Chapter 34: Sickle Cell Disease

INTRODUCTION

- *Sickle cell syndromes*, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are hereditary conditions characterized by the presence of sickle 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) gene. Individuals with SCT are 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.

PATHOPHYSIOLOGY

- Clinical manifestations of SCD are due to impaired circulation, RBC destruction, and stasis of blood flow and ongoing inflammatory responses. These changes result from disturbances in RBC polymerization and membrane damage. In addition to sickling, other factors contributing to the clinical manifestations include functional asplenia (and increased risk of infection by encapsulated organisms), deficient opsonization, and coagulation abnormalities.
- Polymerization allows deoxygenated hemoglobin to exist as a semisolid gel that protrudes into the cell membrane, distorting RBCs into sickle shapes. Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels, leading to local tissue hypoxia that accentuates the pathologic process.
- Repeated cycles of sickling, upon deoxygenation, and unsickling, upon oxygenation, damage the RBC membrane and cause irreversible sickling. Rigid, sickled RBCs are easily trapped, resulting in shortened circulatory survival and chronic hemolysis.

CLINICAL PRESENTATION

- SCD involves multiple organ systems. Clinical manifestations depend on the genotype (**Table 34-1**).
- Cardinal features of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4–6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly, and, in infants, pain and swelling of the hands and feet (eg, hand-and-foot syndrome or dactylitis).
- Usual clinical signs and symptoms of SCD include chronic anemia; fever; pallor; arthralgia; scleral icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart; and hematuria.
- Acute complications of SCD include fever and infection (eg, sepsis caused by encapsulated pathogens such as *Streptococcus pneumoniae*), stroke, acute chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
- Acute episodes of pain can be precipitated by fever, infection, dehydration, hypoxia, acidosis, and sudden temperature changes. The most common type is vasoocclusive pain, which is manifested by pain over the involved areas without change in Hb. Aplastic crisis is characterized by

acute decrease in Hb with decreased reticulocyte count manifested as fatigue, dyspnea, pallor, and tachycardia. Acute splenic sequestration is the sudden massive enlargement of the spleen due to sequestration of sickled RBCs. The trapping of sickled RBCs by the spleen leads to hypotension and shock, and can cause sudden death in young children. Repeated infarctions lead to autosplenectomy; therefore, incidence declines as adolescence approaches.

- Chronic complications involve many organs and include pulmonary hypertension, airway inflammation and hyperresponsiveness, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, depression, hematuria, and other renal complications. Children experience delayed growth and sexual maturation.
- Patients with SCT are usually asymptomatic, except for rare painless hematuria. Other reported complications associated with SCT are delayed hemorrhage after eye trauma, venous thromboembolism, particularly pulmonary embolism, and chronic kidney disease.

TABLE 34-1

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 9–14 g/dL [90–140 g/L; 5.59–8.69 mmol/L])
Sickle cell β^+-thalassemia (HbSβ^+-thal)	Rare pain; milder severity than HbSS because 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

Hb, hemoglobin; HbA, hemoglobin A.

DIAGNOSIS

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing, high-performance liquid chromatography, or electrophoresis.
- Laboratory findings include low hemoglobin; increased reticulocyte, platelet, and white blood cell counts; and sickled red cell forms on the peripheral smear.

TREATMENT

- Goals of Treatment: The goals are to reduce hospitalizations, complications, and mortality.

General Principles

- Patients with SCD require lifelong interprofessional care that combines general symptomatic supportive care, preventative medical therapies, and specific disease-modifying therapies.
- Routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations are recommended.
- Prophylactic **penicillin** is recommended until at least 5 years of age. An effective regimen is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg orally twice daily until age 5 years.

