HSCT with HLA-matched donors.[76]

HSCT with myeloablative conditioning has traditionally been limited to children and young adults with SCD due to an increased risk of GVHD or transplant-related mortality with older age.[77] HSCT with HLA-matched donors and nonmyeloablative conditioning regimens resulted in mixed donor-recipient chimerism, reversal of acute SCD complications, and low rates of transplant-related toxicity or GVHD.[70-72,74] Conditioning with alemtuzumab, total body irradiation, and post-transplant sirolimus in adults with SCD up to the age of 65 years old resulted in stable engraftment in 87% of recipients with no observed chronic GVHD.[78]

TREATMENT OF COMPLICATIONS

Parents and older children should be educated on the signs and symptoms of complications and conditions that require urgent evaluation. During acute illness, patients should be evaluated promptly because deterioration can occur rapidly. Fluid balance should be maintained as either dehydration or fluid overload can worsen complications associated with SCD. Oxygen saturation by pulse oximetry should be maintained at least 92% or at baseline. New or increasing supplemental oxygen requirements should be investigated.

Acute Sickle Cell Pain

Hydration and analgesia are the mainstays of treatment for vasoocclusive (painful) episodes (Table 124-6). Patients with mild pain crises can be treated as outpatients with rest, increased fluid intake, warm compresses, and oral analgesics. Hospitalization is necessary for moderate-to-severe pain or when oral analgesics fail to relieve pain. A pain episode may be precipitated by several risk factors including infection. In the setting of pain and fever, an infectious etiology should be considered and appropriate empiric therapy should be initiated. In patients with severe symptomatic anemia, transfusions may be indicated. Fluid replacement given intravenously or orally to correct or prevent hydration at 1 to 1.5 times the maintenance requirement is recommended. Close monitoring of fluid status is essential as aggressive hydration, particularly with sodium-containing fluids, can lead to volume overload, ACS, and heart failure.[4,10,13,22]

TABLE 124-6

Management of Acute Pain of Sickle Cell Disease

Principles
1. Treat underlying precipitating factors 2. Avoid delays in analgesia administration a. Initiate analgesic within 30 minutes of triage or 60 minutes of registration 3. Use pain scale to assess severity 4. Choice and dose of initial analgesic should be based on the home regimen, previous pain pattern, history of response, current status, and other medical conditions. The following initial dosages may be considered if an individualized plan unavailable: a. Morphine (IV): 0.1-0.15 mg/kg/dose for less than 50 kg; 5-10 mg/dose for greater than 50 kg b. Hydromorphone (IV): 0.015-0.02 mg/kg for less than 50 kg; 1.5 mg/dose for greater than 50 kg c. Ketorolac 0.5 mg/kg IV up to 30 mg/dose 5. Schedule pain medication; avoid as-needed dosing 6. Provide rescue dose for breakthrough pain 7. If adequate pain relief can be achieved with one or two doses of morphine, consider outpatient management with a weak opioid; otherwise hospitalization is needed for parenteral analgesics 8. Frequently assess to evaluate pain severity and adverse drug reactions; titrate dose as needed 9. Treat adverse effects of opioids as part of pain management 10. Consider nonpharmacologic intervention (eg, relaxation techniques, guided imagery, deep breathing) 11. Transition to oral analgesics as the patient improves; choose an oral agent based on previous history, anticipated duration, and ability to swallow tablets; if sustained-release products are used, a product with a rapid onset is also needed for breakthrough pain
Analgesic regimens
Mild-to-moderate pain: nonopioid ± weak opioid
Moderate-to-severe pain: weak opioid or low dose of a strong opioid ± nonopioid
Severe pain: strong opioid + nonopioid
Other adjunct therapy
Hydration, heating pads, relaxation, and distraction
Nonopioid analgesic including transdermal lidocaine and NSAIDs
Laxatives for constipation
Antihistamine for itching
Antiemetics for nausea or vomiting

Data from References 4,10,11,79-81, and 82.

The frequency and severity of acute pain episodes associated with SCD are variable. Pain should be assessed and analgesic therapy should be tailored for each patient and each individual episode. Several verbal and nonverbal pain assessment tools are available to measure pain intensity, but these tools have not been validated for sickle cell pain. Pain scales validated for use in children, such as the Wong-Baker FACES scale, should be used in

pediatric patients with SCD pain. The healthcare provider should choose one tool appropriate for age and use it to assess pain. However, numeric scales alone should not be the only assessment of pain severity. Other useful information to guide the choice of analgesics includes previous effective agents and their dosages, response to therapy and previous clinical course, and duration of pain episodes.[10,83,84] Individualized patient-specific protocols and standardized pathways improve the quality of pain management.[79,81,85]

8 Aggressive therapy that relieves pain and enables the patient to attain maximum functional ability should be initiated in patients with acute pain. Mild-to-moderate pain should be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, unless there are contraindications to their use. Ketorolac may be useful for patients requiring intravenous therapy. Because of the increased risk of gastrointestinal bleeding, the duration of therapy should be limited to 5 days or less. NSAID use has been associated with acute nonreversible kidney failure in a patient with SCD and should be done with caution and monitoring of renal function.[82] When acetaminophen is used, it is important to monitor the total dose of acetaminophen administered because of the risk of hepatic toxicity. Patients may also be receiving the agent for fever or another acetaminophen-containing product for pain. If mild-to-moderate pain persists, an opioid can be added.[10,22,79,80,83]

Severe pain should be treated aggressively until the pain is tolerable. Commonly used opioids include morphine, hydromorphone, fentanyl, and methadone. The weak opioids, codeine, and hydrocodone are used to manage mild-to-moderate pain usually in the outpatient setting. Some patients have clinically demonstrated inadequate relief to analgesic dosing with codeine. Some individuals who failed oral therapy with codeine were found to have a polymorphism in the *CYP2D6* gene resulting in a poor metabolizer phenotype. The CYP2D6 enzyme mediates the metabolism of codeine to morphine.[83,86] These results can lead to early discontinuation of codeine analgesics if no response is seen after their first dose and use of alternative oral analgesics for the treatment of pain at home. Meperidine has no advantages as an analgesic and many disadvantages. Meperidine toxicity is caused by accumulation of the metabolite normeperidine, which can cause adverse drug reactions in the central nervous system, ranging from dysphoria to seizures. Effective combination therapy, such as an NSAID and an opioid, can enhance analgesic efficacy while decreasing adverse drug reactions.

Both prior history and current assessment should be considered in the management of acute sickle cell pain. For patients whose typical pain improves in a short time, preparations with a short duration of action are appropriate. For patients whose pain requires many days to resolve, sustained-release preparations combined with a short-acting product for breakthrough pain are more appropriate. If the patient has been on long-term opioid therapy at home, tolerance can develop. In these cases, acute pain should be treated with an opioid of different potency or a larger dose of the same medication. Low dose ketamine has been evaluated as an adjunct therapy for individuals with severe pain despite high dose opioid therapy. The consensus guidelines on the use of intravenous ketamine for acute pain management recommends that ketamine may be considered for opioid-dependent or -tolerant patients with acute or chronic sickle cell pain. The dosing range is not well defined but the guideline recommends the bolus dose not to exceed 0.35 mg/kg and the infusion rate not to exceed 1 mg/kg/hr.[87]

Intravenous opioids provide a rapid onset of action and therefore are preferred for severe pain. Intramuscular injections should be avoided. Children may actually deny pain due to fear of injections. Analgesics should be titrated to pain relief. In patients with continuous pain, the analgesic should be given as a scheduled dose or continuous infusion. Continuous infusion has the advantage of less fluctuation of blood levels between dosing intervals. As needed dosing is only indicated for breakthrough pain. Patient-controlled analgesia (PCA) is commonly prescribed for severe pain episodes. When used properly, PCA allows patients to have control over pain therapy and minimizes the lag time between perception of pain and administration of analgesics. PCA use reduces the cumulative dosage required for pain control. Another route of administration to produce rapid pain relief is intranasal administration of an opioid such as fentanyl. The transdermal fentanyl patch has also been used successfully, but its role in sickle cell acute pain crisis is unclear because of its slow onset of pain relief (12-16 hours) and fixed dosage form, which makes it difficult to titrate the dose.[4,10,11,13,80,83]