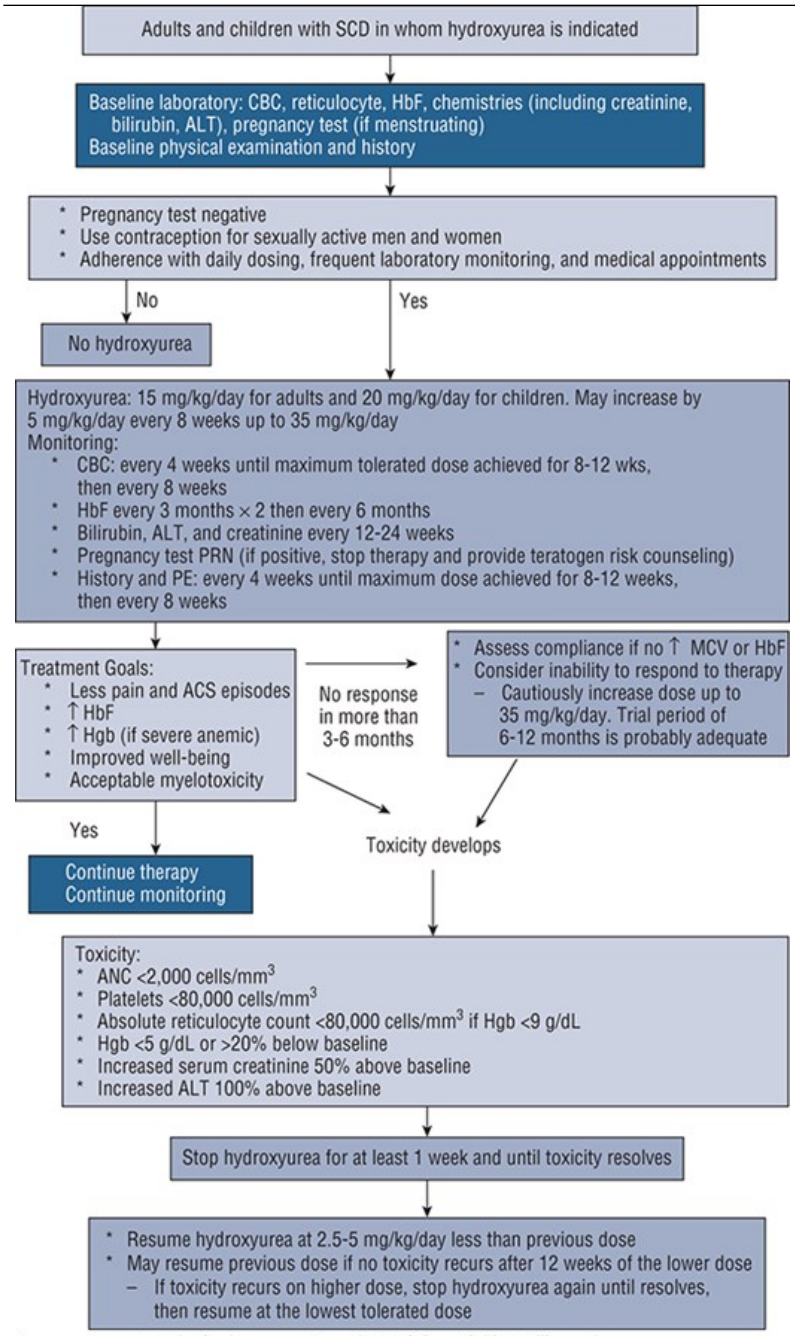
Disease-Modifying Therapies

- HbF directly affects polymer formation. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent pain and higher mortality. HbF levels of 20% or greater reduce the risk of acute sickle cell complications.
- **Hydroxyurea**, a chemotherapeutic agent, stimulates HbF production and increases the number of HbF-containing reticulocytes and intracellular HbF. It is indicated for patients 2 years of age and older with recurrent moderate to severe painful crises to reduce the frequency of pain crises and the need for blood transfusions. The recommended single daily dose for adults is 15 mg/kg and 20 mg/kg for children (**Fig. 34-1**).
- **L-Glutamine** is approved for SCD patients age 5 and older to reduce the acute complications of SCD. Dose is weight-based: 5 g twice a day for <30 kg; 10 g twice a day for 30–65 kg and 15 g twice a day for >65 kg.
- Chronic RBC transfusions are indicated for primary and secondary stroke prevention and amelioration of organ damage. Transfusions are usually given every 3–4 weeks or as needed to maintain desired HbS levels. The optimal duration of primary prophylactic transfusion therapy in children is unknown. Risks include alloimmunization, hyperviscosity, viral transmission (requiring hepatitis A and B vaccination), volume and iron overload, and transfusion reactions.
- Allogeneic hematopoietic stem cell transplantation is the only curative therapy for SCD. The best candidates are younger than 16 years, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include mortality, graft rejection, and secondary malignancies.