Chronic Sickle Cell Pain

As the number of adults living with SCD increases due to improved survival, the prevalence of disease morbidities including chronic pain also increases. As outpatients, 55% of adults reported pain in more than half of the days and 29% of adults reported pain on 95% of the days. The 2014 Export Panel Report described pain as chronic when it lasts more than 3 months. Diagnostic criteria for chronic SCD pain syndrome are available.[88]

Treatment of chronic pain in SCD requires an interprofessional team approach. Most physicians with expertise in treating SCD follow established guidelines for chronic pain. Much of the research has focused on the prevention of pain and the management of acute pain episodes. Central sensitization, neurogenic inflammation, and peripheral neural sensitization have been hypothesized to play a role in the development of chronic SCD

pain.[34,40] The evidence supports other medications such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and anticonvulsants commonly used to treat chronic pain in patients with SCD. In a pilot study, pregabalin reduced pain and improved quality of life scores.[89] Nonpharmacological interventions such as acupuncture, massage, cognitive behavioral therapy, and relaxation therapy have also been used as adjunct therapy.

Episodic Transfusions for Acute Complications

Indications for acute blood transfusion include: (1) acute exacerbation of baseline anemia, such as aplastic crisis if the anemia is severe, hepatic or splenic sequestration, or severe hemolysis; (2) ACS, stroke, intrahepatic cholestasis, or acute multisystem organ failure; and (3) preparation for procedures that require the use of general anesthesia.[22] Acute transfusion is not indicated for priapism, uncomplicated pain or asymptomatic anemia. Simple transfusion or partial exchange transfusion can be used, though red cell exchange has superior outcomes when compared to simple transfusion in overt stroke. If simple transfusion is used, volume overload leading to congestive heart failure can occur if anemia is corrected too rapidly in patients with severe anemia. Acute increases in hemoglobin level to greater than 10 g/dL (100 g/L; 6.21 mmol/L) can cause hyperviscosity and should be avoided.[3,22]

Infection and Fever

Fever in a patient with SCD should be considered a medical emergency with rapid administration of intravenous antibiotics due to the risk of overwhelming sepsis. Patients with SCD should be evaluated as soon as possible for any fever greater than 38.5°C (101.3°F). Criteria for hospitalization include an infant younger than 1 year, history of previous bacteremia or sepsis, temperature greater than 39.5°C (103.1°F), WBC greater than 30,000 cells/mm^3 (30×10^9/L) or less than 5,000 cells/mm^3 (5×10^9/L), platelets less than 100,000 cells/mm^3 (100×10^9/L), or evidence of other acute complications or toxic appearance. Outpatient management can be considered in older nontoxic children with reliable family caregivers. Antibiotic choice should provide adequate coverage for encapsulated organisms.[4,22,32,90]

7 Ceftriaxone should be used for outpatient management because it provides coverage for 24 hours unless the patient has received ceftriaxone in the previous 8 weeks and then ampicillin should be given due to ceftriaxone-induced hemolysis.[91] For patients with cephalosporin allergy, clindamycin can be used. Vancomycin should be considered for acutely ill children or if *Staphylococcus* is suspected. Vancomycin trough levels should be closely monitored to ensure therapeutic levels are attained while minimizing the 4.5-fold greater risk for acute kidney injury with this antibiotic.[92,93] A macrolide antibiotic should be added if *M. pneumoniae* is suspected such as in ACS. Penicillin prophylaxis should be discontinued while the patient is receiving broad-spectrum antibiotics. Acetaminophen or ibuprofen can be used for fever control. Increased fluid requirement may be present because of poor oral intake and/or increased insensible losses contributing to dehydration.[13,32]

Cerebrovascular Accidents

Patients with acute neurologic events must be hospitalized and monitored closely. Physical and neurologic examination should be performed every 2 hours. Acute treatment for children should include exchange transfusion to maintain Hb at about 10 g/dL (100 g/L; 6.21 mmol/L) and HbS less than 30%, anticonvulsants for patients with a seizure history, and therapy for increased intracranial pressure if needed. Chronic transfusion therapy should be initiated for children with ischemic stroke as discussed earlier. In adults presenting with ischemic stroke related to atherosclerotic disease and not occlusion by sickled red cells, thrombolytic therapy should be administered if it is less than 3 hours since the onset of symptoms.[13,22,36,94]

Acute Chest Syndrome

All patients with SCD admitted for a vasoocclusive crisis should use incentive spirometry frequently (eg, at least every 2 hours while awake) to reduce atelectasis development. In addition, proper management of pain is important. The goal is to provide relief while avoiding analgesic-induced hypoventilation. Appropriate fluid therapy is important as overhydration can cause pulmonary edema. For patients who develop ACS, early use of broad-spectrum antibiotics, including a macrolide or quinolone in adults, is recommended. Infection is a common cause of ACS and can involve gram-positive, gram-negative, or atypical bacteria as well as viral infection. Oxygen therapy is indicated for all patients who are hypoxic. In a patient with a history of reactive airway disease, asthma or wheezing on examination, a trial of bronchodilators is appropriate. Transfusions are indicated for severe ACS with worsening hypoxia and increased work of breathing.[13,33,34]

Steroids can decrease inflammation and endothelial cell adhesion. Their use can decrease the duration of hospitalization and need for transfusions and other supportive care but can also increase the readmission rate for other SCD–related complications. Another potential therapy is NO, which relaxes and dilates blood vessels. Its hematologic effects include inhibition of platelet aggregation and reduction in the polymerization tendency of HbS. Marked improvement of pulmonary status and cardiac output were reported in some patients with ACS.[33,34]

Priapism

Stuttering priapism, episodes that last a few minutes to 2 hours, may resolve spontaneously with exercise, warm bath, and oral analgesics. Prolonged episodes lasting more than 2 to 3 hours require prompt medical attention. The initial goals of treatment are to provide appropriate analgesic therapy, reduce anxiety, produce detumescence, and preserve testicular function and fertility. Treatment given within 4 to 6 hours can usually reduce erection. Aggressive hydration and adequate pain control should be initiated. Heat (hot water bottles, hot packs, or sitz baths) can provide comfort without precipitating a pain crisis. Although transfusions have been given to these patients, they are not recommended because they are not efficacious and may be associated with severe neurologic sequelae if the Hb concentration is raised too precipitously.[40,95]

Clinicians have used both vasoconstrictors and vasodilators in the treatment of priapism. Vasoconstrictors, such as diluted phenylephrine (10 mcg/mL) or epinephrine (1 mcg/mL), are thought to work by forcing blood out of the corpus cavernosum into the venous return. In one uncontrolled, open-label study, aspiration followed by intra-penile irrigation of epinephrine was well tolerated and effective in 37 of 39 episodes. The procedure should be performed by a urologist with experience in the treatment of priapism.[13,40,95]

Vasodilators, such as terbutaline and hydralazine, relax the smooth muscle of the vasculature. This relaxation allows oxygenated arterial blood to enter the corpus cavernosum, which displaces or washes out the damaged sickle cells. Terbutaline has been used to treat priapism, but it has not been formally studied in patients with SCD.[40,95] Antiandrogens, bicalutamide and finasteride, have been used in SCD for treatment of recurrent or refractory priapism without major adverse drug reactions.[95] Surgical interventions used in severe refractory priapism have included a variety of shunt procedures. These surgical procedures have been successful in some cases, but they have a high failure rate and potentially serious complications, which include impotence, skin sloughing, cellulitis, and urethral fistulas.[40,95]

Modalities to prevent priapism are limited and not well studied. Pseudoephedrine (30 or 60 mg/day given orally at bedtime) and leuprolide, a gonadotropin-releasing hormone, have been used. In one case report, a single oral sildenafil dose at onset of priapism aborted episodes. However, long-term studies of sildenafil show an increase in the frequency of pain episodes.[40,95] The results of a randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of sildenafil at a dose of 50 mg/day to prevent recurrent episodes was inconclusive partly due to a small sample size.[96] Hydroxyurea promotes NO release but its effect on priapism has not been established.[97] Some clinicians transfuse patients to maintain an HbS level less than 30% to prevent recurrent priapism. Duration of such regimens should be limited to 6 to 12 months. Long-term chronic transfusions to prevent priapism are not recommended.[22,95]