FIGURE 34-1

Hydroxyurea use in sickle cell disease. (*Data from Alrayyes S, Baghdan D, Haddad RY, et al. Sickle cell disease: An overview of the disease and its systemic effects. Dis Mon. 2018;64:283–289; Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390:311–323; Quinn CT. Sickle cell disease in childhood: From newborn screening through transition to adult medical care. Pediatr Clin North Am. 2013;60:1363–1381; National Institutes of Health, National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report.* http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines/. *Accessed, October 15, 2018.*)

(ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSSβ^0, sickle cell β^0-thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.)



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Treatment of Complications

- Educate patients to recognize conditions that require urgent evaluation. Balanced fluid status and oxygen saturation of at least 92% are important to avoid exacerbation during acute illness.
- RBC transfusions are indicated for acute exacerbation of baseline anemia (eg, aplastic crisis, hepatic or splenic sequestration, or severe hemolysis), severe vasoocclusive episodes, and procedures requiring general anesthesia.
- Promptly evaluate fever of 38.5°C (101.3°F) or higher. Empiric antibiotic therapy should provide coverage against encapsulated organisms (eg, **ceftriaxone** for outpatients and **cefotaxime** for inpatients; **clindamycin** for cephalosporin-allergic patients).

- For acute chest syndrome, initiate incentive spirometry; appropriate fluid therapy; broad-spectrum antibiotics, including a **macrolide** or **quinolone**; and, for hypoxia or acute distress, oxygen therapy. Other potential therapies include steroids and nitric oxide.
- Priapism has been treated with analgesics, antianxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (eg, **phenylephrine** and **epinephrine**), and vasodilators to relax smooth muscle (eg, **terbutaline** and **hydralazine**).
- Treatment of aplastic crisis is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia.
- Hydration and blood transfusions are indicated to treat hypovolemia associated with splenic sequestration. Manage recurrent episodes with observation and splenectomy. Consider chronic transfusions in children younger than 2 years of age to delay splenectomy until the age of 2 years. Splenectomy is an option for chronic hypersplenism.
- Hydration and analgesics are mainstays of treatment for vasoocclusive (painful) crisis. Administer fluids IV or orally at 1–1.5 times the maintenance requirement; monitor closely to avoid volume overload. Consider an infectious etiology and initiate empiric therapy if indicated.
- Tailor analgesic therapy to the individual because of the variable frequency and severity of pain. Pain scales should be used to quantify the degree of pain.
- Use **nonsteroidal anti-inflammatory drugs (NSAIDs)** or **acetaminophen** for mild to moderate pain. Consider adding an opioid if mild to moderate pain persists. (eg, **codeine** or **hydrocodone**).
- Treat severe pain aggressively with an opioid, such as **morphine**, **hydromorphone**, **fentanyl**, or **methadone**. Avoid **meperidine** due to accumulation of the normeperidine metabolite, which can cause neurotoxicity, especially in patients with impaired renal function.
- Treat severe pain with an IV opioid titrated to pain relief and then administered on a scheduled basis with as-needed dosing for breakthrough pain. Patient-controlled analgesia is commonly utilized.
- Treatment of chronic pain in SCD requires an interprofessional team approach. Guidelines for chronic pain management are available.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate patients on a regular basis to establish baseline symptoms, monitor changes, and provide age-appropriate education.
- Evaluate CBC and reticulocyte counts every 3–6 months up to 2 years of age, then every 6–12 months. Screen HbF level annually until 2 years of age. Evaluate renal, hepatobiliary, and pulmonary function annually. Screen patients for retinopathy.
- Assess efficacy of hydroxyurea by monitoring the number, severity, and duration of sickle cell crises.

See Chapter 120, Sickle Cell Disease, authored by C. Y. Jennifer Chan and Melissa Frei-Jones, for a more detailed discussion of this topic.