Aplastic Crisis

Treatment of aplastic crisis is primarily supportive. Most patients recover spontaneously within 5 to 10 days. The only treatment may be blood transfusion if the anemia is severe or symptomatic. The reticulocyte count is used to detect the suppression of RBC production and the need for transfusion. The most common cause, parvovirus B19, is contagious and infected patients should be placed in isolation. In addition, contact with pregnant healthcare providers should be avoided because parvovirus infection during the mid-trimester of pregnancy can result in hydrops fetalis and stillbirth.[4,13,32]

Splenic Sequestration

Splenic sequestration is a major cause of mortality in young children with SCD. The sequestration of RBCs in the spleen can result in a rapid drop of hemoglobin, leading to hypovolemia, shock, and death. Immediate treatment with fluid resuscitation and blood transfusions is indicated to correct hypovolemia. Broad-spectrum antibiotic therapy, which includes coverage for *Streptococcus pneumoniae* and *H. influenzae*, can also be beneficial if the patient is febrile as infection can precipitate sequestration.[1,4,22]

Recurrent episodes occur in about half of patients and are associated with increased mortality. Options for the management of recurrence include observation and splenectomy.[22] Increased risk of invasive infection after splenectomy is a concern in young children, but most experts agree individuals with HbSS develop splenic dysfunction as early as 6 months of age and have acquired asplenia by 5 years of age and by 10 to 12 years for those with HbSC. Splenectomy is probably indicated, even after a single sequestration crisis, if that sequestration was life-threatening. Splenectomy should be considered after repetitive episodes, even if they are less serious. For children younger than 2 years of age, some experts recommend chronic blood transfusions to prevent sequestration and delay splenectomy until the age of 2 years, when the risk of post splenectomy septicemia is lower and pneumococcal vaccination has been completed. Splenectomy should also be considered for patients with chronic hypersplenism.[4,13,22,35]

EVALUATION OF THERAPEUTIC OUTCOMES

For infants younger than 1 year, medical evaluations every 2 to 4 months are recommended. Beyond 2 years of age, evaluation can be extended to every 6 to 12 months with modifications depending on the severity of the illness. Routine laboratory evaluation includes complete blood cell counts and reticulocyte counts every 3 to 6 months up to 2 years of age, then every 6 to 12 months; HbF level should be screened annually until 2 years of age. The laboratory evaluation should be performed every 2 to 3 months if the patient is receiving hydroxyurea therapy. Renal, hepatobiliary, and pulmonary function should be evaluated annually. TCD screening is recommended to start at age 2 years and to be performed annually for children with HbSS and HbSβ^0. Ophthalmologic examination to screen for retinopathy is recommended at around age 10 to 12 years for those with HbSC and 14 years for HbSS. In patients with recurrent ACS, pulmonary function tests should be done to establish baseline values and identify declines in lung function as well as an evaluation to screen for lower airway hyper-responsiveness.

Immunizations and prophylactic antibiotics must be given. When infections do occur, appropriate antibiotic therapy should be initiated, and the patient should be monitored for laboratory and clinical improvement. The effectiveness of hydroxyurea can be measured as a decrease in the number, severity, and duration of sickle cell pain episodes. HbF concentrations or MCV values can be used as a biomarker of the patient's response to therapy. When painful episodes do occur, the effectiveness of analgesics can be measured by subjective assessments made by the patient and healthcare practitioners. The success of poststroke blood transfusions can be measured by clinical progression or the occurrence of subsequent strokes.

CONCLUSION

SCD is an inherited disorder in the β-globin gene and involves multiple organ systems. Common complications include vasoocclusive pain crisis, ACS infection, stroke, pulmonary hypertension, etc. Several pharmacologic therapies are available. Hydroxyurea, L-glutamine, and crizanlizumab decrease the frequency of pain crises. Voxelotor increases the Hb level. Transfusion therapy and allogeneic HSCT are also used to manage SCD. Changes in organ function and other healthcare maintenance issues need to be monitored regularly.

ABBREVIATIONS

ACS	acute chest syndrome
DHTR	delayed hemolytic transfusion reactions
GVHD	graft-versus-host disease
HbA	hemoglobin A
HbAS	one normal (hemoglobin A) and one sickle cell hemoglobin (hemoglobin S) gene
HbC	hemoglobin C
HbF	fetal hemoglobin
HbS	sickle cell hemoglobin

HbSβ$^+$-thal	hemoglobin sickle cell β$^+$-thalassemia
HbSβ^0-thal	hemoglobin sickle cell β^0-thalassemia
HbSC	one sickle cell hemoglobin (hemoglobin S) gene and one hemoglobin C gene
HbSS	homozygous sickle cell hemoglobin (hemoglobin S)
HLA	human leukocyte antigen
HPFH	hereditary persistence of fetal hemoglobin
HSCT	hematopoietic stem cell transplantation
ISC	irreversibly sickled cell
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
MSH	Multicenter Study of Hydroxyurea in Sickle Cell Anemia
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
NT-pro-BNP	N-terminal pro-brain natriuretic peptide
PAH	pulmonary artery hypertension
PCA	patient-controlled analgesia
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
RBC	red blood cell
SCA	sickle cell anemia
SCD	sickle cell disease
SCT	sickle cell trait
TCD	transcranial Doppler ultrasound
VTE	venous thromboembolism
WBC	white blood cell

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is incorrect?
   A. Sickle cell disease is a hereditary disorder involving abnormal hemoglobin.
   B. Patients with sickle cell trait usually are asymptomatic but can become symptomatic in extreme conditions.
   C. Sickle cell disease is only seen in those with African ancestry.
   D. The primary clinical manifestations of sickle cell disease are hemolysis and vasoocclusion.
   E. Patients with a higher level of fetal hemoglobin generally have milder disease.
2. Patients with sickle cell anemia have an increased risk of which of the following infections:
   A. *Streptococcus pneumoniae*
   B. *Candida* species
   C. *Aspergillus* species
   D. *Pseudomonas* species
   E. *Enterobacter* species
3. Prevention of pneumococcal infection in sickle cell disease includes:

A. 13-Valent pneumococcal conjugate vaccine

B. Oral penicillin

C. 23-Valent pneumococcal polysaccharide vaccine

D. All of the above

E. None of the above

4. The appropriate penicillin prophylaxis regimen is:

A. Penicillin 125 mg twice daily by mouth from 5 years of age to adolescent

B. Penicillin 125 mg once a day by mouth begin at diagnosis until 5 years of age

C. Penicillin 125 mg twice a day by mouth begin at diagnosis until 3 years of age, then 250 mg twice daily until age 5

D. Penicillin 125 mg twice a day by mouth until the first dose of pneumococcal vaccine

E. Penicillin 250 mg twice a day by mouth begin at diagnosis until the first dose of pneumococcal vaccine then once daily

5. Hydroxyurea is useful in the management of sickle cell disease because:

A. It is a chemotherapeutic agent.

B. It increases fetal hemoglobin production.

C. It suppresses bone marrow production of sickle hemoglobin.

D. It inhibits the cation transport in red blood cell membrane.

E. It has the potential to cure the disease.

6. Which of the following statements is correct?

A. Hydroxyurea is useful in the management of sickle cell disease because the agent is efficacious in reducing pain episodes and has no toxicities.

B. Hydroxyurea is preferred over deferoxamine because of its sustained effect on fetal hemoglobin and lack of adverse drug reactions with long-term use.

C. Hydroxyurea reduces painful crises but close monitoring is needed because of its effect on the bone marrow.

D. Deferasirox is the drug of choice for fetal hemoglobin induction because of its safety profile.

E. Penicillin prophylaxis can be discontinued once a fetal hemoglobin inducer is initiated.

7. The appropriate management of sickle cell patients presenting with fever includes the following except:

A. Cefotaxime or ceftriaxone. Vancomycin should also be considered in acutely ill individuals.

B. Ibuprofen or Tylenol for fever.

C. Fluid.

D. Frequent monitoring.

E. Pneumococcal vaccine.

8. The primary indication for chronic transfusion program is:

   A. Prevention of infection

   B. Prevention of organ damage

   C. Lack of fetal hemoglobin response to hydroxyurea

   D. Bone marrow suppression secondary to hydroxyurea

   E. Prevention of stroke

9. Patients admitted with signs and symptoms of acute chest syndrome should:

   A. Avoid opioid analgesics because those agents may suppress ventilation

   B. Receive twice maintenance fluid to prevent dehydration from hyperventilation

   C. Not receive bronchodilators because those agents cause excessive relaxation leading to the collapse of the airway

   D. Receive appropriate pain management, oxygen, balanced fluid, and antimicrobial agents

   E. Be given corticosteroids because the agents reduce hospital stay, need for transfusions, and supportive care and readmission

10. The most common cause for an aplastic crisis is:

    A. Pneumococcal infection

    B. Delayed hemolytic transfusion reactions occurred after transfusion

    C. Parvovirus B19

    D. Sequestration of red blood cells in the spleen

    E. Splenectomy

11. Which of the following is true in regard to the management of vasoocclusive pain episodes?

    A. Hydration and aggressive analgesia are the primary treatment. Analgesic therapy should be individualized.

    B. Opioid analgesics should be kept at a minimum because patients become addicted to those agents.

    C. Patients who require opioid analgesia more than 24 hours are drug-seeking.

    D. All patients with pain episodes should be hospitalized.

    E. Fluid restriction should be initiated to prevent fluid overload.

12. Analgesic choices for sickle cell patients with mild-to-moderate pain include the following except:

    A. Nonsteroidal anti-inflammatory drugs (NSAIDs)

    B. Acetaminophen

    C. Opioid analgesics

    D. Combination of NSAIDS and opioid analgesics

    E. Intramuscular meperidine

13. Patient controlled analgesia (PCA) is useful in the management of sickle cell pain crisis because

    A. It limits the amount of opioids that can be delivered to the patient; therefore, avoiding confrontation with the patient.

    B. This method of delivery increases the duration of action.

    C. Intramuscular administration of pain medications should be avoided, especially for young children.

    D. It gives the patient control over the analgesic therapy.

    E. It minimizes addiction potential.

14. Newborn screening for sickle cell disease can be cost-effective.

    A. True

    B. False

15. The available curative therapy for sickle cell disease is:

    A. HbF inducer

    B. Hematopoietic stem cell transplant

    C. Corticosteroids

    D. Vaccines

    E. Glutamine

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** SCD can be found in sub-Saharan Africa, Arabian Peninsula, the Indian subcontinent, and the Mediterranean region. The prevalence of SCD is highest in sub-Saharan Africa.

2. **A.** Individuals with SCD are susceptible to encapsulated organisms.

3. **D.** Penicillin prophylaxis should be initiated in patients with HbSS or HbSβ^0-thal in addition to vaccines.

4. **C.** Recommended regimen.

5. **B.** Hydroxyurea is a disease modifying agent that increases fetal hemoglobin, thus reducing HbS polymerization.

6. **C.** Hydroxyurea is a chemotherapeutic agent that requires monitoring.

7. **E.** Pneumococcal vaccine is not for acute treatment of streptococcal infection.

8. **E.** Transfusion is indicated for both primary and secondary stroke prevention.

9. **D.** Overhydration can cause pulmonary edema and exacerbate respiratory distress. Infection is a common cause of acute chest syndrome; therefore, it should be managed appropriately. The goal of pain management is to provide pain relief and maintain respiratory status.

10. **C.** Bone marrow can become hypoplastic and is most often associated with a viral infection.

11. **A.** Principle on pain management is individualized regimen.

12. **E.** Meperidine can develop toxicity caused by the accumulation of the metabolite normeperidine that can cause adverse drug reactions in the

central nervous system. IM is not the recommended route, especially in children.

13. **D.** Giving patients control of their pain management is beneficial. PCA reduces overall opioid needs.

14. **A.** In the United States, newborn screen for SCD is performed in all 50 states.

15. **B.** Hematopoietic stem cell transplant is the only available curative therapy for individuals with SCD. Gene therapy is a promising alternative but is early in development and only available through early phase research studies.